



Turkish Journal of  
**GERIATRICS**

Volume: 24 • Number: 2 • Year: 2021



The Official Scientific Journal of Turkish Geriatrics Society

e-ISSN: 1307-9948

[www.turkgeriatri.org](http://www.turkgeriatri.org)





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e-ISSN: 1307-9948

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Published four times (March, June, September, December) a year

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Date of Publication: 30 June 2021

# Turkish Journal of GERIATRICS

Volume: 24 • Issue: 2 • Year: 2021

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## FROM THE EDITOR IN CHIEF

According to the United Nations, “if our goal is to build the future we want, we must address the population over 60, which is expected to reach 1.4 billion by 2030.”

It is stated that, the most important issue to be addressed on the basis of human rights is that most men and women of advanced age can continue to contribute in society “if adequate assurance and opportunity are provided”.

Furthermore, the theme “The Journey to Age Equality” of the United Nations’ 2019 International Day of the Elderly is in line with “Sustainable Development Goal 10” and focuses on ways to prevent old age inequality.

If efforts to end old age inequality are defined as a journey, progress on this journey can only be achieved by focusing on “changing negative narratives and stereotypes” about old age.

The “leaving no - one behind” approach is adopted from this point of view and must be associated with both the Sustainable Development Goals and the dynamics of society.

Filling all these concepts will be possible by keeping multiple problems of the elderly on the agenda with an interdisciplinary understanding and sharing solutions.

**Yeşim Gökçe Kutsal**





Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.206  
2021; 24(2): 113-121

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Received: Mar 19, 2021  
Accepted: May 20, 2021

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#### RESEARCH

## NON INVASIVE MECHANICAL VENTILATION IN THE ELDERLY UNDER SPECIAL CONDITIONS

### ABSTRACT

The proportion of elderly persons among hospitalized patients, including ICU admissions, is growing rapidly. Because of the severity of their comorbidities, the elderly patients have poorer prognoses than their younger counterparts. Acute respiratory failure (ARF) is the common cause in both ICU and hospital admission, The first method to treat ARF in the elderly is oxygen therapy via a nasal canula, face mask, or high-flow nasal cannula (HFNC) to buy time to reverse the cause of respiratory failure. Non invasive ventilation (NIV) should be the first choice in elderly as in younger when needed to mechanical ventilation for avoiding the need for invasive mechanical ventilation, as well as to prevent its complications. Although NIV could be considered a proper therapeutic tool in elderly population with ARF, some peculiar issues should be considered such as environment, selection of patients, palliative care and “end-of-life” decisions The use of NIV is an important and effective treatment both in de novo, acute on chronic, post-extubation respiratory failure and also, domiciliary and palliative setting in elderly. Age need not be a barrier to NIV treatment. In this review, usage of NIV in elderly in specific conditions will be discussed.

**Key words:** Noninvasive Ventilation; Aged; Respiratory Insufficiency; Critical Care

## INTRODUCTION

People are living longer all around the world. Ten percent of the world's population's age moreover 60 years, and this age group is expected to double by 2050 (1). The population is ageing so it may be concluded that elderly patients represent a distinct and important subgroup of patients. The proportion of elderly persons among hospitalized patients, including ICU admissions, is growing rapidly. Adults older than 65 years of age account for nearly half of ICU admissions (2,3) although the proportion of older patients varies considerably across ICUs and countries.

Elderly patients have poorer prognoses than younger patients, and their mortality or morbidity depends on the severity of the underlying disease (3). Although acute respiratory failure (ARF) is the common cause in both ICU and hospital admission, chronic respiratory failure is also effecting elderly. The first method of treating ARF in the elderly is oxygen therapy via a nasal cannula, face mask or high flow nasal cannula (HFNC) (4,5) to buy time to reverse the cause of respiratory failure. Mechanical ventilation is also an important therapy for this patient population. As for younger populations, non-invasive ventilation (NIV) should be the first technique used on the elderly to avoid the need for invasive mechanical ventilation unless absolutely necessary (6).

Nowadays respiratory failure due to Covid 19 pneumonia has seen frequently in elderly. Cases in those aged 70 to 79 years had an 8.0% and cases in those aged 80 years and older had a 14.8% mortality rates (7). It is important for these patients to support ventilation with NIV. In Covid 19 cases use of helmet mask as interface advised because of staff protection.

For those with ARF, including patients of an advanced age, NIV successfully prevents unnecessary intubation and a prolonged hospital stay, and reduces the hospital mortality rate, particularly for patients with hypercapnic acidosis. However, if

patients with ARF exhibit a lack of airway protection, inadequate cooperation, and a cough reflex, then NIV should be switched off, and intubation for IMV should be considered (6). Many elderly patients, especially chronic patients, are subsequently discharged on NIV home mechanical ventilation (NIHMV) to reduce subsequent hospital admissions, maintain their quality of life, and relieve symptoms of chronic hypoventilation (8).

The elderly is particularly fragile, so the use of NIV on this population invokes specific considerations. It should be considered a good alternative to IMV for treating acute or chronic respiratory failure under specific conditions, even for those with a do-not-intubate order (4,8). Elderly patients with acute hypoxic and /or hypercapnic respiratory failure can be successfully treated with NIV. However, frailty is associated with higher NIV application problems as well as failure and mortality in the elderly, especially in ICU patients, so more attention should be paid to these patients. Frailty scores can be used to identify frail patients, predict NIV success, and improve ICU outcomes.

The success of the NIV technique is variable and depends on various factors, such as the experience of the staff applying it, adherence to the scheduled treatment, air leaks, adequate apparatus (mask, circuit), patient-ventilator synchrony and environment, the pathophysiological pattern, and the timing and severity of ARF and adequate sedation of patient (9) even the patient is fragile or not.

NIV is the first-choice ventilatory technique to treat certain diseases which are highly prevalent among the elderly; e.g., COPD, cardiogenic pulmonary edema, immunosuppression of various origin, neuromuscular disease, obesity hypoventilation syndrome, and chest wall deformity (10). The advantage of NIV is that it offers the same physiological effects of IMV delivered via ETI such as unloading respiratory muscles, improving gas exchange, and augmenting alveolar ventilation. NIV reduces the risks correlated with the use of endotracheal tubes,



such as ventilator-associated pneumonia, for which the incidence rate is especially high in the elderly (8-11). Since most patients receiving NIV are managed with minimal or no sedation because of mask intolerance due to pain, discomfort, or claustrophobia (9), early weaning off from the ventilator is facilitated and sedative drug-related complications are avoided. The early use of NIV in addition to oxygen and medical therapy for the management of ARF reduces the rate of intubation, the length of hospital stays, and the hospital mortality rate, especially in acidotic hypercapnic patients, including those who are elderly (8).

Although NIV can be considered a proper therapeutic tool for the elderly population with ARF, certain issues should be considered pertaining to the environment, selection of patients, palliative care, and "end-of-life" decisions. NIV can be used in the elderly for different purposes: 1) life support without limits, whereby the primary goal is to assist ventilation and reduce the risk of intubation and mortality, eventually restoring health; 2) life support with limits, whereby the goal is to restore health without using endotracheal intubation and the response to failure is mainly to palliate symptoms without using NIV; and 3) comfort measures for palliation to maximize comfort and minimize adverse effects.

The use of NIV is an important and effective treatment for de novo, acute-on-chronic, and post-extubation respiratory failure in both domiciliary and palliative settings for the elderly.

Age need not be a barrier in NIV treatment. In this review, usage of NIV in elderly in specific conditions will be discussed.

### **Acute Respiratory Failure in Elderly**

#### ***De Novo Respiratory Failure***

Acute respiratory failure (ARF) is a devastating condition for patients that results from either impaired function of the respiratory muscle pump or from dysfunction of the lung. ARF is associated with a

high hospital morbidity and mortality rate, ethical issues in managing end of life decisions and increased consumption of healthcare resources.

Acute hypoxaemic failure covers miscellanea of causes of lung damage including pneumonia, acute cardiogenic pulmonary oedema and also trauma in elderly.

The role of NIV in patients with hypoxaemic ARF is controversial. The peculiar advantages of NIV versus IMV should be carefully weighed especially in elderly patients.

The benefit of NIV in patients with pneumonia is controversial due to high failure rates (11-14). NIV can be failed more frequently in subjects with de novo acute respiratory failure (46%) than subjects with previous cardiac or respiratory disease (26%). Worsening radiographic infiltrate 24 h after admission, maximum Sequential Organ Failure Assessment (SOFA) score and, after 1 h of NIV, higher heart rate and lower PaO<sub>2</sub> /FIO<sub>2</sub> and bicarbonate independently predicted NIV failure. Successful NIV was strongly associated with better survival. But if predictors for NIV failure are present, avoiding delayed intubation of patients with de novo acute respiratory failure may reduce mortality. In these patients respiratory muscle resting may improve respiratory mechanics (14).

The best hospital management of NIV in patients at an advanced age as in younger should require well-trained staff and a 24 h observation with an adequate monitoring of patients' condition severity during the NIV application in case a quick move to IMV is required especially in de novo respiratory failure.

#### ***Acute Cardiogenic Pulmonary Edema/Acute Heart Failure***

NIV in addition to standard medical care is an effective and safe intervention for the treatment of elderly patients with acute cardiogenic pulmonary oedema (ACPE).

The common clinical indications for NIV application in ACPE are dyspnea, hypoxemia and pulmonary congestion (15). The extravasation of fluid to alveoli that reduces gas exchange and produce hypoxia and also hypercapnia in severe cases. These symptoms are often caused in old patients mainly by afterload and fluid redistribution rather than a total volume overload in the body (16). The goals of NIV use in the treatment of ACPE are to improve oxygenation, reduce the effort of breathing and increase cardiac output. Continuous positive airway pressure (CPAP) achieves these goals by maintaining positive airway pressure throughout the respiratory cycle thereby preventing alveolar collapse at end-expiration.

CPAP increases lung compliance and decreases the effort of breathing, while decreasing cardiac preload and afterload. It improves arterial oxygenation (PaO<sub>2</sub>) by increasing the functional residual capacity of the lungs and reducing intrapulmonary shunt. When patients are treated using the CPAP, a high mean airway pressure is avoided and a lower mean intrathoracic pressure develops during inspiration, which has favorable effects in terms of the venous return and a reduced risk of barotrauma. Moreover, treatment with CPAP has beneficial effects on hemodynamics. Unlike CPAP, bilevel positive airway pressure (BiPAP) combines inspiratory positive air way pressure with positive end-expiratory pressure. As a result, the BiPAP differs from the CPAP due to providing inspiratory assistance that allows the muscles used in respiration to relax. Both the CPAP and BiPAP approaches are applied using either a nasal or an oronasal mask at the patient-ventilator interface.

Myopathy has been reported to be one of the most common clinical manifestations seen in patients with acute heart failure (HF). It results in muscle fiber atrophy, which leads to the substitution of type I muscle fibers with type II fibers. Consequently, there is a progressive reduction in the patient's capacity for exercise due to early fatigue and hyper-

ventilation. Individuals with HF can develop both peripheral and respiratory muscle weakness (17).

The prevalence of inspiratory muscle weakness in outpatients with chronic HF has been reported to range between 30% and 50% (14). In older patients, the application of ventilatory support (i.e., CPAP or BiPAP) improves lung compliance, recruits previously collapsed alveoli, and reduces both the preload and afterload, which leads to an improvement in oxygenation and a reduction in the workload of the respiratory muscles (17-20). Moreover, it results in significantly reduced endotracheal intubation and mortality rates. Importantly, prior studies have indicated that an advanced age does not represent a limitation when it comes to the safe use of ventilatory support (18-21).

The complications associated with the use of NIV include air leaks, mask-related discomfort, skin breakdown, eye irritation, sinus congestion, oronasal drying, and patient-ventilator dyssynchrony (9). In addition, pneumothoraxes and pneumonias can occur following the administration of NIV, albeit less frequently than in the case of invasive ventilation. NIV may also result in endotracheal intubation being delayed, which can be associated with patient deterioration during the intervening period.

### **Respiratory Failure due to Covid 19 Pneumonia**

Covid 19 pneumonia has seen frequently in elderly and mortality rates were higher than younger patients. NIV is an effective and common treatment for patients with mild to moderate acute respiratory failure. and (22) but it has some concerns in Covid 19 patients because coronavirus diffusion takes place by droplet transmission,(23) aerosolisation during NIV like intubation or bronchoscopy might represent a big danger, because of exposing other patients and health-care staff to an increased risk of infection. (24) Aerosolisation with nosocomial amplification of the infection can also potentially happen around the face mask during non-invasive



ventilation (25). Accordingly, the efficacy and safety of non-invasive ventilation during viral pandemic infection are still debated. However, during pandemics, the number of intensive care unit beds for mechanical ventilation through tracheal intubation could rapidly become insufficient, (24) whereas non-invasive ventilation can be offered also outside the intensive care unit.

To increase staff and other patients safety during NIV, applying in negative pressure rooms, using a helmet mask as an interface can be considered to avoid aerosolisation. NIV should be applied with ICU ventilators which allow the option of FiO<sub>2</sub>, permit visualisation of waveform display and allow separate inspiratory and expiratory circuits. Filters should be attached to the ventilators' inspiratory and expiratory valve. ICU ventilators also recommended because of leak compensation. Accordingly, when facing a patient with acute respiratory failure of suspected Covid 19 the adoption of helmet masks should be preferred as possible. In clinical practice, pressure support ventilation with PEEP support is virtually the only mode. Emergency departments and intensive care units are increasingly applying NIV (22).

### **Acute-on-Chronic Respiratory Failure**

Acute respiratory failure is often the final event in patients with chronic respiratory failure (26) especially those with chronic obstructive respiratory disease ( COPD). No consensus has yet been reached with regard to the best treatment and outcomes for elderly patients who have been admitted to the ICU following an episode of acute respiratory failure (27). However, NIV should be the first treatment choice for acute-on-chronic (AOC) respiratory failure in appropriate patients.

It is important to note that neither ICU admission nor mechanical ventilation are necessarily associated with a poor prognosis in elderly patients who are experiencing acute exacerbations of COPD

(AECOPD). Individuals with chronic respiratory disorders represent a large proportion of those patients over 65 years of age who are admitted to an ICU. Older patients with hypercapnia (i.e., PaCO<sub>2</sub> > 45 mmHg) have been found to have a poor survival rate following an episode of acute hypercapnic respiratory failure (AHRF) (28). In these patients, the success of NIV is related to the number and the severity of their comorbidities.

The use of NIV to treat respiratory failure in old patients reduces the need for intubation, improves survival, and induces a faster resolution of respiratory distress compared with standard medical therapy ( SMT). In fact, rescue therapy involving NIV has been found to be very successful in the majority of cases (75%) (27).

NIV not only improves the survival rate in older patients, but also reduces the major symptoms of respiratory distress, for example, tachypnea and dyspnea. It has previously been reported that the sensation of dyspnea and the respiratory rate are strongly correlated with the inspiratory load (29). Thus, it is likely that NIV could also prove useful in terms of relieving the sense of breathlessness in chronically ill elderly patients. The application of both inspiratory and expiratory support is important in acute and chronic settings in relation to reducing the inspiratory burden (27).

During an episode of AOC respiratory failure in old patients, the use of NIV is associated with a reduced likelihood of meeting the endotracheal intubation (ETI) criteria, a higher survival rate, and the faster resolution of respiratory distress when compared with standard medical treatment. The use of NIV as a rescue therapy in those patients who met the intubation criteria represents the most likely explanation for the low mortality rate. This demonstrates the importance of NIV not only as a palliative measure but, also, as the primary treatment modality when intubation is either not wanted by the patient or not deemed necessary by the physician.

Interestingly, the high NIV success rate reported

in patients with ARF due to AECOPD is also associated with a reduction in IMV-related complications (30).

In elderly patients with AOC respiratory failure due to AECOPD, the initial NIV settings should involve an inspiratory positive airway pressure (IPAP or PS) of 10 cmH<sub>2</sub>O and an expiratory positive airway pressure (EPAP or PEEP) of 4 cmH<sub>2</sub>O. The pressure should then be increased by 2–5 cmH<sub>2</sub>O every 10 minutes for as long as the patient's respiratory effort and arterial blood gas values warrant.

During the early stages of acute respiratory failure, the first application of NIV should last close to 24 hours. Then, on the basis of the patient's clinical and blood gas values, the application time should be reduced, although NIV should still be applied for at least five hours per day. In prior studies, the NIV implementation period has ranged from 4–15 days (31).

The use of NIV can allow patients to talk, eat, and partially clear secretions autonomously. Especially in the usage of appropriate mask. Thus, NIV not only treats the cardiorespiratory problem, but also decreases the risk of delirium and malnutrition. (32). Furthermore, NIV reduces the need for sedatives, compared with IMV, which further contributes to prevent delirium and immobilization (33). The presence of delirium or dementia was not a barrier for the indication or for the administration of NIV; the presence of a pneumo-geriatric team allowed the symptoms to be controlled and the cooperation of the subjects to be obtained. In addition, NIV allows relatives to visit more frequently and for longer time.

### **Palliative Care**

The use of NIV in palliative care settings is very important, especially in elderly patients, because it improves patients' dyspnea and so enhances their quality of life. Breathlessness is a cardinal symptom which progresses with advancing disease and has a

profound impact on patients. The need for mechanical support is theoretically the main intervention when an organ is failing beyond a point in which any pharmacological intervention is ineffective or partially effective. The problem is understanding in the clinical practice as to when mechanical support may prove futile. The failure of weaning from IMV represents one of the major clinical problems in elderly patients, especially those with AOC respiratory failure and those who have several comorbidities.

The feasibility and the usefulness of NIV in relation to the palliative care of patients with acute respiratory failure who are nearing the end of their life have not yet been well demonstrated (34). NIV is often used for patients with terminal diseases to help alleviate their respiratory distress and provide some additional time, for example, to say goodbye to relatives and friends or to solve certain administrative issues, although most clinicians are unclear as to the goals of such care. It has been suggested that NIV may actually be inappropriate in this context due to the increased consumption of medical resources, the prolongation of the dying process, and the intensification of the patient's suffering (35).

### **Domiciliary NIV in Elderly Patients**

The use of NIV is associated with a number of benefits in patients with respiratory conditions, including chronic respiratory diseases such as COPD, obesity hypoventilation syndrome, restrictive lung diseases, and a variety of neuromuscular conditions. However, it remains unclear whether these patients require domiciliary NIV, particularly if they are elderly. Although there is a paucity of data in this regard, it has been reported that the development of more comfortable interfaces, which are associated with more acceptable, safer, and better ventilators, has vastly expanded the patient population that could benefit from NIV (36). The application of domiciliary NIV can serve to reduce hospital and ICU admissions. It can also help to relieve chronic hypoventila-



tion-related symptoms and so to maintain patients' quality of life.

It has been reported that age, in and of itself, is not a barrier to the application of domiciliary NIV (37). NIV is known to be both effective and safe in elderly patients, many of whom have multiple comorbidities (e.g., significant cognitive impairment and acute delirium), at least in terms of acute presentations with respiratory insufficiency.

In conclusion, NIV is widely and successfully used in elderly patients with respiratory failure in an effort either to prevent endotracheal intubation and death (i.e., as supportive care) or to relieve the symptoms of patients' special conditions (i.e., as palliative care).

### Recommendations for NIV protocols:

CPAP/PSV may be sufficient since hypoxemic respiratory failure is prominent. It should be applied between 8-15 cmH<sub>2</sub>O. BIPAP can be applied to patients with hypercapnic or increased respiratory workload requiring ventilation support. The pres-

sure support is adjusted to 8-16 cmH<sub>2</sub>O, PEEP 5-10 cmH<sub>2</sub>O. It should be started with low values at the beginning and should be increased 1 or 2 cmH<sub>2</sub>O at every 10-20 minutes. One and 2 hours from beginning respiratory workload (dyspnea, auxiliary respiratory muscles, respiratory pattern, respiratory rate and depth), state of consciousness and oxygenation should be evaluated.

If there is no response to NIV at the end of the 2nd hour, IMV with intubation should be considered.

NIV non-response / failure criteria: respiratory rate > 30 / min, tidal volume > 9 ml / kg ideal, minute ventilation > 12 L / min, use of auxiliary respiratory muscles, abdominal paradox, increase in respiratory distress, SpO<sub>2</sub> < 0.90, PaO<sub>2</sub> < 60 mmHg, PaO<sub>2</sub> / FiO<sub>2</sub> < 150, hypercapnia, pH < 7.25, mask intolerance, confusion, haemodynamic worsening, acute organ dysfunction (SOFA 2 increase)

NIV should not be administered in the presence of inability to protect the airway, coma, hemodynamic instability.

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## RESEARCH

# LONG-TERM MEDICATION USE AND POLYPHARMACY IN OLDER ADULTS

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.207  
2021; 24(2): 122-133

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Received: Mar 17, 2021  
Accepted: May 21, 2021

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## ABSTRACT

**Introduction:** In Turkey, long-term medication use reports help patients covered by universal health insurance to access drugs without having to make co-payments. Using these reports, the present study investigates the prevalence of polypharmacy and specifically, its relationship with age, gender, diagnosis, number of diseases, and various clinical branches.

**Materials and Methods:** In this descriptive retrospective study, anonymous data obtained from long-term medication use reports were analyzed using SPSS and Microsoft Excel.

**Results:** A total of 66,995 samples were examined, 60.7% of which were female patients. The average number of active substances was  $2.78 \pm 2.11$ , the rate of reports containing five or more active substances (polypharmacy) was 16.1% (10,757 samples), the distribution by gender was 62.7% female and 37.3% male. The distribution of polypharmacy by age groups was 60.1% in the 65-74 age group, 32.5% in the 74-85 age group, and 7.4% in the  $\geq 85$  age group. The most common diagnoses were diabetes mellitus (37.8%), hypertension (12.9%), and hyperlipidemia (8.2%). The clinical branches accounting for the highest rate of polypharmacy were internal medicine (65.1%), cardiology (10%), and chest diseases (6.1%). Acetylsalicylic acid was the most prescribed substance (12.3%) among 657 active substances.

**Conclusion:** The results of this study can be used by regulatory authorities and in clinical practice by physicians. Using a clinical decision system supported by guidelines can help clinicians to optimize drug therapy and reduce polypharmacy in older adults. To reduce inappropriate drug use, such as the Beers, STOPP-START, and TIME criteria were recommended to be used in decision support systems.

**Keywords:** Aged; Chronic Diseases; Multimorbidity; Polypharmacy; Prescriptions



## INTRODUCTION

Life expectancy at birth has increased worldwide over the past 50 years owing to advances in the healthcare field and improved living standards. Consequently, the global population of older adults has also increased. In Turkey, individuals aged  $\geq 65$  years constituted 9.5% of the total population in 2020. Moreover, between 2000 and 2020, whereas the country's total population increased by 25%, the number of those aged  $\geq 65$  years increased by 42% (1). Chronic diseases are becoming increasingly prevalent owing to the aging population and lifestyle changes. Moreover, it is now common for individuals to have two or more co-occurring chronic medical conditions, also known as multimorbidity (2).

The use of multiple medications, or polypharmacy, is common in older adults. Although there is no standard definition, polypharmacy is often referred to as the daily use of  $\geq 5$  medications. This includes over-the-counter, prescription, and/or traditional and complementary medicines (3). The number of prescribed drugs is the most important predictor of inappropriate prescriptions or adverse medication events in older patients (4). Polypharmacy is associated with older age, multimorbidity, recent hospitalization, female sex, depression, and the number of physicians prescribing drugs (5). The issue of polypharmacy in older adults is becoming prevalent in most countries. This is a cause for concern given the observed association between polypharmacy and a broad spectrum of negative health outcomes, including drug-related problems, adverse medication events, physical and cognitive function decline, hospitalization, and increased mortality (6). Polypharmacy is one of the three key action areas of the third World Health Organization Global Patient Safety Challenge (7). It is imperative that patients adhere to the dosage and timing of their prescriptions and that costs are kept to a minimum for them to achieve the best results.

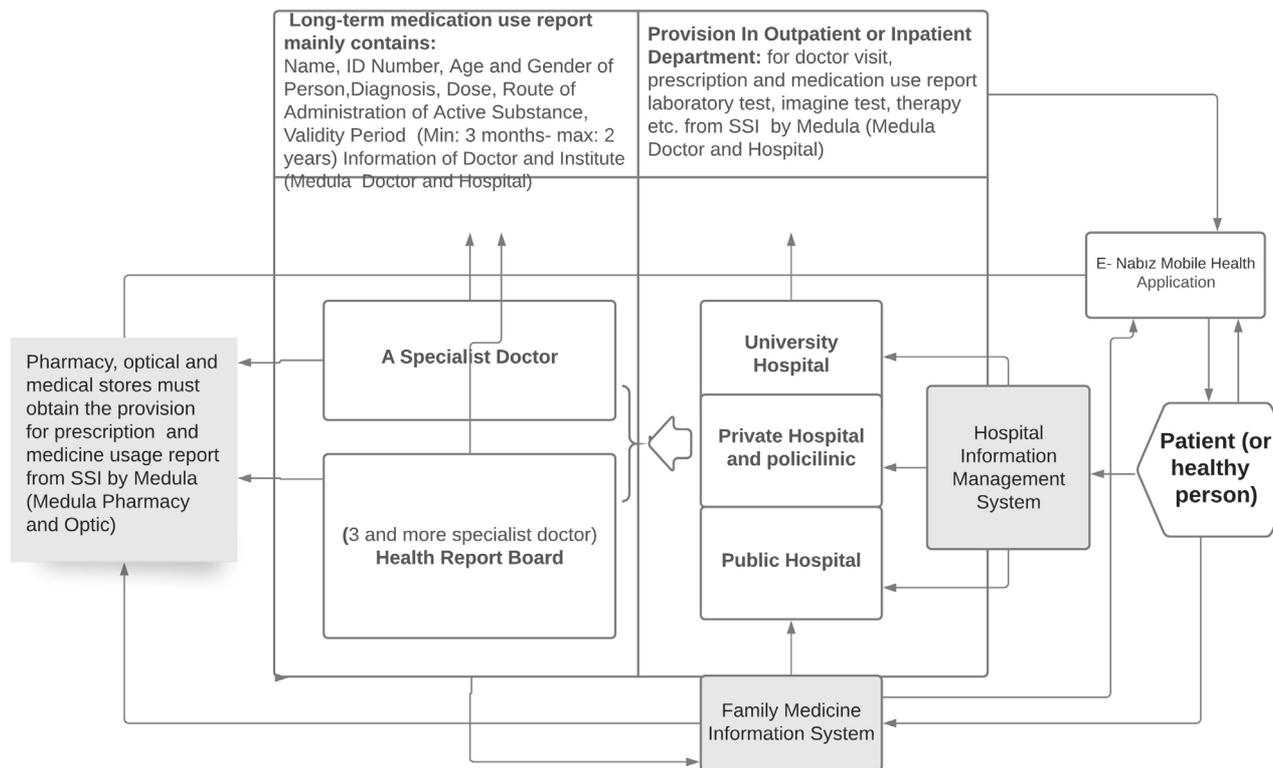
According to the Organisation for Economic Co-operation and Development's (OECD) Health at a Glance 2019 report, which considers data from 14 countries, the polypharmacy rates in older adults vary widely (as much as elevenfold). Turkey reports the lowest rates and Luxembourg the highest. The wide variation can partially be explained through the launch of targeted polypharmacy initiatives in some countries, including related policies on reimbursement and prescriptions (8).

### Long-term Medication Use Report System

Long-term medication use reports prepared electronically by a specialist physician or board are transferred to the pharmacy using information and communication technologies and followed by the pharmacist. These reports are valid up to a maximum of two years and include details regarding the active substances, the amount of each active substance in the medication, and the daily dosages. The electronic prescription and drug report provisioning system operate as part of the web services of the Ministry of Health and the Social Security Institute in Turkey (9,10).

Electronic medical records obtained from health services provided within the scope of universal health insurance are recorded in an electronic database called the Medula system. There are four basic sub-modules in the Medula system: Medula pharmacy, Medula optics, Medula doctor, and Medula hospital (10). E-pulse is a personal health record system through which all health information can be centrally managed and accessed. Physicians can access a patient's previous electronic medical records via the E-pulse mobile application after the patient's permission. The physician from the relevant clinical branch can prescribe the medicines included in the long-term medication use report. Further, family physicians can re-prescribe the medicines for a maximum of 3 months using the Family Medicine Information System (Figure 1).

**Figure 1.** Schematic of Prescription and Long-term Medication Use Report Provisioning System\*



\*(schematized by the authors)

The long-term medication use report system facilitates access to prescription medicines, as a significant proportion of the Turkish population is covered by social security. The Communiqué on the Healthcare Practices determines the payment methods for these drugs, with corresponding payment rules being created in the Medula information system. Additionally, there are no co-payments under the long-term medication use report system.

This study aims to generate insights for regulatory institutions by analyzing the number of drugs and diagnoses and their details in these reports. By ensuring that the reports are prepared based on scientific foundations and guidelines, it will be possible to prevent polypharmacy and inappropriate medicine use.

## MATERIALS AND METHODS

This study retrospectively analyzed 2015–2016 data on the age, sex, diagnoses, and active substances, as available from the long-term medication use reports prepared by specialist physicians or health committees, for patients aged  $\geq 65$  years. The analysis was conducted using the decision support feature of Istanbul’s Region IV Public Hospitals Union’s hospital information management system. Long-term medication use reports with similar content and for the same person were not included in the study results. Data from the reports were anonymized and examined after ethical approval was obtained from the İstanbul Prof. Dr. Cemil Taşcioglu City Hospital Clinical Research Ethics Committee (Approval number: 2020/572).



Statistical analyses and calculations were performed using SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2013 (Microsoft Corp., Redmond, Washington, USA).

While evaluating the study data, frequencies (number, percentage) were used for categorical variables, and descriptive statistics (mean, standard deviation (SD), median (IQR-interquartile range)) for numerical variables. The differences between two independent groups were analyzed using the independent samples t-test.

Differences between more than two independent groups were analyzed using one-way analysis of variance (ANOVA). Tukey multiple comparison tests were used in cases where the one-way ANOVA revealed a difference in group means. The relationships between independent numerical variables were checked with the Pearson correlation coefficient, while the relationships between categorical variables were checked using chi-square analysis. Statistical significance in the analysis was interpreted at the level of 0.05.

## RESULTS

The baseline data collected on each participant consisted of age, gender, all drugs (prescribed) with an ATC (anatomic therapeutic chemical) code fifth level, all diagnoses (using the international classification of diseases, 10th revision (ICD-10) codes), relevant clinical branches, report date, report creator (specialist physician or board), and hospital name.

A total of 66,995 long-term medication use reports were analyzed, 60.7% of which concerned female patients. The average age in the reports was  $74.22 \pm 6.96$  years. The mean age was  $74.37 \pm 7.10$  years in the reports of female patients and  $73.98 \pm 6.71$  years in the reports of male patients. The age data, which are continuous in nature, were grouped as follows: 65–74, 75–84, and 85+. We also found that 60.0% of the reports for patients between the ages of 65–74 or 75–84, and 67.8% of the reports for

individuals aged  $\geq 85$  years, were for women. There was a statistically significant difference ( $\chi^2 = 140.121$ ,  $p < 0.001$ ) between age groups in terms of gender.

The average number of diseases overall was  $2.88 \pm 1.87$ . The average number of diseases for females was  $2.84 \pm 1.92$ , and that for males was  $2.93 \pm 1.76$ . The average number of diseases was  $2.86 \pm 1.86$  for patients aged 65–74 years,  $2.90 \pm 1.86$  for patients aged 75–84, and  $2.90 \pm 1.86$  for patients aged  $\geq 85$  years. The proportion of individuals with multimorbidity (two or more diseases) was 67.3% across all age groups. Distribution of patients with multimorbidity by gender, 55.9% for women and 44.1% for men; The distribution by age groups is 56.1% for 65-74 years, 34.8% for 75-84 years, 9.1% for 85 years and over (Table 1). A statistically significant difference was found between diagnosis groups according to age groups and gender  $\chi^2 =_{\text{age groups}} 27.043$ ,  $p = 0.001$ ,  $\chi^2 =_{\text{gender}} 2721.577$ ,  $p < 0.001$ .

The most common diagnoses were hypertension (18.8%), diabetes mellitus (14.8%), hyperlipidemia (6%), cancer (5%), psychiatric disorders (4.4%), heart diseases (4.4%), and chronic obstructive pulmonary disease (3.3%). The proportion of females was significantly higher in all diagnosis groups, except for cancer (57.3%,  $n=1,915$ ) and chronic ischemic heart disease (52.1%,  $n=558$ ), which were more prevalent among males.

The average number of active substances overall was  $2.78 \pm 2.11$ . The prevalence of polypharmacy overall was 16.1% ( $n = 10,757$ ). The average number of active substances for females was  $2.80 \pm 2.06$ , and that for males was  $2.74 \pm 2.17$ . The distribution of polypharmacy by gender was 62.7% female and 37.3% male. There was a statistically significant difference between men and women regarding the average number of active substances, based on the independent samples t-test ( $t = -3.909$ ,  $p < 0.001$ ) (Table 2).

The average number of active substances was  $2.85 \pm 2.16$  in the 65-74 year age group,  $2.72 \pm 2.06$  in the 75-84 year age group, and  $2.54 \pm 1.95$  in the  $\geq 85$

**Table 1.** Age Groups, Sex, and Number of Diagnoses in Long-term Medication Use Reports

Age groups & Gender	Percent and Number of Diagnosis					Total n%
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	≥5 n (%)	
<b>65-74</b>						
Female	8,861 (39.1)	2,623 (11.6)	4,068 (17.9)	2,363 (10.4)	4,754 (21.0)	22,669 (100.0)
Male	3,657 (24.2)	3,881 (25.7)	2,996 (19.8)	1,503 (9.9)	3,079 (20.4)	15,116 (100.0)
Total	12,518 (33.1)	6,504 (17.2)	7,064 (18.7)	3,866 (10.3)	7,833(20.7)	37,785 (100.0)
<b>75-84</b>						
Female	5,123 (36.9)	1,668 (12.0)	2,479 (17.9)	1,598 (11.5)	3,010 (21.7)	13,878 (100.0)
Male	2,291 (24.9)	2,351 (25.5)	1,782 (19.3)	899 (9.8)	1,894 (20.5)	9,217 (100.0)
Total	7,414 (32.2)	4,019 (17.4)	4,261 (18.4)	2,497 (10.8)	4,904 (21.2)	23,095 (100.0)
<b>≥85</b>						
Female	1,525 (36.8)	494 (11.9)	751 (18.1)	482 (11.7)	893 (21.5)	4,145 (100.0)
Male	469 (23.8)	474 (24.1)	408 (20.7)	233 (11.8)	386 (19.6)	1,970 (100.0)
<b>Total</b>	1,994 (32.6)	968 (15.8)	1,159 (19.0)	715 (11.7)	1,279 (20.9)	6,115 (100.0)
<b>Total Female</b>	15,509 (38.1)	4,785 (11.8)	7,298 (17.9)	4,443 (10.9)	8,657 (21.3)	40,692 (100.0)
<b>Total Male</b>	6,417 (24.4)	6,706 (25.5)	5,186 (19.7)	2,635 (10.0)	5,359 (20.4)	26,303 (100.0)
<b>Total</b>	21,926 (32.7)	11,491 (17.2)	12,484 (18.6)	7,078 (10.6)	14,016 (20.9)	66,995 (100.0)

year age group. As a result of the one-way analysis of variance (ANOVA) applied, the average active substance according to age groups was showed a statistically significant difference ( $F = 71.801$ ,  $p < 0.001$ ). Polypharmacy was found in 60.1% of the cases in the 65–74 age group, 32.5% of the cases in the 75–84 age group, and 7.4% of the cases in the ≥85 age group. The use of ≥ 5 active substances was most prevalent in the 65-74 year age group (Table 2). The active ingredient average was  $2.84 \pm 2.24$  in 1 disease,  $2.74 \pm 2.05$  in 2 diseases,  $2.72 \pm$

$2.04$  in 3 diseases,  $2.72 \pm 1.96$  in 4 diseases, and  $2.79 \pm 2.06$  in ≥5 diseases. As a result of the one-way analysis of variance (ANOVA) applied, the average active substance according to the number of diseases was showed a statistically significant difference ( $F = 65.659$ ,  $p < 0.001$ ). According to the number of diseases, the rate of polypharmacy is 34.1% in 1 disease, 15.9% in 2 diseases, 18.1% in 3 diseases, 10.6% in 4 diseases, and 21.3% in ≥ 5 diseases (Table 2).

**Table 2.** Age Groups, Gender, Number of Diseases, and the Prevalence of Polypharmacy (\* p <0.05)

Baseline characteristics	Number of Drugs			Polypharmacy (≥ 5 drugs)	
	Mean ± SD	Median (IQR)	Statistical Test	N	%
<b>Total</b>	2.78±2.11	2.0 (3.0)		10,757	16.1%
<b>Gender</b>					
Men	2.74±2.17	2.0 (2.0)	t=-3.909 p=0.000*	4,017	15.3%
Women	2.80±2.06	2.0 (3.0)		6,740	16.6%
<b>Age Groups</b>					
65-74	2.85±2.16	2.0 (3.0)	F=71.801 p=0.000*	6,460	17.1%
74-85	2.72±2.06	2.0 (2.0)		3,496	15.1%
≥85	2.54±1.95	2.0 (2.0)		801	13.1%
<b>Number of Diseases</b>					
1	2.84±2.24	2.0 (3.0)	F=65.659 p=0.000*	3,664	16.7%
2	2.74±2.05	2.0 (2.0)		1,713	14.9%
3	2.72±2.04	2.0 (3.0)		1,948	15.6%
4	2.72±1.96	2.0 (3.0)		1,140	16.1%
≥ 5	2.79±2.06	2.0 (3.0)		2,292	16.3%

Specialists from 15 different departments made the diagnoses. A majority of the long-term medication use reports were prepared by the department of internal medicine, at 39.3% (n=26,345); followed by cardiology at 11.1% (n=7,443) and neurology at 10.6% (n=7,078). The average number of active substances in the reports prepared by the departments of medical oncology, internal medicine, and radiation oncology was 4.91±4.98, 3.40±2.40, and 3.24±3.33 respectively. The reports prepared by these departments had higher average numbers of active substances than those prepared by the other

clinical branches. In Table 3, the results of the one-way ANOVA revealed that there was a statistically significant difference in the average number of active substances in reports prepared by each clinical branch (F = 593.269, p <0.001). The three most common branches in those with polypharmacy are Internal Medicine (65.1%), Cardiology (10.0%), and Chest Diseases (6.1%).

When Table 4 is examined, the average number of active substances in patients with diabetes mellitus, cancer, and hyperlipidemia was 4.25±2.35, 3.64±3.98, and 3.11±1.90, respectively. A one-way

**Table 3.** Clinical Branches and Prevalence of Polypharmacy (\* p <0.05)

Clinical Branches	Number of Drugs			Polypharmacy (≥ 5 drugs)	
	Mean ± SD	Median (IQR)	Statistical Test	N	%
1. Internal Medicine	3.40±2.40	3.0 (3.0)	F=593.269 p=0.000*	6,999	65.1%
2. Cardiology	2.66±1.64	2.0 (3.0)		1,071	10.0%
3. Chest Diseases	3.07±1.54	3.0 (2.0)		660	6.1%
4. Neurology	2.14±1.42	2.0 (2.0)		463	4.3%
5. Medical Oncology	4.91±4.98	2.0 (6.0)		381	3.5%
6. Physical Treatment&Rehabilitation	2.54±1.31	2.0 (1.0)		299	2.8%
7. Radiation Oncology	3.24±3.33	2.0 (3.0)		187	1.7%
8. Orthopedics & Traumatology	2.23±1.29	2.0 (1.0)		130	1.2%
9. Family Medicine	2.32±1.71	2.0 (2.0)		94	0.9%
10. Cardiovascular Surgery	2.07±1.48	1.0 (2.0)		91	0.8%
11. General Surgery	1.98±1.57	1.0 (1.0)		65	0.6%
12. Psychiatry	1.90±0.91	2.0 (1.0)		33	0.3%
13. Ophthalmology	1.85±0.74	2.0 (1.0)		19	0.2%
14. Urology	1.54±0.68	1.0 (1.0)		14	0.1%
15. Other	2.54±2.04	2.0 (2.0)		251	2.3%

ANOVA revealed a statistically significant difference in the average number of active substances according to the diagnoses (F = 579.872, p <0.001), (Table 4). The most prevalent diagnoses in individuals with ≥ 5 active substances were diabetes mellitus (37.8%), hypertension (12.9%), and hyperlipidemia (8.2%).

There were 183,667 active substances mentioned in the reports. The reports also included non-pharmaceutical materials used in chronic disease man-

agement, such as needle tips and blood-sugar measuring sticks. Only prescription drugs specified in the Social Security Institution payment list were included in this study, yielding a total of 657 active substances. The most prescribed active substance was acetylsalicylic acid (prescribed 8,245 times), followed by biguanides (6,589), beta-blocking agents (6,267), HMG CoA reductase inhibitors (statins; 6,115), calcium channel blockers (3,868), and angiotensin-converting enzyme (ACE) inhibitors (3,294).

**Table 4.** Diagnoses and Prevalence of Polypharmacy (\* p <0.05)

Diagnoses	Number of Drugs			Polypharmacy (≥ 5 drugs)	
	Mean ± SD	Median (IQR)	Statistical Test	N	%
1. Diabetes Mellitus	4.25±2.35	4.0 (4.0)	F=579,872 p=0.000*	4,064	37.8%
2. Hypertension	2.48±1.71	2.0 (2.0)		1,388	12.9%
3. Hyperlipidemia	3.11±1.90	3.0 (3.0)		884	8.2%
4. Cancer	3.64±3.98	2.0 (3.0)		706	6.6%
5. Atrial fibrillation and flutter	2.47±1.85	2.0 (2.0)		284	2.6%
6. Chronic obstructive lung disease	2.37±1.93	2.0 (2.0)		280	2.6%
7. Depressive episode	2.40±1.46	2.0 (2.0)		178	1.7%
8. Chronic ischemic heart disease	2.18±1.75	1.0 (2.0)		114	1.1%
9. Glaucoma	2.25±1.63	2.0 (2.0)		108	1.0%
10. Retinal deterioration	2.39±1.68	2.0 (2.0)		92	0.9%
11. Anxiety disorders	2.52±1.38	2.0 (1.0)		48	0.4%
12. Asthma	1.97±1.42	2.0 (1.0)		41	0.4%
12. Dementia in Alzheimer's Disease	1.95±1.04	2.0 (1.0)		17	0.2%
14. Nonorganic psychosis	1.86±1.09	2.0 (2.0)		10	0.1%
15. Other	2.40±1.72	2.0 (2.0)		2,543	23.6%

## DISCUSSION

A previous study of 17 European countries and Israel used data for participants aged ≥65 years from Wave 6 of the Survey of Health, Aging, and Retirement in Europe database. In that study, the prevalence of polypharmacy in each country ranged from 26.3% to 39.9%. Polypharmacy prevalence was lower in Switzerland (26.3%), Croatia (27.3%), and Slovenia (28.1%), and higher in Portugal (36.9%), Israel (37.5%), and the Czech Republic (39.9%) (11).

OTC drugs, vitamins, and minerals were included in this study, conducted with 10,989 people aged ≥65 years. It is noteworthy that the polypharmacy rate in Turkey is remarkably lower than in OECD countries (8). In terms of multiple medication use, 16.1% of the patients in this study used ≥ 5 medications, it is seen that the prevalence of polypharmacy is quite low compared to European countries. The exclusion of OTC and similar food supplements plays an important role in our study.

A previous study in Germany included patients aged over 60 years who had made at least one visit to any of the 1,010 general practitioners between January to June 2017—yielding a sample of 564,352 patients for analysis. Of these patients, 85% of males and 86% of females showed multimorbidity. Simultaneously, 38% of males and 37% of females met the criteria for polypharmacy. The mean number of chronic diseases was 5.3 (SD=4.4) in males and 5.7 (SD=4.6) in females. The mean number of prescribed medications was 4.2 (SD=2.7) in both males and females (12). By contrast, our study found that the average number of chronic diseases in Turkish patients aged  $\geq 65$  years was overall  $2.88 \pm 1.86$  and multimorbidity was found overall 67.3%. The average number of active substances used by females was  $2.80 \pm 2.06$ , whereas the number was  $2.74 \pm 2.17$  for males. The prevalence of polypharmacy in the primary care study in Germany was much higher than in our study.

Data obtained from the Irish Longitudinal Study on Aging showed that 27% of the  $\geq 54$  year age group used  $\geq 5$  medications (13). Similarly, in Sweden, out of 1,742,336 individuals aged  $\geq 65$  years who were included at baseline in a prospective cohort study, 44% were exposed to polypharmacy ( $\geq 5$  medications) and used 4.6 different drugs on average (14). Thus, the prevalence of polypharmacy is high among older adults in Ireland and Sweden. Contrastingly, 16.1% of the patients used  $\geq 5$  medications and the average number of active substances was  $2.78 \pm 2.11$  in Turkey.

In another survey in Spain of 164,513 patients with multimorbidity and aged  $>65$  years, the 65–79 year age group was prescribed a median of four medications. The 80–94 years age group was prescribed a median of six medications. At least 45.9% of the 65–79 year age group and 61.8% of the 80–94 year age group were prescribed  $\geq 5$  medications (15). In our study, the average number of active substances was  $2.85 \pm 2.16$  in the 65–74 years age group,  $2.72 \pm 2.06$  in the 75–84 years age group, and

$2.54 \pm 1.95$  in the  $\geq 85$  years age group.

In a study of 1,003 patients in France, polypharmacy (5 to 9 medications) and excessive polypharmacy ( $\geq 10$  medications) were reported in 42.9% and 27.4% of the study cohort, respectively (16). The prevalence of polypharmacy overall was 16.1% ( $n = 10,757$ ) in our study. Thus, the prevalence of polypharmacy in France is almost three times higher than in this study.

A study conducted by Qato et al. used cross-sectional data from a nationally representative of 2,206 United States citizens. The mean age was 71.4 years, and 51.6% of the sample consisted of females. That study found that nearly 87.7% of the subjects used at least one prescription medicine, while 35.8% simultaneously used five or more prescription medications. The use of multiple medications increased from 2005 to 2011, particularly the use of statins (33.8% to 46.2%), acetylsalicylic acid (30.2% to 40.2%), and proton pump inhibitors (15.7% to 18.5%). The use of antihypertensives increased slightly (60.9% to 65.1%), primarily driven by increases in the use of angiotensin-converting enzyme inhibitors (24.5% to 30.4%), which are commonly used as diuretics (29.5%) and  $\beta$ -blockers (31.2%) (17). In the present study, only 16.1% of the patients aged  $\geq 65$  years received prescriptions containing  $\geq 5$  drugs. The most commonly prescribed drugs in our study were similar to those in the USA. Acetylsalicylic acid (12.3%) was the most prescribed active substance, followed by biguanides (9.8%), beta-blocking agents (9.3%), statins (9.1%), calcium channel blockers (5.7%), and ACE inhibitors (4.9%).

One Canadian study found that, in 2016, approximately one-third (35.3%) of Canadian older adults were chronically using  $\geq 5$  medications from different medication classes, and 1 out of 18 (5.5%) were chronically using medications from 10 or more different medication classes. Statins were the most common medication class used by nearly half of all older adults (46.6%). The next most commonly used medication classes were ACE inhibitors—used to



treat high blood pressure and heart failure—used to treat gastroesophageal reflux and peptic ulcer disease—used by 28.2% and 26.9% of older adults, respectively (18). In terms of multiple medication use, 16.1% of patients were using  $\geq 5$  medications in our study. Based on these findings, it can be concluded that, compared to our study, polypharmacy in Canada and the USA are twice as high and the most common medications are generally similar to those covered in Canada and USA studies.

A previous study examined the electronic prescriptions prepared in 2018 by family physicians across Turkey for geriatric patients (aged  $\geq 65$  years), based on the prescription information system. In this geriatric cohort, 6,104,798 individuals (85.0%) had at least one prescription. Moreover, 14.3% of the patients were chronically prescribed  $\geq 5$  medications. Additionally, the percentage of those with polypharmacy ranged between 16.4% and 20.7%. Each prescription contained an average of 2.9 individual drug items, and each medication was prescribed in 2.7 boxes on average (19). The prevalence of polypharmacy in this study, which was conducted with the data obtained from the family medicine information system, was found to be very close to the findings of our study. There was a difference between the drugs prescribed to patients examined in primary care and the long-term drug use reports in our study.

Polypharmacy in older adults requires more attention because of age-related changes in pharmacokinetics and pharmacodynamics, exclusion of these patients from clinical studies, inadequate representation in guidelines, excessive morbidity, the effect of dementia on the course and management of diseases, and poor communication. In the case of such patients, other chronic conditions and their medication use must be thoroughly assessed when taking their medical history (anamnesis), because a detailed evaluation can reduce the number of medications used. When medication is prescribed,

interaction with other existing medications and aging-related factors must be considered.

There are several ways to prevent polypharmacy. Two major approaches to minimize the adverse outcomes of multiple medication use are i) using computerized doctor prescriptions that feature clinical decision support systems based primarily on guidelines on the prescribing process and interventions, and ii) establishing examination processes after computer-assisted or non-computer-assisted prescriptions (20). Bates et al. defined computerized decision support systems as computer-based systems providing “passive and active referential information as well as reminders, alerts, and guidelines” (21). Automated decision support system tools consistently reduce the number of potentially inappropriate prescriptions started and the mean number of potentially inappropriate prescriptions per patient. These tools also increase potentially inappropriate prescription discontinuation and medication appropriateness (22).

The Screening Tool of Older Persons’ Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START) are explicit criteria that facilitate medication review in multimorbid older adults in most clinical settings. Electronic deployment of the STOPP/START criteria is a significant technical challenge; however, recent clinical trials of software prototypes have demonstrated their feasibility (23). The SENATOR and OPERAM trials are ongoing multicenter randomized controlled trials currently being conducted across Europe. These trials employ computerized versions of STOPP and START in their interventions (24).

Prescribing habits and locally available medications vary considerably between countries, and the evidence on appropriate prescriptions for older persons continues to evolve. Within this context, the Turkish Inappropriate Medication Use in the Elderly (TIME) criteria set (TIME-to-STOP/ TIME-to-START)—produced under the leadership of the Rational Drug Use Working Group of the Turkish Aca-

demic Geriatrics Society—provides a guide tailored to the specific needs of the Turkish people as well as an explicit screening tool (25).

Computerized interventions have been suggested as an effective strategy to improve prescription appropriateness for hospitalized older adults. In the hospital setting, the electronic prescribing and computerized physician order entry (CPOE) systems have reduced prescribing errors and help prevent adverse drug events (24). A long-term medication use report system designed similarly, with international medicine usage instructions such as the Beers, STOPP-START, and TIME criteria, would encourage rational medicine use. Future research should continue to focus on evaluating the use of Medula and clinical decision-making system to reduce inappropriate prescribing and polypharmacy in older people.

The study's main limitation was that only long-term medication use reports by specialist physicians or boards were analyzed. Thus, prescriptions without reports written by specialist physicians and

family physicians, as well as OTC medications and dietary supplements obtained from pharmacies without a prescription, were not included in this study.

Re-prescribed data with similar content for the same person in long-term drug use reports were not included in the study results. On the other hand, data from the same person with different diagnoses from different clinical branches were included.

### Acknowledgments

We thank Emre Yasar and Ömer Kaplan for statistical support and Cumali Celik, Meral Kok Can and Hatem Karapinar for their technical contributions to the data.

### Conflict of Interest

The authors declare no potential conflicts of interest concerning the research, authorship, or publication of this article.

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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.208  
2021; 24(2): 134-142

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Received: Jan 04, 2021  
Accepted: Apr 06, 2021

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## RESEARCH

# PREDICTIVE EFFECTS OF FIRST ERYTHROCYTE AND THROMBOCYTE VOLUME INDICES ON MORTALITY OF GERIATRIC PATIENTS WITH SEPSIS HOSPITALIZED IN INTENSIVE CARE UNITS

## ABSTRACT

**Introduction:** Sepsis is a common reason for hospitalization in the intensive care unit and a cause of increased mortality, especially among elderly patients. We aimed to evaluate the relationship between erythrocyte and platelet indices and mortality of elderly patients admitted to the intensive care unit due to sepsis.

**Materials and Methods:** This study was retrospectively performed in patients with  $\geq 65$  years of sepsis who were admitted to the intensive care unit. Hemoglobin, mean corpuscular volume, red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), white blood cell and platelet count results, and demographic and clinical features were compared between survivors and non-survivors.

**Results:** RDW, MPV, PDW, and C-reactive protein were found to be significantly higher in the non-survivors group than survivor group ( $p < 0.001$ ). We also determined that platelet and hemoglobin levels were significantly lower in the non-survivors group than survivor group ( $p < 0.001$ ). In the estimation of mortality, the cut-off value was  $\geq 16.3\%$  for RDW,  $\geq 10$  fL for MPV,  $\geq 11.6\%$  for PDW,  $\leq 281 \times 10^3/\mu\text{L}$  for platelets,  $\leq 9.8$  g/dL for hemoglobin, and  $\geq 86$  mg/L ( $p = 0.0001$ ) for C-reactive protein.

**Conclusion:** Increasing counts for red cell distribution width, mean platelet volume, and platelet distribution width and decreasing counts for platelets and hemoglobin for elderly patients admitted to the intensive care unit with sepsis may alert intensive care specialists to estimate mortality.

**Keywords:** Aged; Blood Platelets; Intensive care units; Erythrocyte Indices; Mean platelet volume; Sepsis.



## INTRODUCTION

The fastest growing age group in the world is  $\geq 80$ -year-old group, which increases by about 3.8% per year (1). According to data from the Turkish Statistical Institute, the geriatric population increased from 7.5% in 2012 to 8.8% in 2018 (2). In many countries, the average age and life expectancy of the population has also increased. Old age is associated with chronic disease and functional impairment, and more elderly patients are being admitted to the intensive care unit (ICU) (1, 2). In addition, about half of ICU days are utilized by patients over 65 years old (3,4).

Sepsis is a systemic inflammatory host response to infection that can lead to acute organ dysfunction and consists of clinical, hemodynamic, and biochemical components (4). Unfortunately, sepsis is a fatal condition with a 20–40% mortality rate and contributes to approximately 20% of in-hospital deaths (5). Elderly patients are more prone to infections due to the effects of aging, various associated comorbidities, the use of invasive devices, and interventions, so the occurrence of sepsis increases with age (1). In addition, the probability of death due to sepsis is higher in elderly patients (4). There is limited epidemiological information about the effect, incidence, and outcomes of sepsis in elderly patients (1). As our population ages, it is expected that the incidences of elderly patients with sepsis will increase and understanding sepsis mortality in this population and how sepsis affects their functional status becomes increasingly important (4). Therefore, it is very important to determine the mortality markers to improve the treatment of elderly patients with high mortality sepsis (6).

Sepsis is an important disease affecting almost all systems and the hematological system specifically is affected negatively (7). Sepsis causes various changes to red blood cell and platelet counts. These changes include indices, such as mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV), and platelet

distribution width (PDW) in the complete blood count (7, 8). The number of studies investigating the clinical results of the changes in these parameters, especially in elderly patients with sepsis, is very limited. Therefore, the primary purpose of our study is to determine the relationship of erythrocyte and platelet volume indices with the mortality of elderly patients hospitalized in the ICU due to sepsis.

## MATERIALS AND METHODS

### Ethical approval and study protocol

Our ICU is a level 3 facility for all patients over 18 years of age. Our study was planned retrospectively in patients  $\geq 65$  years old who had undergone sepsis in our ICU and includes patients hospitalized between March 2017 and March 2019. Patients who were primarily out of sepsis (trauma, intoxication, metabolic disorders, myocardial infarction, etc.) and  $< 65$  years of age were excluded from the study. The local clinical ethics committee approved the research before the study commenced. Our study was carried out in accordance with the principles of the Helsinki Declaration.

### Data sources

Sepsis diagnosis for inclusion in the study was made according to *Third International Consensus Definitions* criteria, which depends on the clinical and laboratory findings of the patients (9). All registered patients were treated according to the *International Guidelines for Management of Sepsis and Septic Shock* after being admitted to the ICU (10). Age, gender, comorbid disease number (diabetes mellitus, hypertension, malignancy / immune deficiency, respiratory system disease, heart disease, renal disease, central nervous system disease), acute physiology and chronic health evaluation (APACHE) II score, sepsis-related organ failure assessment (SOFA) score, duration of mechanical ventilation (MV), hospital stay, C-reactive protein (CRP), complete blood count (CBC) analysis, blood cultures, and mortality data were recorded (11, 12).

### Blood sampling for serum levels for CRP and CBC analysis

Venous blood samples were taken in tubes containing ethylenediamine tetra-acetic acid from patients with sepsis during ICU hospitalization. Hemoglobin, MCV, RDW, MPV, PDW, and white blood cell (WBC) and platelet counts were measured twice-daily with a calibrated Cell-Dyn 3700 automated hemocytometer (Abbott, Abbott Park, IL, USA). Serum CRP concentrations were measured on a Roche Modular P analyzer with a Tinaquant CRP (Latex) highly sensitive immuno-turbidimetric assay (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany). Positive blood cultures were identified with the BACTEC FX automatic blood culture detection system (Becton Dickinson, Sparks, MD, USA) in the medical microbiology laboratory. The antimicrobial susceptibility of isolated strains was determined by the Phoenix Automated Microbiology System (BD Diagnostic Systems, Sparks, MD) in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (13).

### Data analysis

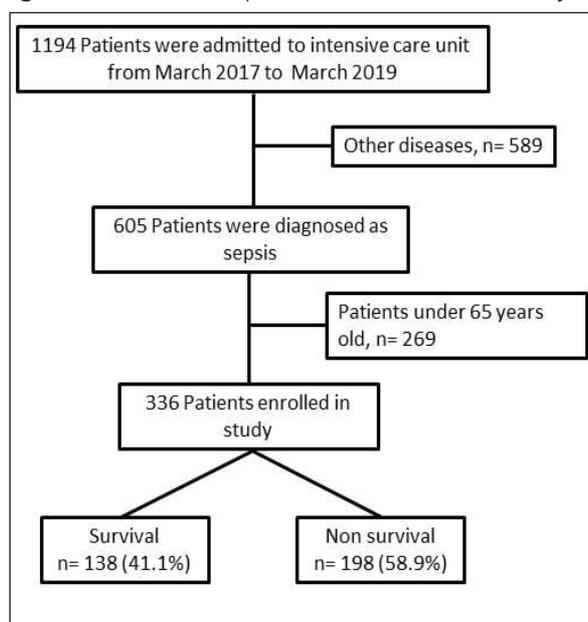
SPSS software 17.0 (SPSS, Chicago, IL) was used for statistical analysis. T-test and/or Mann-Whitney's U-test were used to compare non-parametric continuous variables in independent samples between groups, and chi-square test or Fisher's exact test for categorical variables. Results are given as mean and standard deviation and/or median (minimum-maximum) for continuous variables. Categorical variables were expressed as frequency and percentage distribution. Diagnostic screening tests to determine the cut-off for hemoglobin, platelet, CRP, RDW, MPV, PDW, and receiver operating characteristic (ROC) curve analysis were performed (sensitivity, specificity, positive predictive value, and negative predictive value) and p value <0.05 was considered significant.

### RESULTS

During the study period, 1,194 patients were admitted to our ICU and 336 patients were included in the study according to the inclusion criteria. Of the patients included in the study, 198 (58.9%) patients died and 138 (41.1%) were discharged after treatment (Figure 1). While the age, number of comorbid diseases, duration of MV, hospital stay, APACHE II score, and SOFA score of non-survivor patients were higher than those of survivors ( $p < 0.05$ ), the results were similar in terms of gender and blood cultures ( $p > 0.05$ ) (Table 1).

Among non-survivors and survivors, the results were similar in terms of WBC and MCV ( $p = 0.174$ ,  $p = 0.648$ , respectively). RDW, MPV, PDW, and CRP were higher in the non-survivors group ( $p < 0.001$ ), and platelet and hemoglobin levels were significantly lower ( $p < 0.001$ ) compared to the survivors (Table 2). ROC analysis was implemented for RDW, MPV, PDW, platelet, hemoglobin, and CRP for the prediction of mortality in elderly patients with sepsis. The

**Figure 1.** Flowchart of patient enrolment in the study





**Table 1.** Comparison of demographic and clinical features between survivors and non-survivors

Variables	Survivors (n=138)	Non-survivors (n=198)	P value
Age, (years), <sup>a</sup>	75.1±11.0	82.1±7.9	<0.001*
Male gender, n (%)	65 (47.1)	84 (42.4)	0.230
Comorbid disease, <sup>b</sup>	2 (0-5)	3 (0-6)	<0.001*
APACHE II score, <sup>b</sup>	19 (11-34)	24 (15-47)	0.001*
SOFA score, <sup>b</sup>	7 (3-16)	10 (6-21)	<0.001*
Duration of MV, (days), <sup>b</sup>	4 (1-41)	7 (1-45)	0.001*
Hospital stay, (days), <sup>b</sup>	11 (5-69)	28 (1-144)	<0.001*
Bacteremia, n (%)	31 (22.4)	58 (29.2)	0.291

<sup>a</sup> mean ± standard deviation, <sup>b</sup> median (range), APACHE II: acute physiology and chronic health evaluation score, SOFA: sepsis-related organ failure assessment score, MV: mechanical ventilation

\* Statistically significant p values are highlighted.

**Table 2.** Comparison of laboratory variables between survivors and non-survivors

Variables	Survivors (n=138)	Non-survivors (n=198)	P value
White blood cell count ( $\times 10^3/\mu\text{L}$ ), <sup>a</sup>	12.3±7.1	13.1±11.4	0.174
Hemoglobin (g/dL), <sup>a</sup>	11.2±1.9	9.0±1.1	<0.001*
Platelet ( $\times 10^3/\mu\text{L}$ ), <sup>a</sup>	298.6±129.6	176.0±83.7	<0.001*
C-reactive protein (mg/L), <sup>a</sup>	78.4±67	174.9±105.1	<0.001*
Mean corpuscular volume (fL), <sup>a</sup>	86.2±7.8	85.9±6.2	0.648
Red blood cell distribution width (%), <sup>a</sup>	15.7±2.3	18.2±2.6	<0.001*
Mean platelet volume (fL), <sup>a</sup>	9.4±1.1	11.1±1.1	<0.001*
Platelet distribution width (%), <sup>a</sup>	10.9±2.1	15.0±2.9	<0.001*

<sup>a</sup> mean ± standard deviation

\*Statistically significant p values are highlighted.

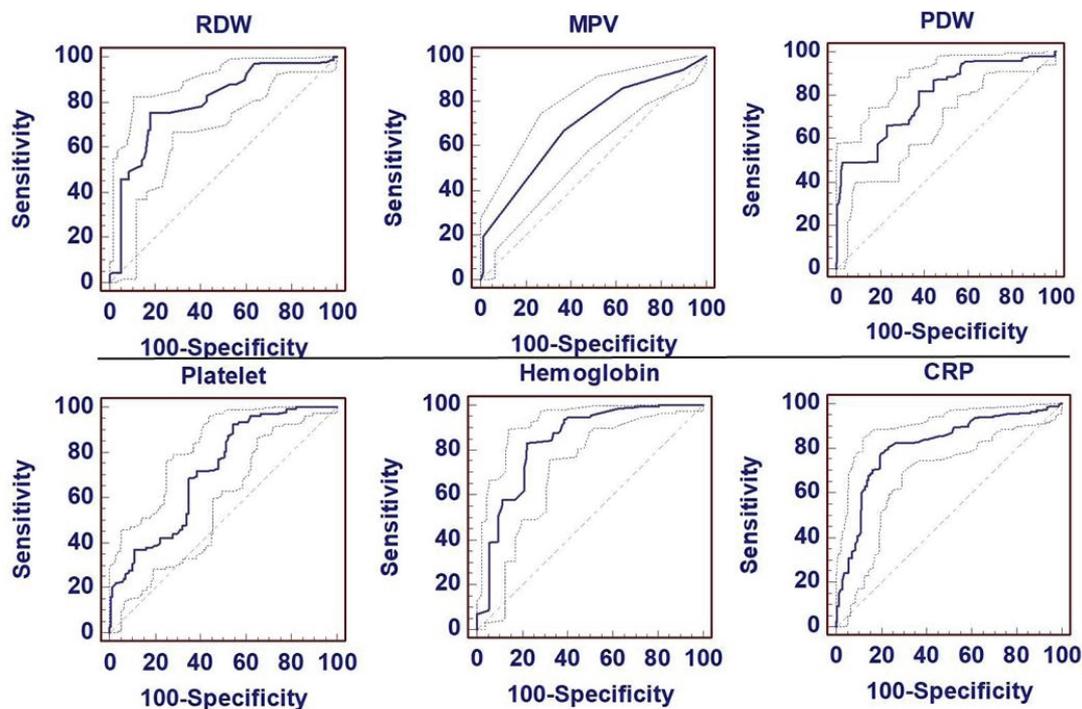
cut-off value for mortality in elderly patients with sepsis was  $\geq 16.3\%$  for RDW,  $\geq 10$  fL for MPV,  $\geq 11.6\%$  for PDW,  $\leq 281 \times 10^3/\mu\text{L}$  for platelet,  $\leq 9.8$  g/dL for hemoglobin, and 86 mg/L for CRP ( $p = 0.0001$ ). The results are presented in Figure 2 as area under curve (AUC), p value, sensitivity, specificity, positive predictive value, and negative predictive value.

## DISCUSSION

Our study is the first to evaluate the relationship between mortality and erythrocyte and platelet indices in elderly patients with sepsis in the ICU. According

to our results, the high levels of MPW, PDW, RDW, and CRP and low platelet and hemoglobin counts were found to be significant indicators of mortality. High specificity, sensitivity, and positive predictive values increase the reliability of these tests' predictability. In the ROC analysis performed on the significance of these six hematological parameters for predicting mortality in elderly patients with sepsis when certain threshold values were exceeded, the AUC values were found to be between 0.7–0.9 and had a moderate degree of accuracy (14). In addition to all laboratory findings, the increase in the num-

**Figure 2.** ROC curve for RDW, MPV, PDW, platelet, hemoglobin, and CRP, predicting mortality in the ICU



Variables	AUC	95% Confidence interval	p values	Cutoff level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Red blood cell distribution width (RDW) (%)	0.798	0.751-839	0.0001	$\geq 16.3$	75	82	86	70
Mean platelet volume (MPV) (fL)	0.701	0.650-0.751	0.0001	$\leq 10$	67	63	72	57
Platelet distribution width (PDW) (%)	0.793	0.746-0.835	0.0001	$\leq 11.6$	69	97	97	57
Platelet ( $\times 10^3/\mu\text{L}$ )	0.716	0.664-0.763	0.0001	$\leq 281$	92	45	71	81
Hemoglobin (g/dL)	0.838	0.794-0.875	0.0001	$\leq 9.8$	83	76	84	76
C-reactive protein (CRP) (mg/L)	0.811	0.765-0.852	0.0001	$\geq 86$	78	80	85	72

AUC: area under the curve, PPV: positive predictive values, NPV: negative predictive values, ROC: receiver operating characteristic



ber of comorbid diseases increased APACHE-II and SOFA scores and also increased old age mortality (15–17).

Sepsis causes alterations in metabolism, a decrease in the level of 2,3-bisphosphoglycerate, erythrocyte deformability, and redistribution of membrane phospholipids on red blood cells (RBC) due to an irregular host response to infection. This dysregulation caused by sepsis is evident in erythrocytes, platelets, mitochondria, and microcirculation (7, 8). The change in RBC deformability is an early indicator of sepsis and reflects an existing inflammatory process size (8, 16). In septic patients characterized by a decrease in hemoglobin, MCV does not change during the first 24 hours of sepsis. Probably for this reason, in our study, MCV values were measured at the time of hospitalization, so the results were similar in the groups with and without mortality. In addition to the hemoglobin drop in sepsis, the oxygen dissociation curve shifts to the left, P50 (hemoglobin is 50% oxygen saturated) decreases, and the oxygen affinity of hemoglobin increases. Through these mechanisms, there is an increase in tissue hypoxia, organ failure, and mortality. However, this relationship grows more complicated in sepsis and is not fully understood (8).

The RDW parameter calculates (coefficient variation of RBC volume) and quantifies the RBC volume (anisocytosis) heterogeneity as the ratio of the standard deviation of the RBC volume to MCV. High RDW reflects the regulation disorder of erythrocyte homeostasis, which includes both impaired erythropoiesis and abnormal RBC survival (18). In cases of oxidative stress, such as sepsis, erythropoiesis is disrupted, anisocytosis increases, RBC membrane deformability changes circulation half-life and eventually increases RDW (19). Different results about the effects of RDW and CRP on mortality in patients with sepsis and the effect of MCV on mortality in patients with sepsis, have been shown in our study (15–17, 19). There are still some uncertainties about the importance of the RDW parameter in septic

patients (20), however, and our study is important in terms of explaining the prognostic factor and mechanism behind RDW in elderly patients with severe sepsis. All these contradictory results show that more research is necessary to determine the relationship between cause and effect, sepsis pathophysiology, and patient outcomes with changes in RBC volume heterogeneity from sepsis (8).

MPV is another prognostic marker for septic shock and its level is higher in patients who die (6). Patrick et al. reports that high PDW levels, in addition to high MPV, had 95% and 79% specificity, respectively, in detecting bacteremia (21). In another study, higher MPV and PDW levels and lower platelet counts were found in sepsis patients compared to the control group. It has been reported that this situation is caused by greater cytokine production, endothelial damage, and bone marrow suppression in septic patients (7). In endotoxemia, the animal experiment was supported by decreasing platelets and increasing MPV and PDW (22). Our results were similar to previous studies with high MPV and PDW and low platelets used as sensitive markers to predict mortality in sepsis patients. As in our results, sometimes a decrease in the platelet count without thrombocytopenia may be associated with increased mortality (23). These results can be explained by the fact that coagulation and platelet activation/hyper-aggregation may occur in the early stage of sepsis, and the platelets transform their discoid shapes into global shapes during activation to obtain a larger surface (7). In addition to the physiologically increased platelet production process, rapid platelet production occurs after cytoplasmic rupture and megakaryocyte rupture in response to a sharp decrease in the platelet count. Thanks to this alternative mechanism, a high rate of MPV is rapidly released into the platelet blood flow. As a result, these large platelets become more active than small platelets (6). This explains the increase in MPV and RDW in sepsis patients and, thus, the increase in mortality.

In our study, it was found that RDW  $\geq 16.3\%$ , MPV  $\geq 10$  fL, PDW  $\geq 11.6\%$ , and platelet counts  $\leq 281 \times 10^3/\mu\text{L}$  increased mortality in septic geriatric patients. Guclu et al. found that having PDW  $> 17.9\%$ , MPV  $> 8$  fL, and platelet counts  $\leq 155 \times 10^3/\mu\text{L}$  predicted sepsis compared to the control group (7). Jiang et al. found that a PDW  $> 13.7\%$  can be evaluated as a parameter for the indicator of 28-day mortality of sepsis patients in the ICU (17). In some studies, evaluating patients admitted to the ICU, different threshold values in the range of 8.9–11.6 (fL) were found in the use of MPV as an independent predictive indicator of mortality. These differences may be a result of the patients' ages and the heterogeneity of the diagnoses in the compared groups (6, 24). Our cut-off results were valid for geriatric septic patients in a single center. In our study, AUC was between 0.7–0.9 for MPV, PDW, RDW, platelet, hemoglobin, and CRP as an indicator of mortality in patients with sepsis in the ICU, and AUC was found to be valuable in the moderate accuracy level in mortality estimation (14). In some studies, using the above parameters as an indicator of mortality, AUC accuracy values were found to be similar to our results with moderate accuracy (0.7–0.9) (6, 7, 19, 24, 25).

### Study limitations

This study has potential limitations due to retrospective cohort analyzes, a single-center study, and unmeasured confounding variables. We did not have any data on pre-hospital laboratory values, previous hematological abnormalities, previous transfusion, blood cell morphology, hemolysis, reticulocytosis, bleeding, iron levels, and vitamin levels. This may have prevented us from identifying the cause and effect relationship in our patients and how these hematological abnormalities can lead to higher mortality. We focused on acceptance laboratory values to estimate mortality and were unable to determine

whether changes in these parameters affect the risk of mortality during hospitalization.

### CONCLUSION

To our knowledge, our study is the first to evaluate the relationship between erythrocyte and platelet indices mortality in geriatric septic patients in the ICU. Our results show that changes in erythrocyte and platelet indices can be used as significant parameters in predicting mortality in septic geriatric patients. All these indices are parameters that can be measured by routine blood count, which can be obtained cheaply and easily. Future studies are needed to determine whether changes in these parameters specifically reflect the underlying pathophysiology or only greater disease severity, to better identify the underlying pathophysiology in geriatric patients with sepsis, and to understand the relationship between abnormal hematopoiesis and outcomes.

### Conflict of Interest, Disclosure Statement

The authors declare that they have no conflicts of interest. The authors have indicated they have no financial relationships relevant to this article to disclose

**Ethical Approval:** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Acknowledgement:** none



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## RESEARCH

# OSTEOPOROSIS AND HIP-FRACTURE RISK ASSESSMENT USING DIFFERENT TOOLS IN THE FIRST YEAR AFTER STROKE

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.209  
2021; 24(2): 143-149

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Accepted: May 02, 2021

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## ABSTRACT

**Purpose:** The aim of this study was to ascertain the frequency of osteoporosis and 10-year hip-fracture risk in patients with post-stroke hemiplegia using two different assessment algorithms.

**Method:** Seventy-seven patients with post-stroke hemiplegia  $\leq 1$  year who were admitted to the stroke unit of a tertiary rehabilitation hospital were included in this cross-sectional study. All patients underwent bone density assessment. Fracture risk assessment tool (FRAX) and QFracture were both used to calculate the 10-year risk probability for hip fracture. Receiver operating characteristic curves were investigated for FRAX and QFracture.

**Results:** Fifteen patients (19.5%) had osteoporosis, and 39 (50.6%) had osteopenia based on dual-energy X-ray absorptiometry measurements. FRAX hip scores were  $\geq 3$  in 7 patients (9.1%). Ten-year hip-fracture risk was high in 26 patients (33.8%) using QFracture. Six patients (7.8%) had low-energy fractures after stroke. Fracture sites were hip in 2 patients, 1 humerus, 1 forearm, and 2 in lower extremities. The receiver operating characteristic area under curve was 0.804 (% 95 CI 0.665-0.943,  $p = 0.002$ ) for FRAX and 0.758 (% 95 CI 0.615-0.901,  $p = 0.009$ ) for QFracture. Cut-off values for the estimation of hip osteoporosis for FRAX and QFracture tools were 1.15 and 1.55, respectively.

**Conclusion:** Findings indicated that 70.1% of patients in this study had osteoporosis or osteopenia within the first year following a stroke. Ten-year hip-fracture risk was 9.1% by FRAX and 33.8% by QFracture. Results of FRAX and QFracture assessment tools demonstrated a significant relationship between ten-year hip-fracture risk and bone mineral density.

**Keywords:** Stroke; Hemiplegia; Osteoporosis; Bone Density

## INTRODUCTION

Fracture risk increases after stroke due to decreased bone density and high fall tendency (1–3). Patients with stroke have 1.4-2.4-fold increased hip fracture risk (4). Advanced age, female gender, a history of previous fractures or falls, having diseases that affect bone metabolism, diminished mental status, and atrial fibrillation may all be risk factors for hip fracture in stroke patients (2,3,5).

Although the fracture risk is high in people with hemiplegia, there are no standardized screening tests. Fracture risk assessment in hemiplegic patients is essential prophylactic prevention of fractures and in identifying the individuals who need osteoporosis treatment. Bone mineral density (BMD) assessment is helpful in recognizing patients with osteoporosis and determining their fracture risk. Usually, osteoporosis treatment is advised for patients with BMD T-scores  $\leq -2.5$  at lumbar spine and/or femoral neck. People with BMD T-scores between  $-1$  and  $-2.5$  are diagnosed as having osteopenia and can be treated for increased fracture risk. BMD measurement can be performed after vital signs are stable in clinical practice, especially for stroke patients at high risk of osteoporosis. Dual-energy X-ray absorptiometry (DXA) measurement rate is very low among stroke patients (6). Stroke is a serious health problem with various complications other than osteoporosis (7). For this reason, importance of screening for osteoporosis and assessing high fracture risk may be overlooked.

Fracture Risk Assessment Tool (FRAX) and QFracture are absolute fracture risk prediction algorithms (8,9). However, the efficacy of these tests in determining hip-fracture risk in stroke patients has not been clearly established. The FRAX tool helps identify individuals with high fracture risk associated with osteoporosis and in determining the need for treatment. FRAX is considered superior to BMD measurement alone in treatment decision-making (8). Twelve items are examined with FRAX, including the presence of secondary osteoporosis. In fact,

there are more diseases that may lead to secondary osteoporosis. No item in FRAX deals with falls that may have been influenced by medical treatment. Stroke may lead to secondary osteoporosis due to immobilization and hemiplegia but it is not presented as a cause of secondary osteoporosis in FRAX.

The QFracture tool was developed in England to calculate the risk of osteoporotic fracture including hip fractures. QFracture was especially promoted for determining both absolute osteoporotic and hip-fracture risks in the primary care setting. The fracture risk calculation with QFracture can be performed in two ways. First, fracture risk is assessed by the clinician according to existing electronic records. Second, the items can be completed by the patient because the test does not involve laboratory or other empirical testing. Items such as fragility, fracture history, ethnic group, epilepsy, and the use of antidepressants, living in a nursing home, inflammatory arthropathies, chronic obstructive pulmonary disease (COPD), type I diabetes mellitus, Parkinson's disease, and dementia leading to immobilization were added to this algorithm in 2012 (9). Both FRAX and QFracture tools can be used to predict hip-fracture risk (10–12), but there is no algorithm specific to stroke for identifying patients who need osteoporosis treatment.

The aim of this study was to assess the rate of osteoporosis and to compare the efficacy of FRAX and QFracture algorithms in identifying patients with high hip-fracture risk at one year after stroke.

## METHODS

Hundred patients with hemiplegia admitted to the inpatient stroke rehabilitation unit between 01.03.2016-30.11.2016 were screened in this cross-sectional study. Stroke diagnosis was made clinically and verified by magnetic resonance imaging studies. Exclusion criteria were age under 40 years, post-stroke duration  $>12$  months, a history of osteoporosis, use of antiresorptive drugs, and hav-



ing a condition affecting bone metabolism. One patient (28 years) was excluded due to very young age. In addition, fourteen patients whose disease durations were >12 months and eight patients who had a previous diagnosis of osteoporosis were excluded from the study. Seventy-seven patients with hemiplegia were enrolled. Disability was assessed by the Modified Rankin Scale which is a valid and reliable test for stroke patients (13). It has six stages: Grade 1 indicates the patients without significant disability, whereas grade 5 indicates severe disability. Grade 6 denotes death. Ambulation status was recorded as non-ambulatory, therapeutic ambulation, household ambulation, and functional ambulation.

Written informed consent was obtained from all patients. The study was approved by the hospital ethical committee.

### **Bone density measurement**

Lumbar region and non-hemiplegic femur neck BMD values were measured using dual-energy X-ray absorptiometry (Lunar Dpx, Pro) and T-scores were recorded. Non-hemiplegic hip bone density values were used in this study. The hemiplegic proximal femur bone density measurement may not be feasible due to factors such as previous fracture or hip prosthesis, heterotopic ossification, and improper positioning of the leg caused by spasticity or contractures. T-score is the standard deviation of the patient's BMD measurement scores from those of a young healthy adult. Lumbar region and/or femur neck T-scores  $\leq -2.5$  indicate osteoporosis, and T-scores between  $-2.5$  and  $-1$  are diagnosed as osteopenia. Low BMD values indicate a higher fracture risk (14).

### **Fracture Risk Assessment Tool (FRAX)**

FRAX is recognized by the World Health Organization for estimation of ten-year major osteoporotic or hip-fracture risks (15). FRAX is an easy web-based tool that helps estimate the probability of ten-year fracture risk as a percentage (16). Age, sex, race, height, weight, body mass index, previous fragility

fracture, family hip-fracture history, treatment with oral glucocorticoids, rheumatoid arthritis, other conditions that may cause secondary osteoporosis, smoking, and daily alcohol intake are inquired in the FRAX. It can be used with or without femur neck BMD values. FRAX without BMD is usually accepted as adequate for making treatment decisions (15,17). In this study, FRAX without BMD was used to compare the results of different tools for the patients who have no access to DXA measurement.

### **QFracture**

The QFracture tool is used to predict the ten-year hip or osteoporotic fracture risk in clinical settings, including primary care. It can also be used as a web-based self-assessment tool (18). BMD values and other laboratory tests are not required for calculating the score. QFracture was updated in 2012 (9). Risk factors questioned in QFracture are age, sex, ethnicity, body mass index, weight, height, smoking, alcohol use, previous fractures or family history of fractures, hormone replacement therapy, menopausal symptoms, endocrine problems, treatment with glucocorticoids, disorders that lead to secondary osteoporosis (type I diabetes, chronic hyperthyroidism, premature menopause, chronic malnutrition, chronic liver disease), asthma, cardiovascular disease (heart attack, angina, stroke, TIA), history of falls, malabsorption, Parkinson's disease, rheumatoid arthritis, SLE, type 2 diabetes, epilepsy or use of anticonvulsants, and treatment with antidepressants. Stroke is appraised as a separate risk factor in QFracture. Completing the QFracture is more time-consuming than the FRAX. QFracture scores are expressed as a percentage for both 10-year osteoporotic and hip-fracture risks. It has been shown that a cut-off value of 5.3% would identify 3295 (59.8%) of the 5509 women with a hip fracture over the next 10 years. Similarly in men the cut-off value for hip fracture was determined as 1.3% with 64.3% sensitivity. Cut-off values are adapted from 10-year predicted risk for hip fracture in the validation cohort by Hippisley-Cox J (9). QFracture

has been developed in England, however, the validation of QFracture for the other countries has not been done (19).

### STATISTICAL ANALYSIS

The suitability of the data was evaluated with the Shapiro-Wilk test and homogeneity was evaluated with the Levene test. Scale data were shown as arithmetic mean  $\pm$  standard deviation or ordinal data were given as median (minimum-maximum) and categorical data were expressed as n (%). The receiver operating characteristic (ROC) curves were evaluated for several variables based on the cut-off value that maximizes both sensitivity and specificity of the tools. Test variables were FRAX without BMD and QFracture; the state variable was the presence of osteoporosis according to T-scores of femoral neck and lumbar spine. The ROC curve was constructed, and the area under curve (AUC) and its 95% confidence interval (CI) were estimated. A p value  $\leq$  0.05 was considered statistically significant. The SPSS 22.0 (IBM Corporation) program was used for variable analyses.

### RESULTS

Demographic features and clinical characteristics are summarized in Tables 1 and 2. Fifteen patients (19.5%) had osteoporosis and 39 (50.6%) had osteopenia. Non-hemiplegic hip T-scores were  $\leq$  -2.5 in 10 patients (13.0%) and between -1 and -2.5 in 35 patients (45.5%). Mean FRAX 10-year hip-fracture score was  $1.4 \pm 2.0$ . Seven patients (9.1%) had FRAX hip scores  $\geq 3$ . Mean QFracture score for hip fracture was  $2.5 \pm 3.5$ . Ten-year hip-fracture risk was high in 26 patients (33.8%) using QFracture. Six patients (7.8%) had low-energy fractures after stroke. Fracture sites were hip in 2 patients, 1 humerus, 1 forearm, and 2 in lower extremities.

The ROC curves of FRAX without BMD and QFracture for the risk of osteoporosis are shown in Figure 1. All variables were found valid for predict-

**Table 1.** Demographic characteristics

Age (yrs)	62.2 $\pm$ 11.1
Female/Male (n, %)	27/50 (35.1/64.9%)
Married/Single (n, %)	56/21 ( 72.3/27.3%)
BMI (kg/m <sup>2</sup> )	26.9 $\pm$ 4.4
Time since stroke (mos)	3.9 $\pm$ 2.6
Right/left hemiplegia (n, %)	38/39 (49.4/50.6%)
Ischemic/haemorrhagic (n, %)	67/10 (87.0/13.0%)

Data were given as the arithmetic mean  $\pm$  standard deviation or number (percent)

ing risk of hip osteoporosis. The area under the ROC curve was 0.804 (% 95 CI 0.665-0.943, p = 0.002) for FRAX and 0.758 (% 95 CI 0.615-0.901, p = 0.009) for QFracture. Cut-off values for the estimation of hip osteoporosis for FRAX and QFracture tools were 1.15 and 1.55, respectively (Table 3).

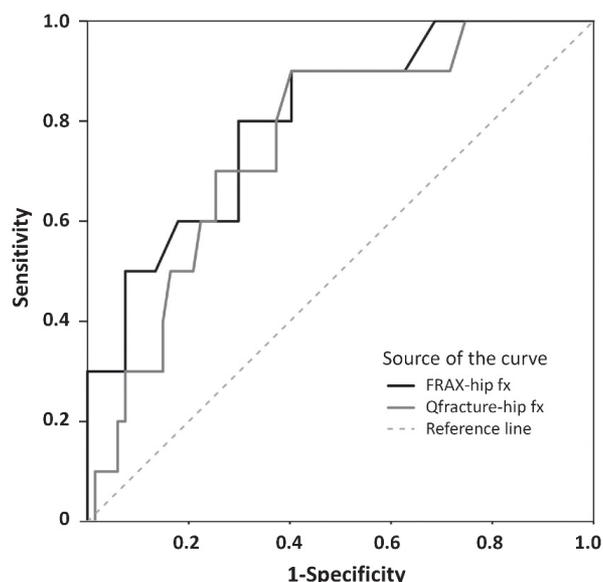
**Table 2.** Clinical characteristics

Brunnstrom stage Upper Extremity	2 (1-6)
Brunnstrom Stage Lower Extremity	3 (1-6)
Modified rankin scores	3 (1-5)
Ambulation status	3 (1-5)
FRAX score	1.4 $\pm$ 2.0
QFracture score	2.5 $\pm$ 3.5
Intact femur neck BMD (g/ cm <sup>2</sup> )	0.903 $\pm$ 0.156
Intact femur neck T-score	-1.1 $\pm$ 1.1

Data were given as the median (min-max) or arithmetic mean  $\pm$  standard deviation



**Figure 1.** Area under curve of FRAX and QFracture for hip osteoporosis



## DISCUSSION

In this study, 19.5 % of the patients with hemiplegia  $\leq 1$  year post-stroke had osteoporosis and 50.6% had osteopenia. The osteoporosis risk increased 1.77-fold after stroke (20). However, routine DXA scanning may not be possible in patients with hemiplegia. In a recent study, the bone density measurement rate was reported as low as 5.1% at one year after stroke (6). Moreover, the authors concluded that only 15.5% had medical treatment for osteoporosis. DXA measurement is usually not possible in

the acute phase following stroke due to many systemic problems. After discharge, access to DXA is usually not easy because of transportation difficulty of the disabled person or accompanying medical conditions. Thus, fracture risk assessment tools can help identify patients who need treatment to prevent low-energy trauma fractures.

An interesting finding of this study is that 9.1% and 33.8 % of the patients had increased 10-year hip-fracture risk according to the FRAX and QFracture tools, respectively. Fall history and neurological diseases including stroke are inquired in the QFracture tool; however, FRAX does not contain any stroke-related items. In a study conducted with Parkinson’s disease patients, it was found that the fracture risk is mildly lower as assessed by FRAX compared to evaluations by QFracture (21). The rate of stroke patients having high 10-year hip-fracture risk was lower by FRAX in this study, in parallel with findings in previous research.

10-year hip fracture risk calculated with QFracture was found significantly higher than the risk calculated with FRAX among women in an osteoporosis outpatient clinic in a previously (22). FRAX and QFracture results are found correlated in the patients with a history of low-trauma hip fracture or injury risk in another study (12). On the other hand, the authors concluded that FRAX is less effective in determining hip-fracture risk. QFracture was found to perform better in identifying patients with a history of falls and determining the treatment threshold. QFracture and FRAX yielded high discriminato-

**Table 3.** Comparison between cut-off values, sensitivities, and specificities of the tools involved in osteoporosis risk assessment

State Variable	Test Result Variables	AUC (95% CI)	P value	Cut-off value	Jouden index	Sensitivity	Specificity
Hip OP	FRAX-hip fx	0.804 (0.665-0.943)	0.002	1.150	0.501	0.800	0.701
Hip OP	QFracture-hip fx	0.758 (0.615-0.901)	0.009	1.550	0.497	0.900	0.597

AUC: area under curve, OP osteoporosis, CI: confidence interval, fx: fracture

ry performance for hip fracture prediction, however, QFracture is thought to be slightly better in a retrospective cohort study with more than 1 million individuals between ages 50-90 (11).

In our study, there was a correlation between FRAX and QFracture results. FRAX scores were significantly high in patients with previous hip and/or peripheral fractures. In addition, among the patients with or without fracture history, no significant difference was detected in terms of QFracture scores. Because of the limited number of the patients with previous fractures, we cannot claim one tool is better than the other.

In this study, six patients (7.8%) had low-energy fractures with a mean disease duration of 3 months. Fracture sites were hip and lower and upper extremities. The hip fracture rate was 2.6%. Lower extremity fractures are common after stroke (23). In a population-based study, 2-year low-trauma fracture frequency was reported to be 5.7%, whereas femur fracture rate was 2.8% in stroke (5).

According to the ROC curves, both osteoporotic fracture risk estimation tools were found satisfactory as compared with BMD values. The predictive value of the tools was determined according to the area under the ROC curve (AUC) as follows: non-predictive (AUC < 0.5), less predictive (AUC: 0.5–0.7), moderately predictive (AUC: 0.7–0.9), highly predictive (AUC: 0.9–1), and perfectly predictive (AUC = 1) (24, 25). If the FRAX hip-fracture score is > 1.2%, os-

teoporosis can be predicted at the plegic hip with a sensitivity of 75%. When the QFracture hip-fracture score is > 4.8%, osteoporosis can be predicted at the plegic hip with a sensitivity of 75%. Some screening tools, including FRAX, were previously reported to be reliable for estimating osteoporosis in postmenopausal women, in line with our results (26).

The main strength of our study is, to our knowledge, it is the first report that compares FRAX and QFracture tools in patients with hemiplegia. A limitation is that QFracture was developed for England, and it has not been validated in Turkey, yet. Lacking long-term follow-up due to its cross-sectional design is another limitation. There were no patients with osteoporosis diagnosis before stroke but not all of them had DXA measurement previously. Moreover, the results cannot be generalized to all stroke patients, because this study included patients with hemiplegia who were admitted to a tertiary rehabilitation hospital.

In conclusion, almost three-fourths of patients have osteoporosis or osteopenia within one year following stroke in this study. QFracture may be better for the hip fracture risk assessment because of the items related with stroke, although it is not validated epidemiologically in Turkey. Stroke-specific fracture tools are needed in performing risk assessment for patients who cannot access BMD measurement.

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## RESEARCH

# DIETARY TOTAL ANTIOXIDANT CAPACITY AND DIVERSITY: A COMPARISON STUDY OF OLDER AND YOUNGER ADULTS

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.210  
2021; 24(2): 150-158

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## ABSTRACT

**Introduction:** The present study aimed to assess the dietary total antioxidant capacity and diversity among older and younger adults.

**Materials and Methods:** In total, 38 older adults aged  $\geq 65$  years and 38 younger adults aged between 19 and 30 years were included in the study. The participants' general characteristics, dietary habits, and three-day dietary intake records were assessed. The dietary total antioxidant capacity and diversity score were calculated from the dietary intake records. Moreover, the serum total antioxidant capacity and oxidant status were assessed using commercial kits.

**Results:** The dietary diversity was greater among the younger adults than among the older adults ( $p < 0.05$ ). According to the dietary total antioxidant capacity values calculated from various databases, in males, the lipophilic and total oxygen radical absorbance capacity values were significantly lower among the older adults than among the younger adults. In females, the hydrophilic and total oxygen radical absorbance capacity, total phenol, and ferric reducing antioxidant power values were significantly lower among the older adults than among the younger adults. The serum total oxidant status and oxidative stress index of the older adults were significantly higher than those of the younger adults ( $p < 0.05$ ). Furthermore, the dietary diversity score and serum total antioxidant capacity were associated with the dietary total antioxidant capacity.

**Conclusion:** With aging, the dietary total antioxidant capacity and diversity decrease, while the oxidative stress index increases. Therefore, the consumption of foods with high antioxidant capacity and dietary diversity should be encouraged among older adults.

Keywords: Antioxidants; Oxidative Stress; Dietary Intake; Aging

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Received: Feb 17, 2020  
Accepted: May 24, 2021

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## INTRODUCTION

As in the rest of the world, the older adult population has substantially increased in Turkey (1). With an increase in life expectancy, the incidence of age-related diseases has also increased (2). Aging is a complex and inevitable process; many theories have been proposed to explain this process. Recently, the oxidative stress (or free radical) theory has become the most important theory explaining aging at the molecular level. According to this theory, the imbalance between antioxidants and oxidants with an increase in age leads to the accumulation of oxidative damage in many macromolecules, thereby diminishing the functions of various systems in the body and giving rise to the phenotype of aging (3). Antioxidants protect cells and organs against oxidative stress. Therefore, the intake of nutrients and dietary components that are rich in antioxidants is crucial for protecting the body against oxidative stress. The dietary intake of antioxidants is greatly influenced by an individual's dietary habits and preferences (4). The dietary total antioxidant capacity (TAC) is a parameter that evaluates antioxidants as a whole and takes into account the synergistic effects among antioxidants. The combination of different antioxidants provides more protection against reactive species than a single antioxidant. The dietary TAC is a valuable screening tool in nutritional epidemiology studies and plays an important role in the development of a better nutrition program for individuals (5). Exogenous and endogenous antioxidants together neutralize reactive species and prevent oxidative stress. Therefore, several ways have been suggested to increase the amount of exogenous antioxidants (4, 5). The present study aimed to assess the daily consumption of some food groups by older and younger adults and to evaluate their dietary and serum TAC status.

## MATERIALS AND METHODS

The present study had a cross-sectional design to evaluate the dietary and serum TAC status of older

and younger adults. In total, 38 older adult volunteers (13 males and 25 females) aged  $\geq 65$  years and 38 younger adult volunteers (13 males and 25 females) aged between 19 and 30 years participated in the study, which was conducted at a private hospital in Ankara between May 2017 and May 2018. The study was conducted with the approval of the Hacettepe University Ethics Commission (dated 03/14/2017 and numbered GO 17/212-30). None of the participants had a history of metabolic or endocrine diseases, except for hypertension. Moreover, none of them had smoked or consumed alcohol and used food supplements in the past year.

### Dietary energy and nutrient intakes, antioxidant capacity, and diversity score

Dietary intakes were recorded for three consecutive days (including a weekend day). Energy and nutrient intakes were calculated using BeBIS 8.1 (Nutrition Information System software 2017). Dietary TAC values were calculated using databases of oxygen radical absorbance capacity (ORAC) and ferric reducing antioxidant power (FRAP) (6, 7). The dietary diversity score (DDS) was calculated by considering five main food groups: cereal, vegetable, fruit, meat, and milk. The serving size was determined to take into consideration the dietary guidelines for Turkey (8). If the mean daily consumption of a food group by an individual was more than half the recommended portion, the individual was considered to have consumed that food group. DDSs were classified as low ( $DDS < 3$ ), medium ( $3 < DDS < 6$ ), and high ( $DDS > 6$ ) (9).

### Serum TAC and oxidant status

The serum TAC and total oxidant status (TOS) were assessed using commercial kits (Rel Assay Diagnostics) (10, 11). The samples were studied in duplicates. The serum TAC was measured according to the bleaching of the characteristic color of a more stable 2,2'-azino-bis (3-ethylbenzothiazol-

line-6-sulfonic acid) (ABTS) radical cation by antioxidants (10). Furthermore, the serum TOS was measured according to the total amount of oxidant molecules present in the sample. The analysis was

calibrated with hydrogen peroxide; the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (mmol H<sub>2</sub>O<sub>2</sub> Eq/L). The serum TOS was measured according to the oxidation

**Table 1.** General characteristics of the study participants

	Older adults						Younger adults						p
	Male (n = 13)		Female (n = 25)		Total		Male (n = 13)		Female (n = 25)		Total		
	n	%	n	%	n	%	n	%	n	%	n	%	
Age (years) <sup>†</sup>	72.1 ± 6.71		71.3 ± 6.71		71.6 ± 6.63		23.5 ± 3.69		24.5 ± 3.37		24.2 ± 3.47		<0.001*
Total duration of education <sup>†</sup> (years)	5.9 ± 5.6		3.3 ± 2.6		4.2 ± 3.3		14.1 ± 3.3		14.2 ± 2.4		14.2 ± 2.7		<0.001*
Marital status (%)													
Married	12	92.3	19	76.0	31	81.6	4	30.8	10	40.0	14	36.8	<0.001 <sup>a*</sup>
Bachelor	1	7.7	6	24.0	7	19.4	9	69.2	15	60.0	24	63.2	
Smoking status (%)													
Never	4	30.8	24	96.0	28	75.7	13	100.0	24	96.0	37	97.4	0.003 <sup>a*</sup>
Yes (except for the past year)	9	69.2	1	4.0	10	23.3	-	-	1	4.0	1	2.6	
Alcohol use (%)													
Never	11	83.3	25	100.0	36	94.7	12	92.3	23	92.0	35	92.1	0.615 <sup>a</sup>
Yes (except for the past year)	2	16.7	-	-	2	5.3	1	7.7	2	8.0	3	7.9	
Disease diagnosis (%)													
No	10	76.9	6	24.0	16	42.1	13	100.0	18	72.0	31	81.6	0.002 <sup>a*</sup>
Yes	3	23.1	19	76.0	22	57.9	-	-	7	28.0	7	18.4	
Type of disease (%)													
Hypertension	3	100.0	14	82.3	17	85.0	-	-	-	-	-	-	
Ulcer-gastritis	-	-	2	11.8	2	10.0	-	-	2	100.0	2	100.0	
Osteoporosis	-	-	1	5.9	1	5.0	-	-	-	-	-	-	
Dietary habits													
Mean meal number <sup>†</sup>													
Main meals	2.6 ± 0.51		2.7 ± 0.44		2.6 ± 0.48		2.8 ± 0.44		2.7 ± 0.46		2.7 ± 0.45		0.460
Snacks	1.1 ± 0.49		1.1 ± 0.57		1.1 ± 0.54		1.5 ± 0.78		1.6 ± 0.76		1.58 ± 0.76		0.001*
Skipping meals (%)													
No	1	7.7	3	12.0	4	10.6	3	23.1	4	16.0	7	18.4	0.368 <sup>a</sup>
Yes	12	92.3	22	88.0	34	89.4	10	76.9	21	84.0	31	81.6	

Mann-Whitney U test; p value: tested between the older and younger adults

<sup>a</sup> Pearson's chi-squared test, \*p < 0.05

<sup>†</sup> (x̄ ± SD)



of the ferrous ion to the ferric ion in the presence of various oxidative species in the acidic medium; the results are expressed in terms of mmol H<sub>2</sub>O<sub>2</sub> Eq/L (11). The oxidative stress index (OSI) was calculated as a percentage by dividing the total oxidant state by the TAC.

### Statistical analysis

Statistical analyses were performed using SPSS 23 (Statistical Software Package 23, IBM Corp., Armonk, NY, USA). The results are presented as the mean  $\pm$  standard deviation ( $\bar{x} \pm SD$ ) values. Qualitative data are expressed as numbers and percentages. Normally distributed data were analyzed using parametric statistical tests (independent two-sample t test and Pearson's correlation), whereas non-normally distributed data were analyzed using nonparametric statistical tests (Pearson's chi-squared test, Mann-Whitney U test, and Spearman's correlation).  $p < 0.05$  was considered the cut-off value for significance.

## RESULTS

In total, 38 older adults and 38 younger adults participated in the present study; their mean ages were  $71.6 \pm 6.63$  and  $24.2 \pm 3.47$  years, respectively. General characteristics of the study participants are provided in Table 2. The mean duration of education was significantly lower among the older adults ( $4.2 \pm 4.0$  years) than among the younger adults ( $14.2 \pm 2.7$  years) ( $p < 0.001$ ). In total, 75.7% of the older adults and 97.4% of the younger adults were non-smokers ( $p < 0.05$ ). Moreover, 57.9% of the older adults and 18.4% of the younger adults were diagnosed with a disease ( $p < 0.05$ ). Hypertension was the most common disease among the older adults (77.3%), while ulcer-gastritis was the most common disease among the younger adults (28.6%). Although their mean main meal numbers were similar, the mean number of snacks consumed by the older adults ( $1.1 \pm 0.54$ ) was significantly lower than that consumed

by the younger adults ( $1.6 \pm 0.76$ ) ( $p < 0.05$ ). However, there was no significant difference between these two groups in terms of skipping meals ( $p > 0.05$ ).

The mean daily food consumption and DDSs of the older and younger adults are provided in Table 2. In males, the daily consumption of meats was found to be significantly lower among the older adults than among the younger adults ( $p < 0.05$ ). In females, bread consumption was found to be significantly lower among the older adults than the younger adults ( $p < 0.05$ ).

According to the DDS classification, 53.2% of the older adults were considered to have a medium DDS, while 36.8% were considered to have a low DDS. These values were 73.7% and 18.4%, respectively, for the younger adults ( $p < 0.05$ ).

The dietary TAC, serum antioxidant capacity, and serum oxidant status of the older and younger adults are provided in Table 3. According to the mean dietary TAC values, in males, the lipophilic ORAC (L-ORAC) and total ORAC (T-ORAC) values were significantly lower among the older adults than the younger adults. Furthermore, in females, the hydrophilic ORAC (H-ORAC), T-ORAC, total phenol (TP), and FRAP values were significantly lower among the older adults than among the younger adults. The serum TOS and OSI were significantly higher among the older adults than among the younger adults ( $p < 0.05$ ). However, there was no significant difference in the serum TAC between the two groups ( $p > 0.05$ ).

The correlations between DDSs and different dietary TAC measures are provided in Table 4. In the study, there was a mid-level correlation between the DDS and L-ORAC ( $r = 0.398$ ,  $p < 0.001$ ). Moreover, there was a mid-level correlation between the DDS and H-ORAC, T-ORAC, and TP values ( $p < 0.05$ ). However, there was a weak correlation between the serum TAC and H-ORAC ( $r = 0.204$ ) and T-ORAC ( $r = 0.203$ ) ( $p < 0.05$ ).

**Table 2.** Mean daily consumption of food groups and dietary diversity scores among older and younger adults

	Older adults (n = 38)		Younger adults (n = 38)		P <sub>1</sub>	P <sub>2</sub>
	Male (n = 13)	Female (n = 25)	Male (n = 13)	Female (n = 25)		
<b>Food groups (g day<sup>-1</sup>)</b>						
Milk and milk products	175.5 ± 70.1	157.9 ± 71.2	163.1 ± 56.6	188.5 ± 115.3	0.555 <sup>a</sup>	0.491 <sup>a</sup>
Bread and cereals	145.0 ± 79.7	142.8 ± 52.4	156.9 ± 118.9	102.8 ± 77.7	1.000 <sup>a</sup>	0.006 <sup>a*</sup>
Vegetables and fruits	169.6 ± 89.9	154.8 ± 77.8	237.7 ± 130.1	193.7 ± 83.4	0.191 <sup>a</sup>	0.093 <sup>a</sup>
Meats	114.6 ± 44.8	117.7 ± 68.1	195.9 ± 144.6	146.4 ± 84.4	0.022 <sup>*</sup>	0.162
Eggs	24.9 ± 23.4	29.8 ± 19.9	37.3 ± 33.6	33.5 ± 32.6	0.429	0.824
Pulses and nuts	7.9 ± 17.2	8.5 ± 11.9	8.1 ± 15.7	11.6 ± 16.0	0.740	0.313
Fats and oils	43.3 ± 14.1	39.4 ± 21.3	44.1 ± 29.5	37.3 ± 17.3	0.573	0.961
Sweets	33.7 ± 94.1	10.7 ± 11.8	12.9 ± 16.1	19.2 ± 37.9	0.979	0.838
<b>DDS†</b>	<b>n (%)</b>		<b>n (%)</b>		<b>p</b>	
<3	14 (36.8)		7 (18.4)		<b>0.033**</b>	
3–6	24 (53.2)		28 (73.7)			
>6	-		3 (7.9)			

Mann–Whitney U test; p<sub>1</sub> value: tested between male older and younger adults; p<sub>2</sub> value: tested between female older and younger adults

<sup>a</sup>Student's t test, \*p < 0.05

†n (%), \*\*Pearson's chi-squared test

DDS: dietary diversity scor

## DISCUSSION

Oxidative stress affects the nervous system, endocrine system, and immune system; it damages cells and consequently causes many diseases (12). Studies have shown that the prevalence of diseases caused by oxidative stress can be reduced by dietary interventions (13, 14). Due to their antioxidant properties, nutrients protect the body against oxidative stress throughout life (5). Because oxidative stress increases during the aging process, the consumption of antioxidant-rich and diverse foods becomes increasingly important with age. The present study aimed to evaluate the dietary TAC and diversity status among older and younger adults. In total, 75.7% of the older adults and 97.4% of the younger adults were non-smokers. The percentage of older

and younger adults who never consumed alcohol was similar (92.1% and 94.7%, respectively). Many studies have shown that smoking and alcohol consumption affect the TAC and oxidative stress markers (15, 16). Therefore, it is important to note that none of the participants had a history of smoking or alcohol consumption in the previous past year. Hypertension commonly occurs in older adults because of vascular damage caused by aging (17). In the present study, 44.7% of the older adults were diagnosed with hypertension. The older adult participants had no chronic or metabolic disease other than hypertension and osteoporosis; this is a relevant observation because diseases and related diets, medications and supplementation may affect nutrition.



In the present study, the participants' daily food consumption was assessed. In females, although meat consumption differed between the younger and older adults, the difference was not significant. However, in males, the daily consumption of meats was significantly lower among the younger adults than the older adults (Table 2) ( $p < 0.05$ ). High consumption of foods such as milk and milk products, meat, and eggs, which are good sources of proteins for older adults, preserves muscle strength (18). In the present study, in females, the consumption of bread and cereals was significantly higher among the older adults than the younger adults (Table 2) ( $p < 0.05$ ). Bread, rice, and bulgur are the most important sources of energy for Turkish people (19). In addition, owing to their simple preparation and easy digestion, the consumption of these foods may have increased among older females. The mean consumption of vegetables and fruits was less than 400 g per day in both the age groups (Table 2). The WHO recommends that the daily consumption of fresh vegetables and fruits should be above 400 g for healthy nutrition (20). The consumption of other foods was similar between the older and younger adults. Regular nutrition and not skipping main meals had a positive effect on dietary intake among the older adults. Thus, in the present study, food consumption was similar between the older and younger adults. Although the daily consumption of most food groups was similar between the two age groups, the dietary diversity was lower among the older adults than among the younger adults (Table 2) ( $p < 0.05$ ). The DDS is an important indicator of a quality diet; a low DDS is associated with significant health problems in both older and younger adults (21). In a 12-year longitudinal study involving 40–79-year-old individuals, Otsuka et al. (22) reported a decrease in DDSs in individuals older than 50–60 years. Many factors, such as physical and physiological changes and socioeconomic circumstances, can affect the nutritional status of older adults. Thus, the dietary diversity decreases in older adults (18).

In males, the L-ORAC and T-ORAC values were significantly lower among the older adults than the younger adults. Moreover, in females, the H-ORAC, T-ORAC, TP, and FRAP values were significantly lower among the older adults than the younger adults (Table 3) ( $p < 0.05$ ). Zujko et al. (23) have reported similar results to those of the present study, with the dietary TAC calculated with FRAP being lower in males and females aged 61–74 years than in younger adults. The dietary TAC may decrease with a change in dietary preferences and a decrease in the dietary diversity due to changes that occur during the aging process (18). In the present study, a significant correlation was noted between the dietary TAC and DDS (Table 4) ( $p < 0.05$ ).

The serum TAC and oxidant status, which are two important indicators of oxidative stress, change during the aging process, thereby increasing oxidative stress (10, 11). In the present study, the serum TAC of the older adults ( $1.586 \pm 0.26$  mmol/L) was lower than that of the younger adults ( $1.684 \pm 0.26$  mmol/L); however, the difference was not significant ( $p = 0.103$ ) (Table 3). The serum oxidant status and OSI were significantly higher among the older adults than among the younger adults ( $p < 0.001$ ), probably due to the increase in reactive oxygen species during the aging process. Narmaki et al. (24) reported that enhancing the dietary diversity can reduce oxidative stress. A weak positive but significant relationship was noted between the dietary TAC and serum TAC ( $p < 0.05$ ) (Table 4). Similarly, Wang et al. (25) demonstrated a significant relationship between the dietary TAC and serum TAC in adults. The contribution of nutrients to the TAC depends on food ingredients (4). In the present study, the percentage of individuals consuming a wide variety of ingredients was low (3.9%) according to the nutrition diversity score.

## CONCLUSION

In the present study, the mean dietary TAC was higher among the younger adults, whereas the serum

**Table 3.** Dietary and serum total antioxidant capacity and serum oxidant status of older and younger adults

	Older adults (n = 38)			Younger adults (n = 38)		p <sub>1</sub>	p <sub>2</sub>
	Male (n = 13)	Female (n = 25)	Male (n = 13)	Female (n = 25)			
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	$\bar{x} \pm SD$	$\bar{x} \pm SD$			
<b>Dietary TAC</b>							
Hydrophilic ORAC (μmol TE)	14111 ± 3493.6	11760 ± 2492.9	16312 ± 4300.9	14895 ± 5031.2	0.086 <sup>a</sup>		<b>0.017*</b>
Lipophilic ORAC (μmol TE)	1087.2 ± 602.2	1121.7 ± 465.2	2089.1 ± 1667.1	1229.1 ± 835.5	<b>0.044*</b>		0.961
Total ORAC (μmol TE)	15210 ± 3921.8	12897 ± 2509.4	18543 ± 5608.6	16159 ± 5407.3	<b>0.046**</b>		<b>0.028*</b>
TP (GAE)	895.6 ± 279.8	734.8 ± 234.4	893.8 ± 276.9	948.1 ± 378.0	0.987 <sup>a</sup>		<b>0.034*</b>
FRAP (mmol)	4.03 ± 1.96	3.10 ± 1.13	3.56 ± 1.07	4.01 ± 1.71	0.739		<b>0.024*</b>
<b>Serum TAC (mmol/L)</b>	1.586 ± 0.26		1.684 ± 0.26		0.103 <sup>a</sup>		
<b>Serum TOS (μmol/L)</b>	13.275 ± 4.267		8.846 ± 1.776		<b>&lt;0.001*</b>		
<b>OSI</b>	0.876 ± 0.359		0.541 ± 0.143		<b>&lt;0.001*</b>		

Mann–Whitney U test; p<sub>1</sub> value: tested between male older and younger adults; p<sub>2</sub> value: tested between female older and younger adults

<sup>a</sup>Student's t test, \*p < 0.05

TAC: total antioxidant capacity, ORAC: oxygen radical absorbance capacity, TE: Trolox equivalents, TP: total phenol, GAE: gallic acid equivalents, FRAP: ferric reducing antioxidant power, TOS: total oxidant status, OSI: oxidative stress index

**Table 4.** Correlation between dietary diversity score, serum total antioxidant capacity, and dietary total antioxidant capacity

Dietary TAC	DDS		Serum TAC	
	r	P	r	p
H-ORAC (μmol TE)	<b>0.237</b>	<b>0.039*</b>	<b>0.228</b>	<b>0.048*</b>
L-ORAC (μmol TE)	<b>0.398</b>	<b>&lt;0.001*</b>	0.145	0.211
T-ORAC (μmol TE)	<b>0.291</b>	<b>0.011*</b>	<b>0.237</b>	<b>0.039*</b>
TP (GAE)	<b>0.256</b>	<b>0.029**</b>	0.196	0.090 <sup>a</sup>

Spearman's correlation. \*p < 0.05

<sup>a</sup>Pearson's correlation

DDS: dietary diversity score, TAC: total antioxidant capacity, ORAC: oxygen radical absorbance capacity, TE: Trolox equivalents, TP: total phenol, GAE: gallic acid equivalents, FRAP: ferric reducing antioxidant power



TOS and OSI were higher among the older adults. Furthermore, the dietary diversity was lower among the older adults than among the younger adults. Nutritional recommendations for healthy individuals and patients, particularly the elderly, should encourage the consumption of various foods belonging to all food groups.

### Acknowledgments

The authors thank the patients who participated voluntarily in this study.

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## RESEARCH

# DOES AGING AFFECT BENIGN PAROXYSMAL POSITIONAL VERTIGO TREATMENT?

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.211  
2021; 24(2): 159-164

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Received: Apr 14, 2021  
Accepted: May 21, 2021

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## ABSTRACT

**Introduction:** Benign Paroxysmal Positional Vertigo is seen in all age groups; however, its incidence increases with age. In addition to many factors affecting its treatment, aging is also thought to have an effect on treatment. The aim of this study is to investigate the relationship between the number of maneuvers applied in treatment and patient's age, gender and the affected canal.

**Materials and Method:** In total 290 subjects, between 18 to 87 years were included in the study. The positional tests were performed and the appropriate maneuver was performed based on affected canal. Following third day the maneuver positional tests were repeated. If the symptoms and / or nystagmus continued, maneuver was performed again.

**Results:** It was found that older adults require higher number of maneuvers to recover ( $p < 0.05$ ,  $r = 0.33$ ). In addition, comorbidities such as hypertension and migraine were observed more frequently in older adults compared to the other groups.

**Conclusion:** Changes and comorbidities caused by aging render treatment process far and difficult in the elderly.

**Keywords:** Aging; Vertigo; Comorbidity; Vestibular Diseases

## INTRODUCTION

Benign Paroxysmal Positional Vertigo (BPPV) is a peripheral vestibular system disorder characterized by a sudden and short-term vertigo, dizziness, nausea, and positional nystagmus caused by the movement and/or placement of the head relative to the affected semicircular canal. Although BPPV is benign, it affects patients' daily life activities and can lead to morbidity or disability due to falls (1-3).

BPPV can be seen in all age groups, however it has been reported that the mean age of onset is in the fourth and fifth decades and its incidence increases with age (3, 4). Additionally, as it has been observed, BPPV is 7 times more likely to be seen in patients over 60 years of age than in the 18-39 age groups (5). It has been stated that morphological damage to otolith organs and decrease in the number of hair cells in these organs due to aging may cause BPPV (5, 6).

In the treatment of BPPV, appropriate maneuvers are applied based on the affected semicircular canal (2). However, while only one maneuver can be sufficient in some BPPV cases, in others, repetitive maneuvers may be required (7). There are many factors affecting the effectiveness of the treatment, among which are age, gender, affected ear and/or canal and comorbidities (8, 9). The aim of this study is to investigate the relationship between the number of maneuvers applied in BPPV treatment and patient's age, gender and the affected canal.

## MATERIALS AND METHOD

The study protocol was approved by Ankara University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (No: İ7 – 440 – 20). According to the national legislations and institutional rules and procedures, all patients are obliged to sign an informed consent form approving analysis of their clinical records, and publication of their anonymous data.

After reviewing the medical records of patients

admitted to Ankara University School of Medicine İbn-i Sina Hospital, Otorhinolaryngology Department, Hearing, Speaking and Balance Disorders Center between September 2018 and June 2020 with dizziness/balance disorder, patients over 18 years of age and diagnosed with BPPV were included in this study. Subjects with neurological disorders and/or with multicanal involvement BPPV were excluded. The age, gender, affected canal, number of maneuvers and comorbidities of BPPV subjects were recorded.

The subjects were divided into three age-based groups: "Group 1" consists of subjects who are 18-44 years of age; "Group 2," of subjects who are 45-64 years of age, and "Group 3" consists of subjects over 64 years of age.

Each subject was initially examined with videonystagmography (VNG) as a standard procedure. Eye movements were recorded using VisualEyes VNG (Chatham, IL, USA). Saccadic and smooth pursuit eye movements, optokinetic, gaze, and spontaneous nystagmus were also recorded. Analysis on saccades was conducted for accuracy, velocity, and latency, whereas smooth pursuit and optokinetic tracking were analyzed for symmetry and gain.

The positional tests were performed with VNG goggles. The Dix Hallpike test was employed for diagnosis in posterior and anterior semicircular canal BPPV, and Roll test was used in the diagnosis of lateral semicircular canal BPPV. Once the affected canal was identified, an appropriate maneuver, chosen in accordance with the BPPV's pathophysiology (canalolithiasis, cupulolithiasis) and affected canal, was performed in the same session (one maneuver per session). Following the maneuver, the patient was recommended to avoid sudden head movements and to keep their head in an elevated position while sleeping. Three days after the maneuver, the test was repeated. In cases where symptoms and nystagmus continued, maneuver was performed again.



## STATISTICAL ANALYSIS

Data were analyzed using SPSS version 26.0. Quantitative data were described as mean  $\pm$  SD ( $X \pm SD$ ), and qualitative data were described in percentage values. The normality of data was evaluated with visual (histogram and stem-leaf plots) and analytic (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. The differences between groups were analyzed with Kruskal–Wallis test, and any differences were to be found, two-way comparisons were held by Mann Whitney U test (the comparisons were between group 1-2, 1-3, 2-3). Additionally, the relationship between age and maneuver count was investigated with Pearson correlation analysis.

## RESULTS

Forty-two of 332 patients diagnosed with BPPV were excluded due to multi-canal BPPV and a total of 290 patients were included in the study. Group 1 consisted of 57 females and 20 males with mean age of  $35.32 \pm 7.33$  years. Group 2 consisted of 95 females and 26 males with mean age of  $55.29 \pm 5.49$  years. Group 3 consisted of 63 females and 31 males with mean age of  $73.08 \pm 5.85$  years.

In an overall assessment, the most affected canal was observed to be the right posterior canal (38.62%), followed by the left posterior canal (29.65%), lateral canals (21.72%), anterior canals (10.68%), respectively.

An evaluation of the medical history of participants provided the following data: In Group 1, 3.89% of participants have hypertension; 5.19% have migraine, and 10.38% are afflicted by other diseases. In Group 2 hypertension rate is 29.75%, diabetes is 21.48%, and 23.14% of the participants had other diseases. In Group 3 the incidence of these factors was 59.57%, 32.97%, and 24.46%, respectively.

The distribution of the average number of maneuvers by groups is given in Table 1. Comparison of the groups provided in Table 2 reveals that statistically, average number of maneuvers in

Group 3 is significantly higher than in Groups 1 and 2 ( $p < 0.001$ ).

**Table 1.** Average Number of Maneuvers by Groups

Maneuver	Group 1	Group 2	Group 3
Minimum	1	1	1
Maximum	5	5	9
Mean-SD	$1.79 \pm 1.04$	$1.80 \pm 0.89$	$2.89 \pm 1.66$

\*SD: Standard Deviation

**Table 2.** Comparisons of the Average Number of Maneuvers Between Groups

Groups	p
Group 1 - Group 2	0.504
Group 1 - Group 3	0.00001*
Group 2 - Group 3	0.00003*

\* $p < 0.05$ , Mann Whitney U Test

## DISCUSSION

The primary purpose of the present study was to investigate whether aging affects the maneuver rehabilitation process of BPPV. Although some studies state that the number of maneuvers required is independent of age (10, 11) the Group 3 results in this study demonstrate that older BPPV patients need more repetitions, and this is thought to be caused by, for example, reduced effectiveness due to waist and neck restrictions from orthopedic problems, comorbidities, or not following post-treatment movement recommendations.

The current BPPV literature suggests many reasons for requiring repeated maneuvers, the most

common of which are comorbidities such as hypertension and diabetes (4, 9, 11, 12). In this study, the group of older participants indicated a hypertension ratio of 59.75% and needed more maneuvers, and this is compatible with these existing reports. Relatedly, it has been suggested that the increased prevalence and prolonged treatment of BPPV due to age may be caused by separation of the otocornia from the macula or degenerative changes in the utricle due to chronic ischemia (12, 13).

Orthopedic problems are also considered to be a reason for the need for multiple maneuvers (14, 15). For example, Balatsouras et al., state that issues such as limited cervical motion, kyphosis, limited range of motion, or low back and neck pain can affect the effectiveness of repositioning maneuvers in BPPV treatment (7). Likewise, it is our experience that orthopedic restrictions have a negative impact on the effectiveness of maneuver treatment, and the use of repositioning chairs in these cases can be beneficial.

In accordance with the literature, the present study indicates that the right posterior is the most commonly affected canal in BPPV diagnosis, followed by the left posterior (16-18). However, there was no significant relationship between the affected canal and the number of maneuvers required for successful treatment.

BPPV in the elderly differs from that in younger patients in terms of pathogenesis, diagnosis, and treatment, and older patients also demonstrate higher prevalence, are less responsive to treatment, and show a greater tendency to recurrence (12, 13). However, the number of participants in the younger Group 2 was higher than in Group 3 in this study,

although this inconsistency in age profile can be attributed to the difficulty of obtaining accurate anamnesis from older patients, misdiagnosis due to similar symptoms of comorbidities, and/or vascular and orthopedic problems and their consequent referral to different departments.

Additionally, 74.13% of the participants in the current study were women, and this majority finding is consistent with previous investigations (19-21), some of which have attributed BPPV to hormonal fluctuations, menopause, and/or osteoporosis (22, 23). One associated limitation of this study is the lack of specific information about osteoporosis and the menopause, and so it is recommended that all comorbidities are examined in greater detail in future studies.

Falls are common in the geriatric population, particularly in those with chronic debilitating conditions such as osteoporosis or neurological limitations (24). In such cases, BPPV is an increased risk factor for falls, and its immediate treatment is therefore crucial. Therefore, the strength of this study is that it draws attention to the factors affecting the BPPV rehabilitation process in geriatric individuals. It was aimed to raise awareness that comorbidities prolong the process and this situation increases the risk of falling.

In conclusion, this study demonstrates that changes and comorbidities due to aging render maneuver treatment for BPPV more difficult in elderly populations. Nevertheless, failure to treat BPPV can increase the risk of falls, negatively affects quality of life, and increases the burden of health-care costs (9, 16).



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## RESEARCH

# COMPLIANCE WITH CPAP THERAPY IN OLDER MEN WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.212  
2021; 24(2): 165-173

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## ABSTRACT

**Introduction:** The aim of our study is to ascertain the factors affecting the compliance of older male patients with obstructive sleep apnea syndrome to continuous positive airway pressure treatment.

**Materials and Method:** Retrospective analysis was done on tests of older male patients who have underwent continuous positive airway pressure treatment for obstructive sleep apnea syndrome. The tests were documented for almost five years and test results of the patients were taken from records of two different hospitals. Compliance with continuous positive airway pressure treatment; using an average of 5 hours or more of continuous positive airway pressure per night was accepted.

**Results:** It was found that 160 of 264 older men patients adapted to continuous positive airway pressure treatment but 104 of them did not.  $68 \pm 3.1$  years were recorded as compliant group mean, while  $74 \pm 4.2$  years was recorded as mean of non-compliant group. Resolution of symptoms a score of 95% were transpire in compliant patients and 87% seen in non-compliant patients. While 95% of the compliant patients took part in the continuous positive airway pressure training meetings, only 53% of the non-compliant patients attended the training meetings. A statistically significant correlation was found between non-compliance with continuous positive airway pressure therapy and smoking, nocturia, and benign prostatic hyperplasia.

**Conclusion:** Symptoms resolution treatment seem has linkage with improved compliance. In older male with obstructive sleep apnea syndrome, compliance with continuous positive airway pressure therapy is associated with the patient's participation in the therapy education group.

**Keywords:** Continuous Positive Airway Pressure; Sleep Apnea, Obstructive; Compliance; Aged

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Received: Apr 05, 2021  
Accepted: May 20, 2021

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## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) refers to a sleep-associated problem that is common in people of different ages: it is identified with irregular upper airway obstruction during sleep. Usually, patients with this problem have a continuous history of apnea, hypopnea, oxygen desaturation, and disturbed sleep. Globally, OSAS is known to be a major problem affecting many people. The usual signs and symptoms are persistent snoring, frequent night awakenings, restless sleep, and immoderate daytime sleepiness (IDS). Age, gender, obesity, and nasal congestion are among the prominent risk factors associated with OSAS (1). Sleep disturbances are more prevalent among overweight people, in children, and in women in the postmenopausal period (2). They are frequently related to comorbidities such as insulin resistance, metabolic syndrome, diabetes mellitus, high blood pressure, stroke, and heart and blood vessel disease, with an increased risk of vehicle accidents and various psychiatric disorders. The management of OSAS requires persistence and an integrative approach. After the diagnosis is made, some patients are offered a consultancy service to help them cope with their illness, including their comorbidities. Recently, awareness has increased of the importance of sleep for overall life quality, as associated with well-being, particularly in older adults. Sleep architecture differs in older adults. Older adults spend more time in the shallow stages of sleep, experiencing frequent awakenings and sleep interruptions (3). However, despite numerous studies and increased awareness of sleep issues, there is no specified and systematic plan regarding the diagnosis or therapy associated with disordered breathing during sleep in older adults.

Continual positive airway pressure (CPAP) is a safe and effective therapy for patients suffering from OSAS. Properly used, CPAP is effective in reducing nocturnal respiratory events and in improving daytime sleepiness and cognitive function (4). However, it is reported that a long-term lack of adherence to

treatment can reduce the compliance rate to 63% (5). Studies have shown that reduced CPAP compliance is associated with increased daytime sleepiness, a high apnea-hypopnea index (AHI), and a low mean oxygen saturation at night (4,5). Individuals who have had palatal surgery report mask problems with CPAP, and this has a negative effect on compliance (6). Studies indicate that regular and uninterrupted use of CPAP therapy, for a minimum of five hours a day, has a significant effect on a patient's sense of well-being. As yet, no single definition of what constitutes good CPAP compliance has been reached, and various healthcare systems suggest different requirements. A widely accepted scale for compliance is the application of CPAP for more than five hours per night on a minimum of 70% of nights. Despite the high efficacy of CPAP therapy, its potency is restricted by variable adherence to the treatment (7). Failure to comply with CPAP treatment happens in up to 25% to 50% of patients, who often abandon the treatment within four weeks of starting it (7). In considering compliance with CPAP, the research includes adults of a wide variety of ages. However, it is known that the prevalence of OSAS increases with age, and 30% of OSAS occurs in the older population (8). Older adults thus make up a high proportion of OSAS clients. It should be kept in mind that treatment compliance factors affecting older adults may differ from the factors affecting the general population. This research considered the clinical and other variables affecting compliance with CPAP in older men (aged 65 years and above). A number of factors were ascertained to detect whether they affect compliance with CPAP among these older men. The variables included factors previously reported as affecting compliance with CPAP use. These factors may be related to the aging process and thus affect compliance indirectly.

## MATERIALS AND METHOD

This research was conducted between March 2014 and April 2019 as a retrospective review of medi-



cal records and sleep analysis of 264 male patients, aged 65 years and above who have underwent continuous positive airway pressure therapy for OSAS. The tests were documented for almost five years and test results of the patients were taken from records of two different hospitals.

Out of 320 older male patients who underwent CPAP for OSAS therapy, 264 were included in this research. Twelve patients were rejected from the study because their medical records were not comprehensive, four patients were excluded because their CPAP device lacked an hour meter, and twelve patients due to missing CPAP data. Twenty eight patients who had undergone surgery with uvulopalatopharyngoplasty and bariatric surgical methods were also excluded from the study.

All patients' medical records were reviewed for age, gender, race, AHI, CPAP pressure, body mass index (BMI), lowest oxygen saturation, tobacco and alcohol use, use of oxygen with CPAP, duration of CPAP therapy, visual and hearing impairments, CPAP complications, psychiatric disorders, change of mask required, current medications, and comorbid conditions. AHI, OSAS symptoms, nocturia, and CPAP treatment were also evaluated.

Nocturia was defined as the frequency of urination from sleep at which patients would complain to healthcare professionals. Benign prostatic hyperplasia (BPH) was diagnosed and recorded following examination by an urologist.

CPAP compliance was equated with the patient applying CPAP for five hours or more per night. All patients included in the research received at least six months of CPAP therapy. Evaluation of compliance with CPAP was calculated from recorded readings on the patient's device over the previous six months.

The term AHI refers to the sum of all apneas and hypopneas divided by the period of hours of sleep (1). Apnea refers to air flow termination of more than ten seconds. Hypopnea refers to airflow

retardation, which has an effect on arterial oxygen saturation, causing desaturation of more than 3%. Within the first month after diagnosis of OSAS and starting CPAP therapy, all patients were examined to document any resolution of sleep abnormalities, a minimum oxygen saturation of 90 and an AHI of less than 5. CPAP titration was applied with increasing pressures of 2.5 cm-H<sub>2</sub>O until the respiratory events resolved to the patients detect with polysomnography. A mask and CPAP were prescribed for all patients by a pulmonologist during the initial diagnosis. During the verification process, all patients were informed about OSAS and about the use of the CPAP mask and machine by a sleep technician. The patients were encouraged to participate in the monthly training provided in a CPAP education group led by a trained sleep technician. Three questions were asked to ascertain the patients' clinical symptoms, complications, and level of comfort with the CPAP device. A check of the equipment and its function was conducted, and any disposable items, such as masks, were changed if necessary. Meter readings were taken from the records at the same time. Patients' questions were answered, and they were allowed to share their experiences. The training sessions often included a lesson on sleep disorders. All patients were invited to the CPAP training group every six months regardless of their previous attendance.

The study had been reviewed and approved by a certified Ethical Committee, and the number of the approval documents included the date of the approval. The registration number is 2011- KAEK-42 2019/12-05.

### Statistical analysis

Fisher's exact test and the paired two-tailed Student's t-test were used for the statistical analysis. Descriptive statistics and the chi-square test were used to evaluate the data, and the within-group difference was analyzed using the Mann-Whitney U

test. Data were expressed as means ± SD. A statistical difference was taken as  $p < 0.05$ .

## RESULTS

The demographic and clinical characteristics of 264 older male patients with OSAS included in this study are presented in Tables 1 and 2. All patients were white Caucasian males, with mean age of  $73 \pm 5.6$  years during the period when the records from their CPAP devices were reviewed. All were typical OSAS patients, without respiratory failure, neuromuscular disease, or severe kyphosis or scoliosis. While 160 of the patients were compliant with the prescribed use of the CPAP device, 104 were non-compliant. As shown in Table 1, the mean age of the patients who were CPAP compliant was statistically significantly lower than that of patients who were not compliant ( $p = 0.03$ ). When CPAP therapy was started with our patients, smoking was found to

be associated with non-compliance. No statistically significant difference was shown in terms of alcohol consumption by the patients. Alcohol consumption rates were 35% in the compliant group and 60% in the non-compliant group ( $p = 0.35$ ). While 95% of the compliant patients took part in the CPAP patient training group for a minimum of six months, only 53% of the non-compliant patients attended the training meetings ( $p = 0.006$ ). Hearing loss was 9% in the non-compliant patients and 58% in the compliant patients. However, the indicated difference was statistically insignificant ( $p = 0.43$ ). There were differences in the level of impairment in walking ability, with 8% impairment in the non-compliant group versus 26% in the compliant group ( $p = 0.35$ ). This difference was statistically insignificant. No significant difference was observed between the groups in patients with visual impairment (66% in the compliant group and 75% in the non-compliant group) ( $p = 0.25$ ). Only 31% of the non-compli-

**Table 1.** Demographic and clinical characteristics of the older male patients who can comply to CPAP therapy

n	Age (Years) (mean ± SD)	Age at Diagnosis of OSAS (Years)	BMI (kg/m <sup>2</sup> )	Baseline AHI (events/h)	AHI on CPAP	CPAP device Pressure (cm-H <sub>2</sub> O)	CPAP education Group Attendance (n, %)	Counter Data (h/night)
160	72 ± 2.9	*68 ± 3.1	36 ± 12.4	41 ± 6	3 ± 2.1	11 ± 2.1	**152, 95%	7.5 ± 1.2

\*Compared with the non-compliant group  $p = 0.03$ , Student t-test. \*\* $p = 0.006$ , Fisher's Exact Test compared to non-compliant group. BMI, body mass index; CPAP, continuous positive airway pressure; AHI, Apnea-hypopnea index.

**Table 2.** Demographic and clinical characteristics of the older male patients who cannot comply to CPAP therapy

n	Age (Years) (mean ± SD)	Age at Diagnosis of OSAS (Years)	BMI (kg/m <sup>2</sup> )	Baseline AHI (events/h)	AHI on CPAP	CPAP device Pressure (cm-H <sub>2</sub> O)	CPAP education Group Attendance (n, %)	Counter Data (h/night)
104	76 ± 3.6	*74 ± 4.2	34 ± 13.1	26 ± 5	5 ± 2.4	11 ± 1.4	**55, 53%	0.4 ± 0.3

\*Compared with the compliant group  $p = 0.03$ , Student's t test. \*\* $p = 0.006$ , Fisher's Exact Test, Compared with compliant group. BMI, body mass index; CPAP, Continuous positive airway pressure; AHI, Apnea-hypopnea index.



ant group and 56% of the compliant group had a previous diagnosis of a psychiatric illness, but this difference was statistically insignificant ( $p = 0.42$ ).

On average, the compliant patients had been using the CPAP for a longer time than the non-compliant patients when the records were reviewed ( $3.5 \pm 0.65$  years,  $2.4 \pm 0.64$  years, respectively;  $p = 0.24$ ). However, this difference is statistically insignificant. The incidence of complications from the use of the CPAP mask tended to be higher in the non-compliant patients. The impediment grade was 41% in non-compliant patients in contrast with 10% in compliant patients ( $p = 0.07$ ), but results obtained from the report reveal that in both groups the complication rate was low. As presented in Table 3, the impediments most frequently seen were mask-related nasal problems.

Complaints of nocturia were higher in the non-compliant group than in the compliant group (82%, 33%, respectively;  $p = 0.02$ ). Remarkably, diuretic medicine was being used by many more patients in the compliance group than in the non-compliant group. Therefore, complaints of nocturia frequency from the non-compliant patients were

not linked with diuretic usage.

An urology specialist physician diagnosed BPH in a significant number of non-compliant patients than in the compliant group (62%, 15%, respectively;  $p = 0.004$ ). However, the available medical records did not indicate the number of night awakenings to urinate.

The baseline AHI value was higher in the CPAP compliant group than the CPAP non-compliant group ( $41 \pm 6$ ,  $26 \pm 5$ , respectively;  $p = 0.08$ ). When the initial sleep research was done, the lowest oxygen saturation recorded for the compliant group was  $76\% \pm 5\%$ , and in the non-compliant group it was  $70\% \pm 2\%$ ; however, the difference between them was statistically insignificant ( $p = 0.25$ ). No statistically significant difference was detected in the mean CPAP pressure required for adequate therapy of the two OSAS groups ( $p = 0.40$ ). While 20% of the compliant patients needed supplemental oxygen with their CPAP therapy, 8% of the non-compliant patients required additional oxygen, and there was no statistically significant difference ( $p = 0.44$ ).

Early improvement of symptoms and resolution of symptoms with CPAP therapy was achieved for

**Table 3.** Complications of CPAP therapy in older male patients with OSAS

Side effect	Compliant group n, (%)	Non-compliant group n, (%)
Nasal congestion	0 (0)	16 (17)
Skin irritation	0 (0)	8 (8)
Mouth dryness	8 (5)	0 (0)
Nose dryness	0 (0)	8 (8)
Ear irritation	8 (5)	0 (0)
Cold nose	0 (0)	8 (8)

152 of the 160 compliant patients and 55 of the 104 non-compliant patients. The usual symptoms reported in both groups were excessive daytime sleepiness, snoring, and sleep obstruction. Excessive daytime sleepiness refers to feeling sleepy during the day. Sleep disturbance was indicated by awakening at night when the patients felt disturbed during their sleep. While an 95% resolution occurred in the OSAS symptoms in the compliant CPAP user patients, only 84% of the patients in the non-compliant group experienced symptom improvement ( $p = 0.002$ ). Excessive daytime sleepiness and sleep disturbances were resolved in 100% of the compliant patients. However, excessive daytime sleepiness and sleep disturbance improved significantly less in the non-compliant group ( $p = 0.0001$ ,  $p = 0.04$ , respectively). Statistically significant variance was not found between the two groups in their mean AHI, as measured during the first CPAP test, in contrast to their overall symptom response ( $p = 0.08$ ).

## DISCUSSION

The research analyzed compliance with CPAP therapy in older male patients with OSAS. Patients selected were males of aged 65 years and above. We measured their compliance with treatment objectively, using the time meter.

Different clinical, behavioral, and functional variables that have a relationship with CPAP device compliance were examined. While some complaints that are encountered infrequently, such as painful eyes, were mentioned in previous studies on general CPAP compliance, due to the retrospective nature of the research, we evaluated only those factors that have been reported as affecting compliance, as these were included in the medical records. The design of this study was subject to certain limitations, and the retrospective design may be a limitation of our study. Furthermore, various comparisons were made, despite the probability that certain factors that were only randomly associated could be excluded (for example, the presence of BPH and

age at diagnosis of OSAS). As a result of the limited number of patients, the research showed a tendency to arrive at statistical significance when comparing variables. Mean age at detection of OSAS indicated a significant difference between the compliant and non-compliant groups. The compliant patients were younger when their OSAS was first detected and their CPAP therapy started. Advancing age in the elderly population affected compliance with CPAP therapy. Certain conditions associated with advancing age affected the use of CPAP, such as cognitive failure and loss of physical ability. Further research should focus on cognitive and physical functioning in elderly patients with OSAS as this could identify factors that may restrict CPAP compliance.

Some studies have suggested that smokers are less compliant with medication than non-smokers (9). When CPAP therapy was started with our patients, smoking was found to be associated with non-compliance, while alcohol intake had no effect on differences relating to CPAP compliance. However, the value of this information is limited due to a lack of information regarding the quantity of alcohol drunk. Larger, prospective studies investigating tobacco and alcohol use in relation to CPAP compliance may determine the impact of these habits on OSAS patients.

The research noticed significant compliance improvement in patients who attended the CPAP education programme. This result is consistent with the results of a similar study investigating CPAP compliance and involving patients of various ages (10). Significant compliance variance can be detected in patient groups that undergo the education program with sleep technicians or with clinicians who are aware of the CPAP devices (11). Voluntary participation in a patient program and support group may reflect individual traits. When patients acknowledge their OSAS, their need for CPAP, and the help they derive from the program, there will be a natural tendency for both compliance and symptoms to improve. However, to ensure the conditions for the



compliance of patients with CPAP therapy, prospective analysis would need to be applied.

Nocturia refers to awakenings at night during sleep to urinate for a minimum of two times in a total ten-hour period of sleep (12). Nocturia mostly affects older patients and is reported in 80% of adults aged 65 and above (13). Untreated OSAS was stated as a cause of nocturia in one study (14). It was described previously that 79.4% of awakenings are caused by the need to urinate when sleeping; however, the same study showed that the awakenings were actually caused by sleep apneas, hypopneas, snoring, or regular limb motion. It has been suggested that OSAS patients feel an urgent need to urinate when they are awakened during sleep by apnea or hypopnea due to an abnormal urine output pattern. It is shown that patients with OSAS have higher fractional urine streams and a lower percentage of filtered sodium reabsorption than patients who do not (15). Renal function has an effect on atrial natriuretic peptide (ANP) levels, where more negative intrathoracic pressure from respiratory effort against a closed glottis generates additional venous return and hypoxemia. As a result, hypoxemia has an effect on pulmonary vasoconstriction and right ventricular overload with right atrial distension, which is another trigger for ANP release (16). OSAS therapy with CPAP suggests a lowered urine output, but the ANP volume indicates no relationship to the extent of CPAP therapy (17). In this study, despite the application of the instruments provided, there was a rise in complaints of nocturia among the non-compliant patients; however, we discovered that the incidence of BPH detected by the physicians was significantly higher in the non-compliant group. Unless the symptoms of BPH have been resolved, the existence of a subset of OSAS patients who are less likely to follow the CPAP therapy plan must be acknowledged.

Interestingly, the incidence of diuretic use was higher in the compliant patients. There is a possibility that the use of diuretics might have an effect

on the congestive heart failure therapy that is associated with sleep-disordered breathing. However, a prospective trial would be needed to authenticate or reject the clinical significance of the use of diuretics on CPAP compliance among older patients with OSAS.

It is unlikely that the factors that differ between the compliant and non-compliant groups are prostate-related, except for the age factor. In our study, we discovered that the younger patients complied better with the CPAP therapy. Statistical assessment of this possible interdependence is determined by the size of the study population. We discovered statistically insignificant variance between compliant and non-compliant patients in the baselines for AHI, mean lowest oxygen saturation levels in the first sleep study, and prescribed CPAP pressure. Furthermore, the percentage of patients responding to CPAP therapy rose significantly in the compliant group. This is in uniformity with other research in the literature (18-20). It can be considered that the resolution of symptoms is the primary reason for patients continuing with such a potentially disturbing treatment. Problems with the CPAP mask increase the risk of non-compliance. Therefore, it is vital for patients to maintain a CPAP pressure that effectively treats their OASA so that compliance with CPAP and symptom resolution will increase. For this reason, impediments produced by the mask need to be ascertained and redressed in CPAP immediately. In addition, it is important for the elderly with OSAS to access a trained healthcare technician with knowledge of CPAP devices in order to be equipped with a suitable apparatus that will ensure their comfort.

## CONCLUSION

The CPAP records for the last 6 months of older men with OSAS were examined to ascertain factors that linked with treatment compliance. Compliant patients were, on average, younger than non-compliant patients when their OSAS was diagnosed, and they participated better in the CPAP patient

training group. Complete resolution of OSAS symptoms through the use of CPAP happened more frequently in the compliant patient group. Non-compliant patients smoked more, complained more of nocturia, were more often diagnosed with BPH, and experienced more side effects from the CPAP

mask. Some of these factors, particularly BPH, are peculiar to older men with OSAS. To validate our study, a huge prospective trial would be required. Additional research is needed to contrast the rates of compliance and the factors affecting compliance between young and old patients.

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## RESEARCH

# BLADDER PRESERVATION WITH IMAGE-GUIDED RADIOTHERAPY FOR ELDERLY PATIENTS WITH MUSCLE-INVASIVE BLADDER CANCER: A SINGLE INSTITUTION EXPERIENCE

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.213  
2021; 24(2): 174-184

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Received: Mar 04, 2021  
Accepted: May 16, 2021

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## ABSTRACT

**Introduction:** The number of elderly patients with bladder cancer is expected to triple in the coming years in proportion to the increasing elderly population in the world. The aim of this study was to identify the prognostic factors affecting survival among elderly patients undergoing chemoradiotherapy for muscle-invasive bladder cancer.

**Materials and Method:** We retrospectively reviewed medical records from 93 biopsy-proven nonmetastatic elderly patients with bladder cancer  $\geq$  65 years who were treated with helical tomotherapy. The patients received 64.8 Gy to the bladder with concurrent intravenous cisplatin (40 mg/m<sup>2</sup>) chemotherapy weekly as a radiosensitizer.

**Results:** The mean follow-up time was 34.1 months (range, 4.0–99.1 months). The two- and five-year overall survival, disease-free survival, and cancer-specific survival rates were 70.6%, and 36.9%, 50.6% and 28.5%, 89.1%, and 58.5%, respectively. Multivariate analysis indicated that urothelial obstruction was an independent prognostic factor affecting survival rates. No grade 4 adverse events and deaths attributable to treatment occurred during chemoradiotherapy

**Conclusion:** Image guided radiotherapy with chemotherapy as a bladder-sparing approach is a tolerable alternative therapeutic option without severe acute and late toxicities in elderly patients who are unfit for radical cystectomy or refuse surgery.

**Keywords:** Radiotherapy, Image-Guided; Chemoradiotherapy; Urinary Bladder Neoplasms



## INTRODUCTION

Bladder cancer (BC) represents about 5%–10% of male cancers in Europe and United States and is the fourth most common cancer in men in the western world after prostate, lung, and colon cancers (1). Tobacco smoking and occupational exposure to aromatic amines are the most commonly accepted risk factors for BC. Age, stage, and gender are also the main recognized factors affecting the survival and prognosis of patients with BC (2).

BCs are often classified as non-muscle invasive, muscle-invasive, or metastatic. If left untreated, muscle-invasive bladder cancer (MIBC) is potentially lethal, with a five-year survival rate of ~15%. The mainstay treatment for MIBC is radical cystectomy and bilateral pelvic lymph node dissection with neoadjuvant cisplatin-based chemotherapy (3).

In recent years, there has been an increasing trend for organ-preserving approaches across multiple cancer types (e.g., breast, kidney, prostate, anal, and laryngeal cancers). This trend includes the development of various strategies involving definitive non-cystectomy surgical resection in combination with chemotherapy and radiation therapy (RT), which achieves five-year survival rates of 50%–60% and maintains an intact bladder in over 70% of patients (4). Although RT alone is a method of bladder preservation, the treatment response is lower at 56%; there is also a relatively high rate of local recurrence or persistence that can lead to a need for salvage cystectomy (5).

The addition of chemotherapy to RT resulted in improved local control, good long-term bladder function, and a reduced rate of the need for cystectomy (6). Based on data from trials, RT alone has been avoided in cases who can tolerate concurrent chemoradiotherapy (CRT). However, concomitant therapy may be more challenging due to the severe hematologic and renal toxicities. Bladder-preservation strategies are attractive for elderly patients with greater comorbidities who are not candidates for surgery (7), but it is also known that these patients

cannot tolerate most chemotherapy regimens. In this study, we aimed to identify the prognostic factors affecting survival among elderly patients undergoing chemoradiotherapy for muscle-invasive bladder cancer.

## MATERIALS AND METHOD

The current study protocol was approved by the Ethics Committee in our hospital. Data from 93 patients with biopsy-confirmed MIBC who underwent concurrent CRT between January 2011 and December 2018 at our Radiation Oncology Department were retrospectively reviewed. All the involved patients included either rejected surgery or were not suitable for surgery due to comorbidities. Table 1 shows the patient and tumor characteristics.

Cystoscopic evolution with transurethral resection (TUR) was applied prior to CRT. The American Joint Committee on Cancer 7th edition 2010 TNM staging system was used as a reference for tumor staging. Computed tomography (CT) and magnetic resonance imaging (MRI) were used to detect intrapelvic and regional lymph nodes.

### CRT

RT was performed by a tomotherapy accelerator using 6 MV photons and delivering a median total dose of 64.8 Gy (range, 40.6–66.6) in a 1.8 Gy/fraction. Daily megavoltage computed tomography was acquired for patient positioning. Clinical target volume encompassed the urinary bladder, which was identified on contrast-enhanced CT or MRI with a 2 cm margin. In each fraction, an empty bladder was compulsory. Cisplatin at 40 mg/m<sup>2</sup>/week was started on day 1 and given within 60 minutes of IV infusion, which was continued weekly until the last week.

Total blood counts and kidney function tests were performed weekly, and chemotherapy dose reduction was applied when ≥ grade 3 hematologic and renal toxicities were experienced

**Table 1.** Patient and tumor characteristics

Characteristic		n (%)
Gender		
	Male	84 (90.3)
	Female	9 (9.7)
Age (years)		
	Mean ± SD	73.86 ±9.1
	Range	44-91
Tumor size (cm)		
	≤5	46 (49.5)
	>5	18 (19.4)
	Unknown	29 (31.1)
Procedure		
	Complete TUR	29 (31.9)
	Incomplete TUR	62 (68.1)
Histopathological type		
	LGPUC	6 (6.5)
	HGPUC	72 (77.4)
	Mixt, Other	15 (16.1)
T Stage		
	I	4 (4.3)
	II	70 (75.3)
	IIIa	9 (9.7)
	IIIb	-
	IVa	10 (10.7)
Node Status		
	N0	80 (89.9)
	N1-2	9 (10.1)
Grade		
	I- II	6 (6.5)
	III-IV	87 (93.5)
Urothelial obstruction		
	No	76 (82.6)
	Yes	16 (17.4)

Abbreviations: TUR=transurethral resection of the bladder, HGPUC= high-grade papillary urothelial carcinoma, LGPUC= low-grade papillary urothelial carcinoma; Mixt = adenosquamos; Other = Squamos, adeno cancer, undifferentiated carcinoma, small cell carcinoma.

### Evaluation and follow-up

Tumor response was assessed through a combination of cystoscopy and CT four to six weeks after finishing treatment. Subsequent radiologic and cystoscopic follow-up was performed once every three months for two years and then once every six months.

### Statistical analysis

The analysis was performed using SPSS version 13 software. Overall survival (OS) was calculated from the completion of CRT to the date of death or last follow-up. Disease-free survival (DFS) was defined as the time from the completion of CRT to the date of local recurrence or progression. Cancer-specific survival (CSS) was documented as the time from completion of CRT to death due to disease.

Kaplan–Meier survival analysis was used to examine the distribution of survival times. A Log-rank test was used to determine the difference in survival between the groups. Bonferroni correction was applied in the comparisons between the groups. In the multivariate analysis, independent predictors of survival were examined using Cox regression analysis. Chi-square and Fisher's exact test were used to determine the factors influencing treatment response. Cases below 5% of type-1 error levels were accepted as statistically significant.

## RESULTS

### Patients and tumor characteristics

A total of 93 patients were included in this study. The mean follow-up time was 34.1 months (range, 4.0–99.1 months). By the end of the follow-up period, 39 patients were still alive while 54 had died. The median age of patients was 75 years (range, 44–91). Data showed a clear male preponderance of approximately 9.3:1. Overall, 77.4% of the patients had high-grade disease. About 32% of the patients



had undergone complete TUR, and 68% underwent incomplete TUR. Table 1 summarizes the patient characteristics.

#### Proportional hazards analysis

Multivariate and univariate analyses were used to provide quantitative estimates of the association of the following 10 clinical and pathological tumor factors with OS, DFS, and CSS in the 93 patients studied: age (<70 and >70), gender, tumor histology, tumor size (5 cm and >5 cm), tumor grade (good, medium, and poor or undifferentiated), T stage (1, 2, and 3–4), nodal status, urothelial obstruction, initial TUR procedure (complete or incomplete), and treatment response.

The results of univariate analysis to determine the prognostic factors showed that urothelial obstruction ( $P = 0.013$ ) and treatment response ( $p < 0.001$ ) had significant effects on OS. TUR procedure ( $P = 0.062$ ) was closely significant (Table 2). The multivariate analysis revealed a significant relationship between urothelial obstruction and OS (hazard ratio [HR]: 1.5; 95% CI: 3.6 (1.4–9.3);  $P = 0.007$ ) (Table 3).

Urothelial obstruction ( $P = 0.038$ ), TUR procedure ( $P = 0.047$ ) and treatment response ( $p < 0.001$ ) had significant effects on DFS in the univariate analysis (Table 4). The multivariate analysis indicated that urothelial obstruction (HR: 1.5; 95% CI: 5.6 (1.8–17.3);  $P = 0.003$ ) was significant (Table 3).

From univariate analyses, the variables determined as statistically significant prognostic factors on CSS included urothelial obstruction ( $p < 0.001$ ) and treatment response ( $P = 0.001$ ) (Table 5). Multivariate analysis indicated that urothelial obstruction (HR: 1.5; 95% CI: 2.7 (1.1–6.5);  $P = 0.031$ ) was significant (Table 3).

#### Overall Survival

The median OS was 36.6 months (95% CI: 19.6–53.7). The two- and five-year OS rates were 70.6%

and 36.9%, respectively (Figure 1). The overall actuarial survival was significantly better among the 60 patients with complete responses than among the 25 with incomplete responses to the CRT. The five-year OS rate was 49.1% for patients with complete responses but dropped to 10.6% for patients with incomplete responses ( $p < 0.001$ ). The 76 patients who did not have urothelial obstruction at presentation had significantly better OS. The two-year OS rate was 74.4% for patients without urothelial obstruction at presentation but dropped to 57.4% for patients with urothelial obstruction ( $P = 0.007$ ).

#### Disease-Free Survival

The median DFS was 24.5 months (95% CI: 14.5–34.6). The two- and five-year DFS rates were 50.6% and 28.5%, respectively. The 29 patients with initial complete TUR had significantly better DFS than did the 62 with incomplete TUR. The five-year DFS rate was 50.7% for patients who underwent complete TUR but dropped to 20.9% for patients with complete TUR ( $P = 0.047$ ). The overall actuarial survival was significantly better among the 60 patients with complete responses than among the 25 with incomplete responses to the CRT. The five-year DFS rate was 39% for patients with complete responses but dropped to 6.4% for patients with incomplete responses ( $p < 0.001$ ). OS was significantly better among the 76 patients who did not have urothelial obstruction at presentation. The two-year DFS rate was 54.3% for patients without urothelial obstruction at presentation but dropped to 36.5% for patients with urothelial obstruction ( $P = 0.038$ ).

#### Cancer-Specific Survival

The median CSS was 69.3 months (95% CI: 39.6–99). The two- and five-year CSS rates were 89.1% and 59.5%, respectively. The overall actuarial survival among the 60 patients with complete responses was significantly better than among the 25 with incomplete responses to the CRT. The five-year CSS

**Table 2.** Results of log-rank univariate analysis for overall survival

Variable	n	Median Survival (95% CI)	2-y OS (%) (±SE)	5-y OS (%) (±SE)	p value
Age (year)					
<70	23	57.4 (38.8-76.0)	74.8 (±0.11)	58.2 (±0.14)	0.345
70≤	70	46.3 (38.1-54.5)	69.7 (±0.06)	32.4 (±0.07)	
Gender					
Male	84	36.6 (21.6-51.7)	71.5 (±0.05)	38.5 (±0.07)	0.363
Female	9	24.5 (19.0-30.1)	62.5 (±0.17)	25 (±0.15)	
Tumor diameter (cm)					
≤5	46	55.2 (15.2-95.3)	74 (±0.07)	46.6 (±0.09)	0.455
> 5	18	33.5 (13.8-53.3)	75 (±0.11)	32.1 (±0.13)	
Tumor histologic					
LGPUC	6	54.4 (2.5-106.3)	66.7 (±0.19)	50 (±0.20)	0.305
HGPUC	72	33.5 (26.9-40.2)	69.5 (±0.06)	30.7 (±0.07)	
Mixt, Other	15	67.9 (0-136.9)	76.9 (±0.12)	52.7 (±0.14)	
Histologic grade					
G1-G2	6	54.4 (2.5-106.3)	66.7 (±0.19)	50 (±0.20)	0.835
G3-G4	87	34.4 (23.2-45.6)	70.9 (±0.05)	35.8 (±0.06)	
T Stage					
T1	4	17.9 (6.8-29.1)	33.3 (±0.27)	33.3 (±0.27)	0.878
T2	70	36.6 (18.2-55.1)	70.6 (±0.06)	39.5 (±0.07)	
T3-4	19	33.5 (0-72.9)	76.5 (±0.10)	27.9 (±0.13)	
Node Status					
N0	80	40.4 (23.2-57.5)	73.8 (±0.05)	38.4 (±0.07)	0.511
N1-2	9	29.6 (0.2-59.1)	66.7 (±0.16)	22.2 (±0.19)	
Urothelial obstruction					
No	76	49.9 (29.9-69.9)	74.4 (±0.05)	42.9 (±0.07)	0.013
Yes	16	29.6 (16.6-42.7)	57.4 (±0.13)	0	
Procedure					
Complete TUR	29	65.1 (31.3-98.8)	79.1 (±0.08)	54.1 (±0.12)	0.075
Incomplete TUR	62	29.6 (22.4-36.9)	67.9 (±0.06)	30.5 (±0.07)	
Treatment response					
No	25	24.5 (12.6-36.5)	50.1 (±0.10)	10.6 (±0.09)	<0.001
Yes	60	55.2 (36.5-73.9)	81.3 (±0.05)	49.1 (±0.08)	

Abbreviations: TUR=transurethral resection of the bladder, HGPUC=high-grade papillary urothelial carcinoma, LGPUC= low-grade papillary urothelial carcinoma.



**Table 3.** Results of multivariate analysis for overall survival, cause-specific survival and disease-free survival by Cox proportional hazard model

Variable	Overall survival		Cause-specific survival		Disease-free survival	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age (year) <70 vs 70≤	1.9 (0.6-5.3)	0.255	1.1 (0.3-4.2)	0.851	1.3 (0.5-3.3)	0.542
Gender Male vs Female	0.8 (0.2-2.6)	0.665	2.2 (0.6-8.6)	0.247	0.8 (0.2-2.7)	0.677
Tumor diameter (cm) 5≤ vs >5	1.0 (0.4-2.4)	0.990	0.9 (0.3-2.8)	0.894	0.9 (0.4-2.1)	0.778
Tumor histologic LGPUC vs HGPUC LGPUC vs Mixt, Other	0.5 (0.1-2.4) 0.3 (0.1-1.9)	0.449 0.410 0.214	2.2 (0.2-22.6) 0.8 (0.1-10.1)	0.392 0.503 0.831	0.6 (0.1-2.6) 0.3 (0.1-1.9)	0.405 0.501 0.218
T Stage T2 vs T1 T2 vs T3-4	1.6 (0.2-13.5) 1.5 (0.6-3.9)	0.641 0.652 0.383	0.9 (0.4-1.2) 2.5 (0.8-8.1)	0.304 0.986 0.123	0.8 (0.1-6.5) 1.5 (0.6-3.5)	0.643 0.849 0.372
Node Status N0 vs N1-2	0.6 (0.1-2.8)	0.507	0.9 (0.2-4.6)	0.899	0.7 (0.2-3.3)	0.676
Urothelial obstruction No vs Yes	3.6 (1.4-9.3)	0.007	5.6 (1.8-17.3)	0.003	2.7 (1.1-6.5)	0.031

Abbreviations: CI=confidence interval; HGPUC=high-grade papillary urothelial carcinoma; LGPUC= low-grade papillary urothelial carcinoma.

rate was 69.6% for patients with complete responses but dropped to 35.4% for patients with incomplete responses (P = 0.001). CSS was significantly better among the 76 patients who did not have urothelial obstruction at presentation. The two-year CSS rate was 93.3% for patients without urothelial obstruction at presentation but dropped to 68.4% for patients with urothelial obstruction (p ≤ 0.001).

### Toxicity

Grade 1 and 2 toxicities could not be evaluated due to the missing files and records of the patients. We recorded higher grade toxicities from registered nurses orders and patient recipes. Concurrent chemotherapy was interrupted in an overall four pa-

tients due to grade 3 hematological toxicities were observed. The percentages of patients sustaining acute bladder irradiation, fatigue, and diarrhea were 32%, 43%, and 10%, respectively. There were no late grade 4 toxicities and deaths attributable to the treatment.

### DISCUSSION

Population aging is a shift in the distribution of people toward older ages with increasing life expectancy. Although age is known as a poor prognostic factor, the geriatric patient population is a heterogeneous group, and the chronological age of the patient does not always reflect their actual health status (8). To choose treatments wisely, an estimate

**Table 4.** Results of log-rank univariate analysis for disease-free survival

Variable	n	Median Survival (95% CI)	2-y DFS (%)	5-y DFS (%)	p value
Age (year)					
<70	23	14.9 (4.4-25.3)	40.9	40.9	0.825
70≤	70	28 (18-38)	53.2	25.2	
Gender					
Male	84	25.5 (14.9-36.2)	50.7	28.7	0.679
Female	9	17.9 (7.5-28.3)	50	25	
Tumor diameter (cm)					
≤5	46	32.3 (8.9-55.8)	53.4	35.2	0.686
>5	18	40.4 (0-86.7)	57.1	34.8	
Tumor histologic					
LGPUC	6	14.9 (0-54)	50	33.3	0.170
HGPUC	72	21.9 (13.5-30.2)	46.7	20.9	
Mixt, Other	15	67.2 (0-134.9)	69.2	52.7	
Histologic grade					
G1-G2	6	14.9 (0-54)	50	33.3	0.505
G3-G4	87	24.5 (14.9-34.2)	50.7	28	
T Stage					
T1	4	17.9 (6.8-29.1)	33.3	33.3	0.979
T2	70	25.5 (14-37.1)	50.5	27.8	
T3-4	19	24.5 (0-52)	53.5	28.5	
Node Status					
N0	80	25.5 (14.5-36.6)	51.5	28.2	0.906
N1-2	9	29.6 (19.8-39.4)	55.6	27.8	
Urothelial obstruction					
No	76	31.8 (13.4-50.2)	54.3	33.1	0.038
Yes	16	19.1 (7.1-31.2)	36.5	0	
Procedure					
Complete TUR	29	65 (25.1-105)	71.9	50.7	0.047
Incomplete TUR	62	21.1 (14.8-27.5)	43.3	20.9	
Treatment response					
No	25	43.5 (21.5-65.6)	21.2	6.4	<0.001
Yes	60	10.7 (6.5-15)	63.2	39	

Abbreviations: TUR=transurethral resection of the bladder, HGPUC= high-grade papillary urothelial carcinoma, LGPUC= low-grade papillary urothelial carcinoma; Mixt = adenosquamos; Other = Squamos, adeno cancer, undifferentiated carcinoma, small cell carcinoma.

of life expectancy should be considered against the risk of cancer relapse or cancer-related death during treatment plan.

BC is an age-associated malignancy with increased prevalence in patients aged ≥ 65 years (9). Bladder tumors are the fourth most frequently diagnosed cancer type in males and the ninth in females (10). The histological grade of BC is eventu-

ally determined by examining the resected tumor. The most widely used classification for grading non-MIBC (G1, G2, and G3) was the 1973 World Health Organization (WHO) classification (11). However, a revised grading system for urothelial carcinoma (low grade and high grade) was proposed and adopted by the WHO in 2004 to replace the 1973 classification system. The natural history of BC is heteroge-



neous, ranging from a low-grade variant to a high-grade subtype (12,13). Wakai et al. reported the distribution of tumor grades were as follows: 74% high grade and 26% low grade (14). In our study high, low, and mixed grades were present in 77%, 7%, and 16% of patients, respectively.

Thus far, bladder-sparing approaches using RT alone have not yielded comparable results with radical cystectomy and lymphadenectomy. To improve the efficacy of radical RT, neoadjuvant or concomitant chemotherapy has been administered. Currently, platinum-based chemotherapy has been advocated for CRT as an alternative to radical cystectomy in MIBC (15). The most comprehensive TUR for invasive BC, followed by RT with the concurrent administration of cisplatin, was fairly well tolerated by the patients we studied. Treatment-related toxicities are generally reversible and comparable and are slightly lower than with other studies (16). The typical dose schedules of RT would be 64 Gy in 32 fractions or hypofractionated schedules such as 55 Gy in 20 fractions. Many studies have used 64–66 Gy, but the definite optimal RT dose is unknown (17). Korpics et al. conducted a retrospective cohort study involving 843 patients with cT2-4 N0-3 M0 transitional cell MIBC treated with RT and found that patients receiving RT were more likely to receive an RT dose of 60 Gy. The two-year OS rates, when divided by RT doses, were 26%, 31%, 56%, and 55% for <50, 50–59, 60–66, and >66 Gy, respectively, and analyses showed that <50 Gy doses were associated with worse survival outcomes (18). In our study, we utilized 64 Gy, and the two-year OS rate was 70.6%. The obtained OS rate was higher than that in Korpics et al.'s study, and this difference could be due to the addition of chemotherapy and RT technique.

Neoadjuvant or concomitant chemotherapy has been added to improve the efficacy of radical RT. The addition of chemotherapy is aimed to eliminate the micrometastases and increase the radiation sensitivity. In this way, the Radiation Oncology

Group (RTOG) designed a series of studies that examined the efficacy of peritreatment chemotherapy. In the first study, RTOG 8512, 64 Gy RT with cisplatin was administered in 42 patients. The five-year OS rate with radiosensitizing cisplatin was 52% (19). The RTOG 99-06 study assessed the effect of chemotherapeutic agents on the weekly use of cisplatin and paclitaxel simultaneously with RT, and the five-year OS rate was reported to be 50% (20). The five-year survival reported by other authors ranged from 47% to 54%. Concurrent chemotherapy was continued in 80.7 % of patients. Gemcitabine was interrupted due to grade 3 thrombocytopenia in one patient (21). In our study, we found a five-year OS rate of 36.9 %, which is lower than those of other studies. This result may be due to the inclusion of more patients undergoing incomplete TUR and our cohort being older. Concurrent chemotherapy was given as a part of CRT in 89 patients (95.6%).

There are two randomized trials of radiosensitization using UK schedules: the BC2001 and BCON studies. These trials use radiosensitization with either concurrent chemotherapy (BC2001) or carbogen and nicotinamide (BCON). BC2001 has shown significant improvement in DFS with concurrent 5-fluorouracil and mitomycin C of 34% (22,23). Hussain et al. reported a phase I/II study of synchronous CRT with mitomycin C and 5-FU in 41 patients and obtained two- and five-year OS rates of 49% and 36%, respectively (24). In our study, we found the two-year OS rates were 70.6% respectively, which is higher than those of the above-mentioned trials due to the addition of cisplatin.

The radicality of TUR in bladder-sparing treatment was reported to be an independent prognostic factor for the survival of patients with MIBC. Asadauskienė et al. showed a statistically significant difference between complete and incomplete TUR in terms of OS. Data from this study demonstrated an impact of patient age, T stage, and dose of radiation on survival of patients treated by radiotherapy. (25). In the current study, we characterized urothelial

**Table 5.** Results of log-rank univariate analysis for cause-specific survival

Variable	n	Median Survival (95% CI)	2-y CSS (%)	5-y CSS (%)	P value
Age (year)					
<70	23	63.9 (46.9-80.8)	84.6	65.8	0.731
70≤	70	65.9 (55.7-76)	89.9	57.4	
Gender					
Male	84	81.5 (65-98.1)	89.6	63.6	0.256
Female	9	25.4 (0-61.2)	83.3	33.3	
Tumor diameter (cm)					
≤5	46	69.3 (53.3-85.3)	88.6	66.2	0.357
>5	18	40.4 (13.1-67.6)	85.7	36.7	
Tumor histologic					
LGPUC	6	77.3 (64.3-90.2)	100	75	0.245
HGPUC	72	61.1 (50.4-71.7)	86	52.8	
Mixt, Other	15	79.3 (60.8-97.8)	100	80	
Histologic grade					
G1-G2	6	77.3 (64.3-90.2)	100	75	0.360
G3-G4	87	65.8 (56.2-75.4)	88.4	59.4	
T Stage					
T1	4	80.1 (63.2-97)	100	100	0.204
T2	70	70.8 (60.7-81)	89.1	68.7	
T3-4	19	51.6 (34.5-68.7)	87.1	31.7	
Node Status					
N0	80	81.5 (59.5-103.5)	90.4	60	0.339
N1-2	9	34.3 (4.6-64)	76.2	38.1	
Urothelial obstruction					
No	76	97 (65-128.9)	93.3	67.9	<0.001
Yes	16	33.5 (13.8-53.3)	68.4	0	
Procedure					
Complete TUR	29	73.9 (57.4-90.3)	91.1	62.3	0.371
Incomplete TUR	62	63.7 (52.4-75)	87.7	58	
Treatment response					
No	25	48.1 (27.8-68.4)	75.1	35.4	0.001
Yes	60	74.9 (64.9-84.9)	94	69.6	

Abbreviations: TUR=transurethral resection of the bladder, HGPUC=high-grade papillary urothelial carcinoma, LGPUC= low-grade papillary urothelial carcinoma



obstruction and the status of treatment response as significant prognostic factors that predict OS and CSS in the univariate analysis. However, the status of treatment response lost its statistical significance when included in a multivariate analysis with the factors that were significantly associated with survival in the univariate analysis. Considering the likelihood of 76 patients without urothelial obstruction surviving two years with a functioning, treated bladder (54.3%), the bladder-sparing approach is relatively encouraging compared to 16 (36.5%) patients with urothelial obstruction.

### Study Limitations

Our study includes the following limitations: first, our study was single institutional and retrospective; and second, T stage was not detected as a signifi-

cant prognostic factor for a relatively small number of patients.

### CONCLUSION

Our study supports the utilization of CRT for BC in routine practice. Concomitant cisplatin was administered in all patients without any omission due to toxicity. There was no grade 3 intestinal or genitourinary side effects recorded. Grade 3 hematologic post-treatment toxicity occurred in four patients.

The authors declare no conflict of interest.

Funding: The funders had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.214  
2021; 24(2): 185-195

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Received: Feb 17, 2021  
Accepted: Apr 16, 2021

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#### RESEARCH

## RETINAL NEURODEGENERATION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE AN OPTICAL COHERENCE TOMOGRAPHY STUDY

### ABSTRACT

**Introduction:** Recent developments suggest that optical coherence tomography can play an important role in diagnosing and following-up neurodegenerative diseases, including Alzheimer's disease. This study evaluates optical coherence tomography findings in mild cognitive impairment and middle-stage Alzheimer's disease patients.

**Materials and Method:** Seventy patients with amnesic type mild cognitive impairment, 54 patients with middle-stage Alzheimer's disease, and 54 cognitively healthy individuals were included. All study participants were evaluated with neuropsychological tests, ophthalmological examination, and optical coherence tomography. Ganglion cell complex and retinal nerve fiber layer thicknesses were measured, and comparisons were made between groups.

**Results:** Inferior temporal and inferior retinal nerve fiber layer thicknesses were thinner in the middle-stage Alzheimer's disease group than in the control and mild cognitive impairment groups. After statistical corrections, the inferior and inferior temporal retinal nerve fiber layers were thinner in the middle-stage Alzheimer's disease group compared to the control and mild cognitive impairment groups. Besides, the nasal and nasal lower retinal nerve fiber layers were thicker than the control group. No statistically significant difference was found between the groups in terms of mean, superior and inferior ganglion cell complex thickness.

**Conclusion:** The results showed that retinal axon loss might develop in Alzheimer's disease. This loss may be focal, and the inferior temporal region may have selective sensitivity. Optical coherence tomography might reflect the neuropathological process in Alzheimer's disease, contribute to the diagnosis and follow-up. However, it is not helpful in the early diagnosis of Alzheimer's disease because of the lack of difference between mild cognitive impairment and control groups.

**Keywords:** Alzheimer Disease; Tomography, Optical Coherence; Retinal Degeneration; Dementia; Cognitive Dysfunction

## INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of neurofibrillary tangles containing intracellular hyperphosphorylated tau protein and extracellular amyloid  $\beta$  (A $\beta$ ) protein in the brain, clinically resulting in dementia. It is accepted that these neuropathological changes begin 15-20 years before the clinical development of dementia. Mild cognitive impairment (MCI) defines AD's prodromal stage, where objective cognitive problems but not functional loss are observed.

Advances in neuro-electrophysiological examinations and optical imaging have made it possible to evaluate neurodegenerative diseases' effects on the eye. Abnormal bioelectric activity and retinal microvascular changes, especially of retinal ganglion cells, photoreceptors, and the optic nerve, are associated with AD and aging-related pathological processes and cognitive impairment (1, 2). The retina can offer an examination opportunity for early diagnosis of neurodegenerative diseases because it originates from the diencephalon during embryological development and contains a high density of neuronal cells and fibers. The possibility of the coexistence of retinal and brain pathologies is due to their common embryological origins and the similarity of blood-ocular and blood-brain barriers, common immunological responses, and similar sensitivity to damage (3). In the AD mouse model, amyloid- $\beta$  plaques, tau nodes, neurodegeneration, and astrogliosis have been detected in retinal ganglion cells starting from the pre-symptomatic stage (4). Postmortem studies also showed a decrease in the number of ganglion cells in the retina and thinning of the nerve fiber layer in AD (5). In AD, it has been suggested that retinal nerve fiber layer (RNFL) thickness may decrease due to retrograde degeneration of retinal ganglion cell axons (6), and it has been shown that these changes in the retina may occur before the memory is affected (7).

With its high spatial resolution, optical coher-

ence tomography (OCT) is an easily applicable and non-invasive examination that allows the detection of neuro-axonal degeneration by visualizing the retinal nerve tissue with biopsy-like sensitivity. OCT findings consistent with retinal neurodegeneration have been found in AD patients compared to healthy controls, but few studies have evaluated OCT findings in MCI patients (8). On the other hand, it has been shown that RNFL thinness is associated with inferior cognitive functions in individuals without neurodegenerative diseases in baseline evaluation, and it has been reported that retinal neurodegeneration may be a preclinical biomarker for dementia (9,10).

Determining the relationships between retinal changes and aging-related brain processes in healthy older adults, and distinguishing them from pathological changes associated with AD also defining retinal markers, is essential for detecting the transition from the asymptomatic stage of AD to the symptomatic pre-dementia stage or from the symptomatic pre-dementia stage to the dementia stage. OCT examination will be able to contribute to meeting this requirement in the following years. This study evaluates the OCT findings that may be markers of retinal neurodegeneration in middle-stage AD and MCI patients and compares these findings with healthy individuals with normal cognitive functions.

## MATERIALS AND METHOD

### Patient Selection

This study included patients diagnosed with amnesic MCI (aMCI) and mid-stage AD, in addition to volunteers without cognitive impairment. The file records of the patients being followed up in the dementia outpatient clinic of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Neurology, were examined. The selected patients were re-evaluated with a neurological examination, neuropsychologi-



cal tests, and brain imaging, and their diagnosis was confirmed. In addition, patients who applied to the neurology outpatient clinic with complaints of forgetfulness were evaluated similarly, and those diagnosed with aMCI and mid-stage AD were included in the study.

Neuropsychological tests (MMT, MOCA, clock scratching, geriatric depression scale) determined according to the patients' educational status included in the study and the volunteers included in the control group were performed. The patients were evaluated by two different neurology physicians and a psychologist, using neuropsychological tests and their addiction status in daily living activities and clinical observations. Amnesic MCI was diagnosed according to Peterson criteria, and mid-stage AD diagnosis was made according to DSM-V and National Institute on Aging-Alzheimer's Association (NIA-AA) criteria. Ophthalmologic examinations and OCT examinations, including corrected visual acuity, ocular motility, pupillary reflexes, slit-lamp biomicroscopy of the anterior segment, intraocular pressure measurement, and fundus examination, were performed in our hospital's ophthalmology department.

Exclusion criteria applied to patient and control groups included: failure to distinguish between AD and other types of dementia clinically, mixed type dementia, non-amnesic MCI, subjective cognitive impairment, cognitive impairment secondary to depression, systemic, psychiatric, or another neurological disease that may cause cognitive damage, and pathological findings that may affect cognitive functions in brain magnetic resonance imaging (MRI) (except atrophy), diabetes mellitus, inability to perform OCT due to cooperation difficulties, refractive error of more than 3 diopters spherical, 2 diopters cylindrical, glaucoma, retinal vascular occlusive disease, anterior ischemic optic neuropathy, ocular media opacity due to corneal abnormality, cataracts, macular edema, age-related macular degeneration interfering with ocular and/or OCT ex-

amination, and retinal involvement due to diseases such as hypertension and diabetes mellitus.

### Optical Coherence Tomography

After detailed ophthalmological examinations of the patients were performed, an OCT examination was performed by experienced practitioners on the same day using the RTVue SD-OCT system (RTVue-XR 100 Avanti software v.6.1, Optovue, Inc., Fremont, CA, USA). While evaluating the macula and optic nerve head, RNFL and ganglion cell complex (GCC) thickness were measured separately in both eyes. The measurements were repeated three times for each eye to reduce measurement errors.

The RSLT 3.45 protocol was used for peripapillary RNFL analysis, and peripapillary RNFL thickness was measured in a circular area of 3.45 mm diameters around the center of the optic disc. Peripapillary RNFL thickness maps were expressed as a numerical value, and each of the eight segments in four quadrants was evaluated by color-coding (superior:  $46^\circ$  -  $135^\circ$ ; nasal:  $316^\circ$  -  $45^\circ$  for right,  $136^\circ$  -  $225^\circ$  for left; inferior:  $226^\circ$  -  $315^\circ$ ; temporal:  $136^\circ$  -  $225^\circ$  for right and  $316^\circ$  -  $45^\circ$  for left). Parameter values within the normal range ( $p > 5\%$ ) are in green, parameter values outside the normal range for age ( $p < 5\%$  and  $\geq 1\%$ ) in yellow, and abnormal parameter values ( $p < 1\%$ ) in red. The results were displayed on a color map with customized software with normative data adjusted for age and optical disc size.

RNFL thickness was obtained from all octameric section parameters: temporal upper (TU), superior temporal (ST), superior nasal (SN), nasal upper (NU), nasal lower (NL), inferior nasal (IN), inferior temporal (IT), and temporal lower (TL). Also, RNFL thicknesses for each of the temporal, superior, nasal, and inferior quadrants were obtained by averaging the octameric results: (TU TL)  $\div 2$  for the temporal, (ST SN)  $\div 2$  for the superior, (NU NL)  $\div 2$  for the nasal, and (IT IN)  $\div 2$  for the inferior quadrants.

Macular GCC layer extends from the internal limiting membrane to the inner nuclear layer and

includes the ganglion cell layer. GCC thickness was measured using the GCC protocol, which consisted of 15 vertical B scans (800 A scans for each) 7.0 mm long, each 0.50 mm separated, a single 7.0 mm long horizontal B scan (12.934 A scan). All measurements were centered on the macula. The center of the GCC scan was temporarily shifted 1.0 mm to better sample the temporal peripheral macula with the nasal visual field. Images were taken from a 6 mm x 6 mm area for GCC scanning.

Quantitative OCT examinations were carried out following APOSTEL recommendations (Advised Protocol for OCT Study Terminology and Elements) (11). For some patients and control groups, the OCT examination could only be performed in one eye, either due to difficulties in cooperation or the ocular reasons specified in the exclusion criteria. In these cases, data belonging to one eye were evaluated.

The study was conducted under the Helsinki Declaration and with the approval of the Ethics Committee of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (15.10.2018, 55/07). Written informed consent was obtained from all patients participating in the study.

### **Statistical Analysis**

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the distributions of continuous variables were normal, and the Levene test was used to examine the assumption of homogeneity of variances. The descriptive statistics for continuous variables were expressed as median (IQR); otherwise, the number of cases and percentages were used for categorical data. The continuous variables in which the parametrical test assumptions were not met were evaluated by the Kruskal-Wallis test. When the p-values from the Kruskal-Wallis test were statistically significant, Dunn-Bonferroni tests were used to determine which group differed from which others. Categorical data were analyzed by

Continuity corrected or Pearson's Chi-square tests, where applicable. The Wilcoxon Sign Rank test was used to evaluate whether the differences in the thickness of the ganglion cell complex and retinal nerve fiber layer between the left and right sides were statistically significant. Multiple linear regression analyses were performed to examine whether the difference in the thickness of the ganglion cell complex and retinal nerve fiber layer among groups persisted after adjusting for age and gender. Coefficients of regression, 95% confidence intervals, and t-statistics for each independent variable were also calculated. Because of non-normal distribution, logarithmic transformation was used for the thickness of the ganglion cell complex and retinal nerve fiber layer in regression analysis. A p-value of less than 0.05 was considered statistically significant. However, for all possible multiple comparisons, the Bonferroni correction was applied for controlling Type I error.

### **RESULTS**

Seventy patients diagnosed with MCI (28 females, 42 males), 54 patients (34 females, 20 males) diagnosed with mid-stage AD, and 54 cognitively healthy individuals (32 females, 22 males) as the control group were included in the study. The groups showed a statistically significant difference in terms of mean age ( $p < 0.001$ ). Patients in the MCI and middle-stage AD groups were found to be older than the control group ( $p = 0.048$  and  $p < 0.001$ , respectively), while there was no statistically significant difference in age between the MCI and middle-stage AD groups ( $p = 0.188$ ). There was a statistically significant difference between the groups in terms of gender distribution ( $p = 0.021$ ). The proportion of males in the MCI group was higher than in the middle-stage AD and control groups ( $p = 0.033$  and  $p = 0.011$ , respectively). On the other hand, there was no statistically significant difference between the middle-stage AD and the control group in terms of female and male distribution ( $p = 0.844$ ) (Table 1).



It was found that MMT scores decreased in the control, MCI, and mid-stage AD groups, respectively, and there was a statistically significant difference between all three groups ( $p < 0.001$ ) (Table 1).

The OCT evaluated 138 eyes in the MCI group (two eyes in 68 patients, one eye in 2 patients (2 right)), 91 in the middle-stage AD group (two eyes in 37 patients, one eye in 17 patients (6 right and 11 left)), and 105 in the control group (two eyes in 51 patients, one eye in 3 patients (3 right)) (Table 1).

No statistically significant difference was found between the middle-stage AD, MCI, and control groups in terms of mean, superior, and inferior GCC thickness in the OCT examination (Table 2). The effects of MCI and middle-stage AD on GCC thicknesses were evaluated by multivariate linear regres-

sion analysis by making adjustments according to age and gender. It was determined that the mean, superior and inferior GCC thicknesses of the control group and MCI and middle-stage AD groups were statistically similar.

When the control, MCI, and middle-stage AD groups were compared in terms of RNFL thickness, except for the inferior quadrant and the inferior temporal sector, RNFL thicknesses of the other quadrants and sectors were statistically similar (Table 3). It was determined that inferior quadrant RNFL thicknesses showed a statistically significant difference between the groups ( $p = 0.007$ ), and inferior RNFL was thinner in the middle-stage AD group compared to the control and MCI groups ( $p = 0.014$  and  $p = 0.020$ , respectively). (Table 3).

**Table 1.** Demographic characteristics, MMT scores of control, MCI and middle-stage AD groups, and the number of patients for whom OCT was evaluated bilaterally or unilaterally

	Control (n=54)	MCI (n=70)	Middle-stage AD (n=54)	P
Age (years) *	68.0 (9.25) <sup>a,b</sup>	72.5 (10.00) <sup>a</sup>	77.0 (16.00) <sup>b</sup>	<0.001†
Gender **				0.021‡
Male	22 (%40.7) <sup>a</sup>	42 (%60.0) <sup>a,c</sup>	20 (%37.0) <sup>c</sup>	
Female	32 (%59.3) <sup>a</sup>	28 (%40.0) <sup>a,c</sup>	34 (%63.0) <sup>c</sup>	
MMT *	28.0 (2.00) <sup>a,b</sup>	25.0 (3.00) <sup>a,c</sup>	13.0 (5.00) <sup>b,c</sup>	<0,001†
<b>OCT (number of patients, %)</b>				
Bilateral	51 (%94.4)	68 (%97.1)	37 (%68.5)	
Unilateral	3 (%5.6)	2 (%2.9)	17 (%31.5)	
Right	3 (%5.6)	2 (%2.9)	6 (%11.1)	
Left	0 (%0,0)	0 (%0,0)	11 (%20,4)	

\* Descriptive statistics shown as median (IQR), \*\* Data presented as number of cases and (%), † Kruskal-Wallis test, ‡ Pearson's Chi-square test, a: Control vs. MCI ( $p < 0.05$ ), b: Control vs. middle-stage AD ( $p < 0.001$ ), c: MCI vs. middle-stage AD ( $p < 0.05$ ). MCI: Mild cognitive impairment, AD: Alzheimer's disease, MMT: Mini Mental Test

**Table 2.** GCC thicknesses in control, MCI, and mid-stage AD groups

	Control	MCI	Middle-stage AD	p †
Average	96.75 (10.75)	94.00 (12.00)	95.75 (14.63)	0.097
Superior	96.75 (9.75)	92.75 (10.75)	95.00 (10.63)	0.065
Inferior	96.75 (12.38)	96.00 (11.00)	95.25 (14.63)	0.270

\* Data shown as median (IQR), † Kruskal-Wallis test. MCI: Mild cognitive impairment, AD: Alzheimer's disease, MMT: Mini Mental Test, The unit for GCC thickness value is  $\mu\text{m}$ .

Inferior temporal sector RNFL thicknesses showed a statistically significant difference between the groups ( $p = 0.002$ ); it was observed that inferior temporal RNFL was thinner in the middle-stage AD group compared to the control and MCI groups ( $p = 0.002$  and  $p = 0.021$ , respectively). (Table 3).

When adjusted for age and gender, inferior RNFL ( $B = -0.054$ ; 95% CI: -0.103 - -0.005 and  $p = 0.030$ ) and inferior temporal RNFL were found to be

thinner ( $B = -0.088$ ; 95% CI: -0.153 to -0.023 and  $p = 0.008$ ) in the middle-stage AD group compared to the control group (Table 4). Again, when the effects of age and gender were kept constant, nasal RNFL ( $B = 0.098$ ; 95% CI: 0.013 - 0.183 and  $p = 0.024$ ) and nasal lower RNFL ( $B = 0.111$ ; 95% CI: 0.020 - 0.202 and  $p = 0.017$ ) were found to be thicker in the middle-stage AD group compared to the control group (Table 4).

**Table 3.** RNFL thicknesses in control, MCI, and middle-stage AD groups

	Control	MCI	Middle-stage AD	p †
Average	97.75 (11.25)	97.25 (14.38)	96.25 (14.63)	0.664
Superior	119.75 (20.25)	114.25 (15.25)	112.50 (17.75)	0.215
Temporal	75.00 (11.25)	71.75 (14.13)	70.50 (19.50)	0.284
Inferior	119.50 (13.63) <sup>a</sup>	120.00 (19.00) <sup>b</sup>	111.50 (19.50) <sup>a,b</sup>	<b>0.007</b>
Nasal	79.25 (14.75)	80.00 (21.38)	81.00 (25.00)	0.136
Superior nasal	105.75 (18.00)	101.75 (21.63)	102.50 (23.00)	0.512
Superior temporal	125.00 (21.75)	125.50 (19.13)	119.25 (26.88)	0.083
Temporal upper	79.75 (12.13)	75.50 (13.63)	77.75 (24.38)	0.291
Temporal lower	66.00 (11.25)	65.75 (11.50)	61.50 (19.50)	0.253
Inferior temporal	128.75 (18.00) <sup>a</sup>	126.75 (18.88) <sup>b</sup>	115.00 (25.00) <sup>a,b</sup>	<b>0.002</b>
Inferior nasal	109.25 (19.88)	112.00 (24.25)	106.25 (23.88)	0.377
Nasal lower	74.75 (15.25)	76.25 (23.00)	80.00 (30.88)	0.100
Nasal upper	82.75 (17.13)	81.75 (21.88)	83.75 (29.63)	0.288

\* Descriptive statistics shown as median (IQR), † Kruskal-Wallis test, a: Control vs. middle-stage AD ( $p < 0.05$ ), b: MCI vs. middle-stage AD ( $p < 0.05$ ). MCI: Mild cognitive impairment, AD: Alzheimer's disease, MMT: Mini Mental Test, The unit for RNFL thickness value is  $\mu\text{m}$ .



**Table 4.** Effects of MCI and middle-stage AD on RNFL thickness according to the control group when adjusted for age and gender with multivariate linear regression analysis

	B	95% CI for B		t	p †
		LL	UL		
Average					
MCI	0.003	-0.032	0.038	0.179	0.858
Middle –stage AD	0.001	-0.037	0.039	0.056	0.956
Superior					
MCI	-0.007	-0.052	0.039	-0.293	0.770
Middle –stage AD	-0.019	-0.069	0.030	-0.761	0.448
Temporal					
MCI	-0.009	-0.066	0.047	-0.323	0.747
Middle –stage AD	-0.021	-0.083	0.041	-0.678	0.499
Inferior					
MCI	0.001	-0.043	0.046	0.053	0.958
Middle –stage AD	-0.054	-0.103	-0.005	-2.186	<b>0.030</b>
Nasal					
MCI	0.046	-0.032	0.123	1.156	0.249
Middle –stage AD	0.098	0.013	0.183	2.274	<b>0.024</b>
Superior nasal					
MCI	-0.028	-0.085	0.030	-0.953	0.342
Middle –stage AD	-0.016	-0.078	0.046	-0.498	0.619
Superior temporal					
MCI	0.015	-0.046	0.077	0.491	0.624
Middle –stage AD	-0.014	-0.080	0.053	-0.401	0.689
Temporal upper					
MCI	-0.028	-0.090	0.034	-0.898	0.370
Middle –stage AD	-0.003	-0.070	0.063	-0.097	0.923
Temporal lower					
MCI	0.007	-0.065	0.079	0.196	0.844
Middle –stage AD	-0.037	-0.116	0.041	-0.941	0.348
Inferior temporal					
MCI	-0.004	-0.065	0.056	-0.144	0.886
Middle –stage AD	-0.088	-0.153	-0.023	-2.672	<b>0.008</b>
Inferior nasal					
MCI	0.010	-0.051	0.071	0.316	0.752
Middle –stage AD	-0.013	-0.079	0.053	-0.395	0.693
Nasal lower					
MCI	0.043	-0.041	0.127	1.012	0.313
Middle –stage AD	0.111	0.020	0.202	2.406	<b>0.017</b>
Nasal upper					
MCI	0.019	-0.060	0.098	0.472	0.637
Middle –stage AD	0.077	-0.009	0.162	1.776	0.077

CI: Confidence interval, LL: Lower limit, UL: Upper limit. MCI: Mild cognitive impairment, AD: Alzheimer's disease

When adjusted for age and gender, inferior RNFL ( $B = -0.055$ ; 95% CI:  $-0.100 - -0.010$  and  $p = 0.016$ ) and inferior temporal RNFL ( $B = -0.084$ ; 95% CI:  $-0.144 - -0.024$  and  $p = 0.007$ ) were thinner in the middle-stage AD group compared to the MCI group (Table 5).

## DISCUSSION

Our study results indicated that RNFL was affected in middle-stage AD patients and that this involvement was limited to inferior and inferior temporal RNFL regions. Despite the effect on RNFL, no change in GCC thickness was found in patients with middle-stage AD and MCI. Data obtained from histopathological studies on retinal involvement in AD showed a significant loss of retinal ganglion cells and a decrease in RNFL thickness in individuals with AD compared to the controls (5, 10, 12).

It has been suggested that it may be possible to affect specific retinal cell types in AD; in particular, the ganglion cell-inner plexiform layer (GC-IPL) complex in the macula has been associated with AD (13). It has also been suggested that the measurement of macular GC-IPL thickness would be a suitable predictor for AD (14). On the other hand, if ganglion cells are damaged throughout the retina, this can be best evaluated by peripapillary RNFL measurements that reflect all axonal bumps that leave the retina to join the optic nerve. The thickness of RNFL has also been thought to decrease in AD due to retrograde degeneration of retinal ganglion cell axons (6).

In our study, although there was thinning in RNFL in AD patients, no change was detected in GCC thickness, and it was thought that this finding could be explained by the metabolic failure and energy deprivation caused by neurodegenerative events, primarily by affecting the axons of ganglion cells. In a population-based prospective cohort study, thinner RNFL thickness was associated with the risk of developing dementia, including AD, independent

of cardiovascular risk factors (10). Our study showed selectivity in the decrease in RNFL thickness in middle-stage AD patients; it was determined that the inferior and, especially, the inferior temporal region were affected. We thought that RNFL measurements in these regions could better reflect neurodegeneration and axon loss associated with AD.

Our study found that, after multivariate linear regression analysis, RNFL thickening was found in the nasal and nasal lower regions in the AD group compared to the control group. However, the clinical significance of this finding is not fully understood. While most OCT studies have reported a general thinning in RNFL by combining data from all quadrants (15-17), other studies have reported that RNFL thinning is more pronounced and selective in the inferior (18-20) or superior quadrants (21). It was found that inferior quadrant RNFL thickness had the strongest correlation with the results of cognitive tests, and the risk of cognitive decline was higher in older adults with RNFL thinning in this quadrant (18).

The answer to the question of why the degenerative process affects certain retinal regions in AD is unclear. It has been suggested that the superior and inferior quadrants contain more large-diameter axons, which degenerate more rapidly, and which may be the reason for the sensitivity of these quadrants (22). Another possibility that comes to mind regarding regional involvement in the retina is that the pathology in the primary brain regions affected by the neurodegenerative process associated with AD shows somatotopic organization while reflecting on retinal nerve fibers, which can be proven by advanced histopathological and imaging studies.

As our study results indicate, focal damage can occur in RNFL in AD. Therefore, it may be a useful approach to investigate the potential focal effects of AD and measure changes in the most affected area of the retina using customized nerve fiber layer thickness maps or other new techniques. However, with the disease's progression, retinal nerve fibers



**Table 5.** Effects of control and middle-stage AD on RNFL thickness according to the MCI group when adjusted for age and gender with multivariate linear regression analyses

	B	95% CI for B		t	p †
		LL	UL		
Average					
Control	-0.003	-0.038	0.032	-0.179	0.858
Middle-stage AD	-0.002	-0.037	0.033	-0.119	0.906
Superior					
Control	0.007	-0.039	0.052	0.293	0.770
Middle-stage AD	-0.012	-0.058	0.033	-0.534	0.594
Temporal					
Control	0.009	-0.047	0.066	0.323	0.747
Middle-stage AD	-0.012	-0.069	0.045	-0.414	0.679
Inferior					
Control	-0.001	-0.046	0.043	-0.053	0.958
Middle-stage AD	-0.055	-0.100	-0.010	-2.425	<b>0.016</b>
Nasal					
Control	-0.046	-0.123	0.032	-1.156	0.249
Middle-stage AD	0.052	-0.026	0.131	1.319	0.189
Superior Nasal					
Control	0.028	-0.030	0.085	0.953	0.342
Middle-stage AD	0.012	-0.045	0.069	0.414	0.679
Superior temporal					
Control	-0.015	-0.077	0.046	-0.491	0.624
Middle-stage AD	-0.029	-0.091	0.033	-0.924	0.357
Temporal upper					
Control	0.028	-0.034	0.090	0.898	0.370
Middle-stage AD	0.025	-0.037	0.086	0.793	0.429
Temporal lower					
Control	-0.007	-0.079	0.065	-0.196	0.844
Middle-stage AD	-0.045	-0.117	0.028	-1.215	0.226
Inferior temporal					
Control	0.004	-0.056	0.065	0.144	0.886
Middle-stage AD	-0.084	-0.144	-0.024	-2.749	<b>0.007</b>
Inferior Nasal					
Control	-0.010	-0.071	0.051	-0.316	0.752
Middle-stage AD	-0.023	-0.084	0.038	-0.744	0.458
Nasal lower					
Control	-0.043	-0.127	0.041	-1.012	0.313
Middle-stage AD	0.068	-0.016	0.152	1.593	0.113
Nasal upper					
Control	-0.019	-0.098	0.060	-0.472	0.637
Middle-stage AD	0.058	-0.021	0.137	1.451	0.149

CI: Confidence interval, LL: Lower limit, UL: Upper limit. MCI: Mild cognitive impairment, AD: Alzheimer's disease

may be affected in all regions, and to demonstrate this, evaluations or long-term follow-up studies are required in advanced-stage AD.

Our study found that RNFL was affected only in patients with middle-stage AD; similar effects were not observed in patients with MCI, and no difference was found between patients with MCI and healthy individuals in terms of retinal involvement. It was thought that retinal degeneration findings might run parallel to the progression of AD pathology, and therefore, while OCT was affected in AD patients, normal findings could be detected in MCI. Although the number of studies evaluating OCT findings in MCI patients is relatively small, several studies have reported OCT abnormalities in patients with MCI (17, 19, 23). Attention was drawn to the relationship between inferior quadrant RNFL thickness and episodic memory in MCI patients; it has been suggested that it can be used as a biomarker in MCI and AD patients (20).

While our study found no abnormality in OCT in the control group and MCI patients, changes in RNFL thickness were detected only in mid-stage AD, and it was thought that OCT findings might not have a predictive feature for MCI or AD. The definition of MCI shows a heterogeneous feature since it includes cognitive disorders that can turn into different types of dementia. While patients diagnosed with MCI were not sub-grouped in most other OCT studies, in our study, patients with amnesic MCI with a high probability of conversion to AD were selected; non-amnesic MCI, which may be the pre-

stage of other dementias, were excluded. We considered this selectivity preferable to the ones used in other studies.

The absence of early or advanced AD patients in our study groups may have restricted the OCT examination to give clearer results concerning the stages of the disease; However, it may be challenging to differentiate mild stage AD from MCI; It may not be possible for patients with advanced-stage AD to adapt to OCT and other eye examinations. Another limitation of our study was the statistical difference between the groups in terms of age and gender distribution. However, the possible effect of this difference in other analyzes was eliminated by making statistical corrections according to age and gender. Due to the difficulty of cooperation and ocular reasons specified in the exclusion criteria, OCT examination could be performed in only one eye in some of the patients in the patient groups, and the data belonging to one eye were evaluated. This was a limitation of our study due to the participants' advanced age or impaired cognitive functions, or both.

In conclusion, our study results indicated that retinal axon loss might develop in AD, that this loss may have a focal feature, and that the inferior temporal region may have a selective sensitivity. OCT can reflect the neuropathological process in AD and could contribute to patients' diagnosis and follow-up. However, to fully enlighten the predictive value of OCT, long-term studies covering all stages of the disease will be needed.

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## RESEARCH

# THE ETIOLOGY OF UNILATERAL AND BILATERAL BLINDNESS IN THE ELDERLY AND THE DIFFERENCES BY GENDER

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.215  
2021; 24(2): 196-203

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Received: Jan 30, 2021  
Accepted: Apr 07, 2021

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## ABSTRACT

**Introduction:** The aim of this study was to investigate the causes of unilateral and bilateral blindness in elderly patients and to evaluate its distribution by gender.

**Materials and Methods:** Data from 22055 patients examined in the Ophthalmology Department between 2013-2020 were retrospectively analyzed. Patients 65 years or older were selected, and the causes of unilateral and bilateral blindness were evaluated. The patients were divided into two groups: 65-74 years old were presenile and 75 years or older were senile group. The factors causing blindness were evaluated separately by gender and age group.

**Results:** 452 patients (213 females, 239 males) were 65 years or older with unilateral and bilateral low vision. A total of 193(42.7%) were in the presenile, and 259(57.3%) were in the senile group. Age-related macular degeneration was the most common cause of unilateral and bilateral blindness in both genders, followed by diabetic retinopathy in females and glaucoma in males. The most common cause of blindness in both presenile and senile groups was age-related macular degeneration, followed by diabetic retinopathy in the presenile, glaucoma in the senile group.

**Conclusions:** In the presenile and senile groups, age-related macular degeneration was the most common cause of unilateral and bilateral blindness in females and males. Other leading causes were diabetic retinopathy in females and glaucoma in males.

**Keywords:** Blindness; Aged; Gender Identity



## INTRODUCTION

According to the World Health Organization (WHO), at least 2.2 billion people globally have visual impairment or blindness. Of those, over 1 billion cases could have been prevented. Although visual impairment can affect people of all ages, the majority are over the age of 50. An increased risk of visual impairment is expected with population growth and aging (1, 2).

According to the WHO, the leading causes of visual impairment are often preventable, including uncorrected refractive errors and cataracts. AMD, glaucoma, and diabetic retinopathy (DRP) are other causes. Several studies reported that the incidence of blindness increases with age (3-6).

The causes and incidence of blindness and visual impairment vary in different societies based on their level of development (7). For example, blindness due to cataracts is more frequent in low- and middle-income countries than high-income countries. Diseases such as DRP, glaucoma, and AMD are more common in high-income countries (1).

Low vision and blindness in middle and old age are critical public health problems affecting all aspects of life, including daily personal activities, interaction with society, and access to public services. Adverse effects include a deterioration in the quality of life, falls, and even death (1,8). It is essential to determine the preventable causes of blindness due to cultural, socioeconomic, and demographic differences (3). One of the most important demographic characteristic is gender and the differences in blindness etiology according to this parameter was not assessed in Turkish geriatric population.

The quality of the life might be affected by unilateral and bilateral blindness in geriatric population and to find out the etiologies of blindness might help to detect the preventable ones. Our study aimed to determine the causes of unilateral and bilateral blindness in the senior age groups and determine the differences in impacts between fe-

males and males. In addition, the causes of blindness were examined separately in the presenile and senile groups.

## MATERIALS AND METHODS

In this study, data from 22055 patients examined in the Ophthalmology Department between March 2013 and January 2020 were retrospectively analyzed. Best-corrected visual acuity (BCVA)  $\leq 0,05$  (measurement by the Snellen chart) in one eye was defined as unilateral, and in both eyes was defined as bilateral blindness (1,9). Among these data, patients 65 years or older were selected; and the causes of unilateral and bilateral blindness were evaluated. In addition, patients were divided into two groups according to age: ages 65-74 were presenile and 75 years or older were senile.

Prior approval was received from the Institutional Review Board (Ethical Board, IRB number: 71522473/050.01.04/25). This retrospective study was performed in accordance with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards.

The patients' demographic characteristics, detailed ophthalmologic examination, including BCVA measurement and the Snellen chart, slit-lamp biomicroscopy, fundus observation, and other systemic diseases were analyzed. Snellen metric converting chart was used for the assessment of patients who have BCVA values lower than 0.05. Etiological factors evaluated included cornea, lens, and retinal diseases such as AMD, DRP, retinal vascular occlusion, degenerative myopia, retinal detachment, retinitis pigmentosa, optic nerve diseases such as glaucoma and optic neuropathy, genetically inherited diseases, strabismus, and uveitis causing blindness. If more than one condition was present in the same patient, the condition causing the most visual impairment was recorded according to WHO guidelines. Patients with a follow-up period of less than one year were not included in the study.

The causes of unilateral and bilateral blindness were evaluated and compared between female and male groups and the presenile and senile groups separately.

SPSS (Statistical Package for Social Sciences Inc., Chicago, IL, USA) 23.0 Windows program was used for the statistical analysis. Sex, unilaterality-bilaterality, etiological diagnosis, and frequencies between groups were compared using the Chi-square test. The suitability of the variables for normal distribution was examined using visual and analytical methods. Descriptive analyses were conducted using means and standard deviations for normally distributed variables. Age-dependent values showed normal distribution, so they were compared with the Student's t-test (Independent Samples Test). The p-value was less than 0,05 and statistically significant.

## RESULTS

In this study, data from 22055 patients were analyzed and 3372 of these patients were in presenil and senil

age groups. Geriatric patients with blindness comprised 2.05% of the total. There were 452 patients over 65 years of age with unilateral and bilateral low vision. Of the total, 193 (42.7%) were presenile, and 259 (57.3%) were senile, and 303 (67.04%) had unilateral, and 149 (32.96%) had bilateral blindness.

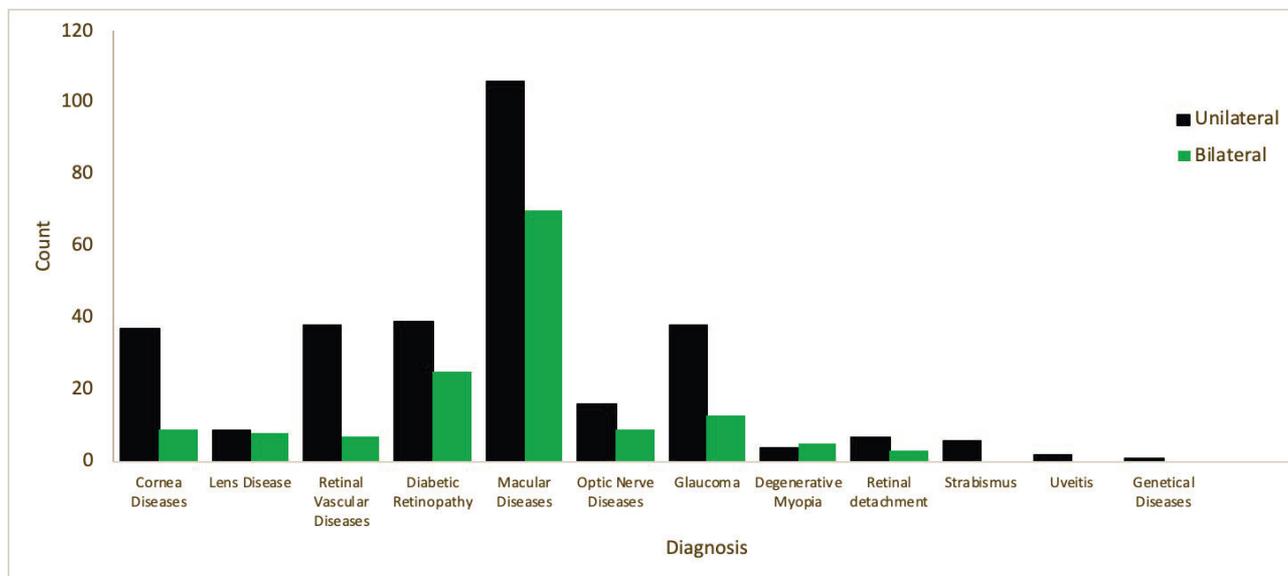
The mean age of the patients 65 to 95 years old was  $76.73 \pm 7.63$ . Of the total, 213 (47.1%) were female, and 239 (52.9%) were male. The mean age was  $76.98 \pm 7.67$  for the females and  $76.51 \pm 7.60$  years for the males. Gender groups were similar in terms of age ( $p: 0.654$ , Independent Samples Test).

The BCVA was  $0.03 \pm 0.01$  in males and  $0.02 \pm 0.01$  in females. There was no statistically significant difference between genders ( $p: 0.666$ ).

The causes of unilateral and bilateral blindness are shown in Figure 1 and the causes by gender are summarized in Table 1.

Overall, the most common causes of blindness were AMD at 38.9%, DRP at 14.2%, and glaucoma at 11.3%. The causes of unilateral and bilateral blindness were similar in both genders ( $p: 0.337$ , Chi-square).

**Figure 1.** Causes of unilateral and bilateral blindness





**Table 1.** Causes of unilateral and bilateral blindness of males and females

Diagnosis	Gender				Total
	Females n=213 (47,1%)		Males n=239 (52,9%)		
	Unilateral 137(%30.4)	Bilateral 75 (%16.6)	Unilateral 165 (%36.6)	Bilateral 74 (%16.4)	
Age related Macular Diseases	<b>82 (18,1%)</b>		<b>94 (20,8%)</b>		<b>176 (38,9%)</b>
	<b>49</b>	<b>33</b>	<b>57</b>	<b>37</b>	
Diabetic Retinopathy	<b>37 (8,2%)</b>		27 (6,0%)		64 (14,2%)
	20	17	19	8	
Glaucoma	22 (4,9%)		<b>29 (6,4%)</b>		51 (11,3%)
	19	3	19	10	
Corneal diseases	17 (3,8%)		29 (6,4%)		46 (10,2%)
	13	4	24	5	
Retinal vascular diseases	19 (4,2%)		26 (5,8%)		45 (10,0%)
	17	2	21	5	
The other diseases of optic nerve	13 (2,9%)		12 (2,7%)		25 (5,5%)
	7	6	9	3	
Diseases of lens	8 (1,8%)		9 (2,0%)		17 (3,8%)
	3	5	6	3	
Retinal detachment	4 (0,9%)		6 (1,3%)		10 (2,2%)
	2	2	5	1	
Degenerative myopia	6 (1,3%)		3 (0,7%)		9 (2,0%)
	3	3	1	2	
Strabismus	4 (0,9%)		2 (0,4%)		6 (1,3%)
	4	0	2	-	
Uveitis	1 (0,2%)		1 (0,2%)		2 (0,4%)
	1	0	1	-	
Genetically transmitted diseases	-		1 (0,2%)		1 (0,2%)
			1	-	
Total	213 (47,1%)		239 (52,9%)		452 (100,0%)
	<b>138</b>	75	165	74	

**Table 2.** Gender and unilateral-bilateral blindness in presenile and senile groups

	Presenile group (65-74 yaş) n=193 (%42.7)	Senile group (75 yaş ve üzeri) n=259 (%57.3)	P (Chi-Square)
Female/ Male (n: 213/239)	87/106 (%19.2- %23.5)	126/133 (%27.9- %29.4)	0.505
Unilateral/Bilateral(n)	142/51 (%31.4- %11.3)	161/98 (%35.6- %21.7)	<b>0.012</b>

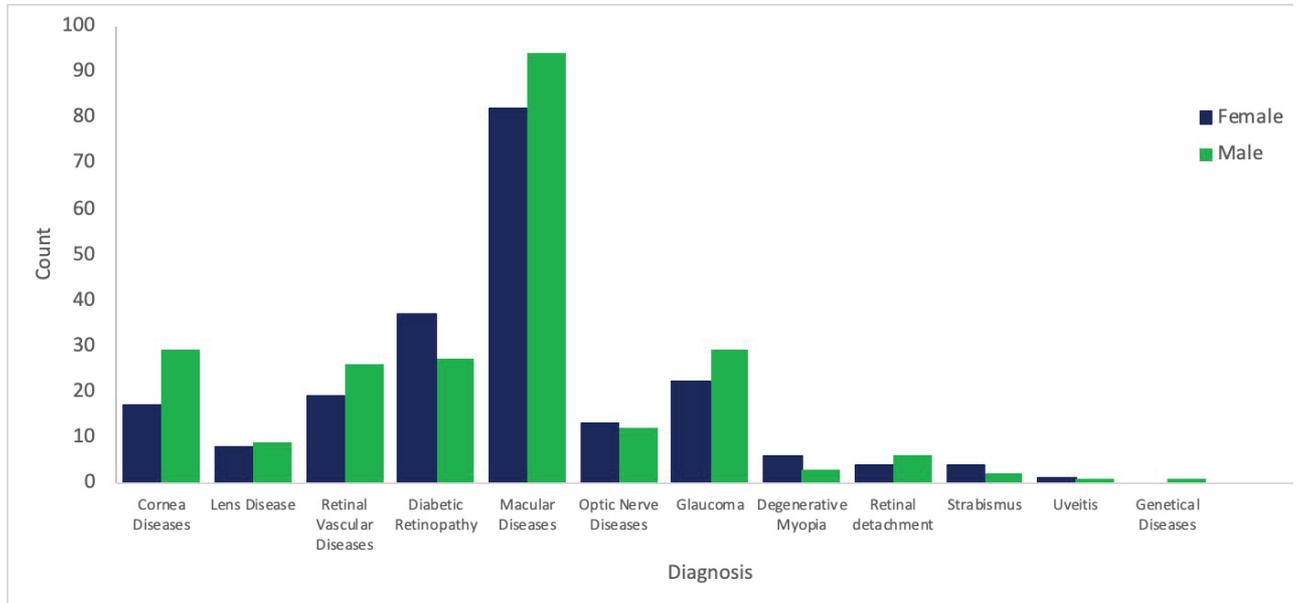
AMD was the most common cause of unilateral and bilateral blindness in both sexes (18.1% in females and 20.8% in males). AMD was followed by DRP (8.2%) and glaucoma (4.9%) in females and glaucoma (6.4%), and corneal diseases (6.4%) in males (Figure 2).

The most common causes of unilateral blindness were AMD, DRP, and glaucoma in females; AMD, corneal and retinal vascular diseases in males, respectively.

The most common causes of bilateral blindness in females were AMD, DRP, optic nerve diseases. AMD, glaucoma, and DRP were the most common causes of bilateral blindness in males.

As shown in Table 2, there was no difference between genders in the presenile and senile groups (p: 0.505 chi-squares). Unilateral and bilateral blindness were observed more frequently in the senile group and statistically significant (p: 0.012 chi-squares). The causes of blindness in these groups are summarized in Table 3.

**Figure 2.** Causes of blindness in male and female genders





## DISCUSSION

Increasing life expectancy and an aging population raise individual and socioeconomic challenges. One of the systems most affected by advanced age is the visual system (3). It is essential to determine the causes to improve quality of life and economic prosperity (10). Cataracts was the leading cause of visual impairment with 51% consistent with global data on low vision (11).

Our study demonstrated that, in the presenile and senile groups, AMD was the most common cause of unilateral and bilateral blindness in both females and males. The other leading causes were DRP in females and glaucoma in males. Similar to our results, Tunay et al. reported that AMD was the most common cause of low vision in the senior age group. DRP was the most common cause in the presenile group, and glaucoma was the most common cause in the senile group (3). In a study conducted by Mirza et al., the leading cause of unilateral-bilateral blindness in presenile and senile age groups was cataracts (12). Klaver et al. reported that AMD

was the most common cause of blindness in the presenile and senile groups; this was followed by glaucoma, cataracts, optic neuropathy, and myopic degeneration (13).

In this study, the most common causes of blindness were AMD, retinal vascular diseases, and DRP in the presenile group. In the senile group, they were AMD, glaucoma, and corneal diseases. After AMD, the common causes of blindness in the presenile age group were systemic diseases; in the senile age group, the most common cause was ocular diseases. These results may be related to the high number of deaths from systemic diseases in the presenile period.

In another study, no difference was found between genders in patients aged 50-69 and over 70 years in the frequency of blindness (10). Similarly, Esteban et al. found no significant difference between genders in the frequency of blindness (14). Zetterberg et al. reported that 2/3 of the patients they observed due to blindness were women. Similarly, Klaver et al. reported a 75% higher incidence

**Table 3.** Causes of blindness in presenile and senile groups

		Presenile group (65-74 years) n=193 (%42.7)	Senile group (≥75 years) n=259 (%57.3)
Diagnosis	Age related Macular Diseases	<b>59 (%13.1)</b>	<b>117 (%25.9)</b>
	Diabetic Retinopathy	<b>47 (%10.4)</b>	17 (%3.8)
	Glaucoma	19 (%4.2)	<b>32 (%7.1)</b>
	Corneal diseases	16 (% 3.5)	<b>30 (%6.6)</b>
	Retinal vascular diseases	<b>22 (%4.9)</b>	23 (%5.1)
	The other diseases of optic nerve	15 (%3.3)	10 (%2.2)
	Diseases of lens	4 (%0.9)	13 (%2.9)
	Retinal detachment	2 (%0.4)	8 (%1.8)
	Degenerative myopia	2 (%0.4)	7 (%1.5)
	Strabismus	5 (%1.1)	1 (%0.2)
	Uveitis	2 (%0.4)	-
	Genetically transmitted diseases		1 (%0.2)

of blindness in women (13,15). Khanna et al. concluded that aging and female gender were the risk factors for blindness (16). The differences between women's and men's daily lives and physical conditions, including access to adequate healthcare increased the incidence of diseases that cause blindness in women (17). In our study groups, the number of females (47.1%) and males (52.9%) in the presenile and senile groups and the unilateral and bilateral groups were similar. These varying results might be related to demographic and cultural differences.

In a 2015 study, the causes of blindness and low vision were examined in all age groups. While the incidence of cataracts and DRP was higher in women, the frequency of glaucoma and corneal opacity was higher in men. The frequency of AMD was found to be equal for both genders (8). The frequency of AMD in our study was similar. The next leading causes were DRP and glaucoma in women; and glaucoma, corneal diseases, and DRP in men. The differences in these results may be related to changes in demographic properties.

In a study conducted in Somalia, the most causes of unilateral blindness were trauma complications, cataracts, and DRP, respectively. The most causes of bilateral blindness were cataracts, DRP, and glaucoma. In this study, the effects of trauma were due more to geographical reasons (7). In our research, the most common cause of unilateral blindness in men and women was AMD, similar to developed countries. Other causes included ocular diseases. The most common causes of bilateral

blindness, other than AMD, were DRP and optic nerve diseases.

A meta-analysis that analyzed data from studies in six regions and 39 countries worldwide reported that the most frequent causes of blindness were cataracts (51%), glaucoma (8%), and AMD (5%) (11). In our study, blindness due to cataracts ranked 7th with 3.8%. These results may be due to the early admission, diagnosis, and treatment of cataracts patients. In developing countries, the delay in cataracts operations may result in underestimation of the rates of AMD.

Our study has several limitations. First, the socioeconomic levels of the study groups were not known or evaluated. Grouping the patients according to their socioeconomic status, would have provided additional data. Another feature of this study was the limited number of patients that prevented the results from being generalized to society.

In conclusion, the most common cause of both unilateral and bilateral blindness in both genders was AMD. The other leading causes were DRP in females and glaucoma in males. In both the presenile and senile groups, the primary cause of blindness was AMD. We believe that determining the factors that cause blindness in different age and gender groups might guide individual, cultural, and socioeconomic diagnosis, and treatment strategies.

### **Conflicts of interest**

The authors of this article state that they have no conflict of interest.



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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.216  
2021; 24(2): 204-211

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Received: Nov 27, 2020  
Accepted: Mar 30, 2021

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## RESEARCH

# THE IMPACT OF CLOSURE DEVICES ON VASCULAR COMPLICATIONS DURING TRANSCATHETER AORTIC VALVE IMPLANTATION PROCEDURES IN GERIATRIC PATIENTS

## ABSTRACT

**Introduction:** In transcatheter aortic valve implantation, some closure devices can be used as an alternative to the surgical exploration of the femoral artery for vascular access. This study aimed to compare closure devices and surgical exploration techniques in terms of vascular access complications, particularly in geriatric patients.

**Materials and Methods:** This study included 169 patients who had undergone transcatheter aortic valve implantation at a cardiology clinic between August 2014 and January 2019. The patients' mean age was 76.62 years; 53.30% were male. The preferred access site was the femoral artery in all the patients. Patients in whom a closure device was used were included in the Prostar and ProGlide groups, and those who underwent surgical exploration of the femoral artery were included in the Surgery group. The endpoints of the study were postoperative bleeding, infection, and a recurring need for surgical repair.

**Results:** Of the patients, 55.60%, 29.60%, and 14.80% were included in the Prostar, ProGlide, and Surgery groups, respectively. No significant differences were observed between the Prostar and ProGlide groups regarding the rate of need for emergency surgery due to bleeding. During post-procedure follow-ups, the emergency surgery and bleeding rates were significantly higher in the Prostar and ProGlide groups than those in the Surgery group.

**Conclusion:** Although no difference exists between the closure devices used for vascular access in terms of complications, surgical exploration reduces the rate of bleeding-related complications thereby reducing the complication risk, except for the possible occurrence of surgical site infections.

**Keywords:** Transcatheter Aortic Valve Replacement; Vascular Closure Device; Femoral Artery



## INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an alternative to conventional aortic valve replacement in patients with symptomatic severe aortic stenosis (1). Transcatheter aortic valve implantation (TAVI) was first adopted in 2002. Since then, it has been increasingly used globally to reduce mortality and morbidity in patients with high or prohibitive surgical risks (2). In the recent years, TAVI has also been frequently and successfully performed as an alternative to the cardiopulmonary bypass (CPB) technique, which is currently used for aortic valve replacement, particularly in geriatric patients. The elderly population is a rapidly growing demographic characteristic of Western countries. By 2050, the global number of individuals aged  $\geq 60$  years is expected to reach nearly 2 billion, and the population aged  $\geq 80$  years is projected to exhibit a 26-fold increase (3).

According to the Guidelines on Valvular Heart Diseases published in 2017 by the European Society of Cardiology (ESC), TAVR should be considered a primary treatment option in patients with symptomatic severe aortic stenosis who also have a history of porcelain aorta, radiation therapy, and sternotomy along with a Society of Thoracic Surgeons or Euro SCORE II  $> 4\%$  and a logistics Euro SCORE I  $> 10\%$  (4).

During the initial days of the employment of the TAVR technique, various methods have been used for vascular access, including the transapical approach (5). The transfemoral approach is recommended by international guidelines owing to its advantages in terms of reduced procedure time and risk of cerebrovascular injuries. (4, 6). Although various closure devices are used in TAVR, Prostar and ProGlide (Abbott Vascular Inc., Santa Clara, CA, US) are the most commonly used devices. Surgical exploration is another option in cases of anatomical unsuitability, device failure, or vascular complications.

This study aimed to compare the two different

closure devices used for access in TAVI procedures that are commonly performed worldwide, particularly in geriatric patients using the open approach, that is, femoral artery exploration, in terms of mortality and morbidity. Impairment of the vascular structure, especially in elderly patients, can reduce the success of these closure devices, thereby leading to bleeding or the need for emergency surgery. In elderly patients, repairing the artery used as an access route for TAVI with closure devices provides benefits such as shorter operative time, less sedation, and lower surgical stress. Moreover, reduction of risk factors is vital in this age group, as geriatric patients are often considerably frail. In patients with unsuitable vascular structures for closure devices (anterior artery calcification and plaque structure), accessing the artery with surgical exploration and performing primary repair after the procedure appears to minimize potential complications.

## MATERIALS AND METHODS

Patients who were symptomatic owing to severe aortic valve stenosis with comorbidities and in whom conventional surgery posed a high risk were evaluated for TAVR by the cardiology and cardiovascular surgery clinics in a single center. Anatomical features were evaluated using computed tomography (CT) and coronary angiography. The patients were informed if they were suitable for TAVR, and the procedure was planned by the heart surgery team. Ethical approval was obtained from the local ethics committee (27.09.2019-350399), and patient recruitment was initiated.

The data of 189 patients who underwent TAVR between August 2014 and January 2019 were retrospectively analyzed. The first 10 patients in the closure device group were excluded to minimize the statistical effects of the learning curve. A total of 169 patients were included in the study. The mean age was 76.62 years (standard deviation [SD]: 6.30) with an age range of 65–92 years, and 90 of the patients were male (53.30%). All patients were considered

to be in the geriatric age group. The patients were divided into three groups according to vascular closure type: Prostar, ProGlide, and Surgery. For TAVR, three types of transcatheter valves (Edwards Sapien, Edwards Lifesciences Corporation, Irvine, CA, USA), Abbott Symetis (Abbott Laboratories, Illinois, USA), and Medtronic CoreValve (Medtronic Corp. Minneapolis, MN, USA) were used. The endpoints for vascular access were the need for emergent re-exploration for bleeding and groin infection. All patients were contacted for follow-up checks on the 15<sup>th</sup> day and at the first and third months after the intervention. The patients were examined for access site complications, heart rhythm, and echocardiography was performed.

### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS 21, Chicago, IL, USA) was used for the data analysis. The distribution of continuous variables was determined using the Kolmogorov–Smirnov, and Shapiro–Wilk normality tests in the data analysis. Parametric data were expressed as mean ± standard deviation values, whereas nonparametric data were expressed as median (minimum-maximum) and categorical data were expressed as percentage values. The Kruskal–Wallis test was used to compare more than two groups that did not conform to the normal distribution. The Mann–Whitney U test was used to determine the relationships between the two groups. The chi-square test (crosstab) was used to compare categorical data, and statistical significance was set at  $p < 0.05$ . The characteristics of the groups and comorbidities are presented in Table 1.

### RESULTS

For TAVR, the Edwards Sapien, Abbott Symetis, and Medtronic CoreValve transcatheter valves were used in 116 (68.60%), 32(18.90%), and 21 (12.40%) patients, respectively. The Prostar group consisted of 94 (55.60%) patients, and the ProGlide group

consisted of 50 (29.60%) patients. The remaining 25 (14.80%) patients underwent surgical exploration of the femoral artery and primary closure because of unfavorable vascular anatomy. The mean age of this group was 76.62 years. The mean EuroSCORE was 7.40, and the valve types and rates in the groups are provided in Table 2.

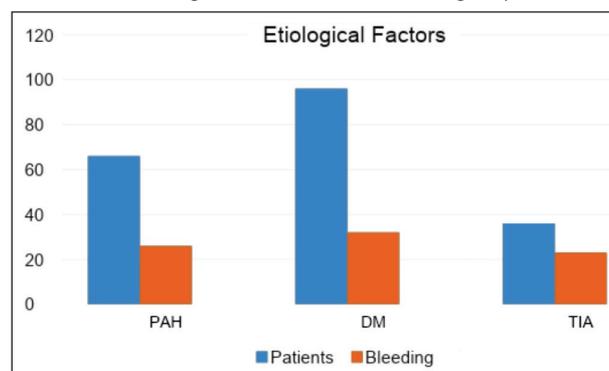
There was no significant difference in the rates of need for emergency surgery due to bleeding between groups 1 and 2 ( $p = 0.292$ ). The rates of postoperative emergency surgery and bleeding were significantly higher in both groups that were treated with closure devices than in group 3 ( $p = 0.001$ ) (Table 2).

There was a history of peripheral arterial disease in 66 patients, of whom 26 (56.50%) underwent emergency surgery because of bleeding. This value was statistically significant ( $p = 0.007$ ) (Figure 1).

There was a history of diabetes mellitus in 96 patients, of whom 32 (33.33%) underwent emergency surgery because of bleeding. This value was statistically significant ( $p = 0.009$ ) (Figure 1).

There was a history of transient ischemic attacks in 36 patients, of whom 23 (63.90%) underwent emergency surgery because of bleeding. This value was also statistically significant ( $P = 0.006$ ) (Figure 1).

**Figure 1.** Comparison of bleeding events between the etiological factors of the three groups





**Table 1.** Preoperative demographics and surgical characteristics of the patients

	Group 1	Group 2	Group 3	P
Sex (M/F)	94 (47/47)	50 (27/23)	25 (16/9)	0.456
Age (years)	76.06	77.30	77.36	0.412
Ejection Fraction	38.19	38.30	34.60	0.105
Body Mass Index	27.15	27.04	27.06	0.123
EuroSCORE	7.40	7.12	7.22	0.101
Chronic Obstructive Pulmonary Disease n (%)	41 (43.60)	20 (40)	13 (52)	0.613
Reoperation	7 (7.40)	4 (8)	3 (12)	0.761
Hypertension	51 (54.30)	28 (56)	13 (52)	0.946
Aortic Regurgitation	2 (2.1)	2 (4)	4 (16)	0.014
Coronary Disease	28 (29.80)	16 (32)	9 (36)	0.832
Chronic Renal Failure	10 (10.60)	4 (8)	3 (12)	0.830
Peripheral Arterial Disease	40 (42.60)	14 (28)	12 (48)	0.143
Diabetes Mellitus	47 (50)	33 (66)	16 (64)	0.134
Transient Ischemic Attack	30 (31.90)	6 (12)	0	0.001

## DISCUSSION

Vascular complications, which are frequently observed during TAVR, may affect early mortality and morbidity. Suture-based closure devices generally shorten the operative time and reduce bleeding-related vascular complications (7–9). The effectiveness of such devices varies depending on the diameter of the access artery, device quality, presence of a calcified plaque structure, and diameter of the system to be used. There are many problems related to vascular structures that can negatively impact the effectiveness of these closure devices, especially in geriatric patients (10). Therefore, exploration of the femoral artery, which is an alternative option, combined with primary repair of the entry site, is the safest option, and features the lowest complication

rate in the patients in this study. Few studies have compared the results obtained using Prostar and ProGlide. To the best of our knowledge, no study has compared the results of the two devices with the results of artery exploration and primary repair. In addition to comparing both devices, this study also compared the effects of arterial exploration and primary repair, a procedure that is considered more reliable in terms of preventing complications, on the mortality and morbidity of patients using these devices. This study showed that the complication rates of both closure devices were similar. However, the rates of bleeding and emergency surgical complications, excluding postoperative entry site infection, were significantly higher than those in the exploration and primary repair groups.

**Table 2.** Valve types, times, and postoperative details in all groups

	Group 1	Group 2	Group 3	P
<b>Sapien</b>	76.6% (n=72)	76% (n=38)	24% (n=6)	
<b>Symetis</b>	9.6% (n=9)	12% (n=6)	68% (n=17)	
<b>CoreValve</b>	13.80% (n=13)	12% (n=6)	8% (n=2)	
<b>Bleeding</b>	32 (34) *	14 (28) *	0 <sup>^</sup>	0.292*, 0001 <sup>^</sup>
<b>Operative Time (min)</b>	54*	57*	82 <sup>^</sup>	0.610*, 0.001 <sup>^</sup>
<b>Infection</b>	0	0	2 (8)	0.001
<b>Mortality</b>	7 (7.4)	3 (6)	2 (8)	

Major and minor complications of TAVI-related vascular interventions are listed in the VARC II classification. These include stenosis, occlusion, dissection, surgical repair, suture rupture, bleeding, the need for endovascular stenting, and pseudoaneurysm formation (11, 12). The rates of these complications were 34% (n = 32) in the Prostar group and 28% (n = 14) in the ProGlide group. There were no complications in the surgical exploration group. The complication rates reported for both devices were comparable to those reported in previous studies (13, 14). However, it is noteworthy that no complications were observed in the surgery group, in which only two patients had surgical site infections during the postoperative period. Nevertheless, their length of hospital stay was higher than that of the other two groups, with 10 days of regular antibiotic use and wound care.

The mean age and EuroSCORE of the patient population were similar to those of patients who underwent the TAVI procedure in similar clinics and fell within the range required to qualify for official health insurance coverage in Turkey (15). The mean follow-up period for the patients was 12 months, which is believed to be sufficient for comparing mortality and morbidity beyond the length of hospital stay. There were no significant correlations

between the EuroSCORE values and the rates of bleeding and emergency surgery ( $p = 0.101$ ).

A previous study showed that the sex of the patient influenced the rate of TAVI complications; women were at greater risk (16). This increased risk is thought to stem from the smaller vessel diameter and the fact that vessels can rupture more easily in women (17). According to the results of the present study, there was no significant difference between men and women with respect to complications ( $p = 0.456$ , chi-square test).

Many studies have reported that anticoagulation, peripheral artery disease, or the EuroSCORE value do not have a significant effect on vascular complications on their own (2, 18, 19). In this study, no significant difference was detected in intergroup comparisons of patients with peripheral artery disease, but the rate of complications such as bleeding and the need for emergency surgery was found to be significantly higher according to the intragroup comparison. It is recommended that patients who are on long-term anticoagulants should be treated with TAVI through open exploration instead of using a closure device. Owing to the atherosclerotic and fragile vascular structure in geriatric patients, being selective in terms of preferred access to the



femoral artery for TAVI is essential. CT angiography images should be evaluated in detail, and the use of closure devices through the femoral artery access route should be the first option if no calcification is detected in the anterior wall of the femoral artery. When diffuse calcification and plaque are detected on CT examination, closure devices should not be insisted on, and surgical exploration of the femoral artery followed by primary repair of the artery entry site should be performed with local anesthesia and sedation. This would prolong the operative time by nearly 20 minutes but would lead to a significant increase in mortality and morbidity.

This study also showed that although there was no significant difference between the patients with peripheral artery disease included in each of the closure device groups according to the intergroup comparison, the rates of bleeding and the need for emergency surgery were significantly higher than those found in intragroup comparisons. In our opinion, the sole presence of peripheral artery disease does not require an open exploration approach. However, the presence of a calcified plaque at the access site extending to the anterior wall or lateral walls according to the tomographic examination requires the use of a closure device, which is effective in relation to the calcification of the posterior wall of the access vessel. Therefore, all patients should be examined thoroughly to evaluate vascular structures before the procedure (20, 21).

Another result obtained in our study was that in patients with diabetes mellitus, the rates of bleeding and the need for emergency surgery were significantly higher in the groups treated with closure devices. Since damage to the vascular structure caused by diabetes is well known, TAVI with open exploration and primary repair for diabetic patients is also recommended (22, 23).

Bleeding is known to have a significant effect on 12-month mortality; it is the most important complication of closure devices (24, 25). Although many studies have shown that Prostar causes life-threat-

ening bleeding more frequently than ProGlide, in the present study, there was no significant difference between the two groups.

A closure device was used in 144 patients, and 46 patients underwent urgent medical intervention. Of these 46 patients, 32 were in the Prostar group and 14 in the ProGlide group. Furthermore, 25 patients who were previously treated with femoral exploration did not require emergency medical intervention after primary repair. Recovery problems related to the wound site were identified in only two of the 25 patients; accordingly, the length of hospital stay was extended to 8–12 days. There was no significant difference between these patients in terms of the 12-month postoperative mortality.

No clear data have been found to determine what lies beneath a vascular complication in the literature, but possibilities can be foreseen to a far enough extent to allow a cardiac team of cardiologists and cardiovascular surgeons, when combined with their clinical experience, to make a TAVI decision. In all patients, access angles should be observed with CT angiography for calcifications, plaques, artery wall irregularities, and folds at the access site, particularly in geriatric patients. Surgical exploration of the femoral artery and subsequent primary repair is believed to be more effective because the diameter of the system is wider in some valve models, especially in patients who will receive valve no. 29. Furthermore, we believe that closure materials should not be used in cases where the diameter of the femoral artery is less than 8 mm, particularly when the anterior or lateral walls are covered by a calcified plaque. In our opinion, posterior wall calcification alone does not prevent the use of closure materials, and the effectiveness of closure devices is decreased in patients with a high skin-artery distance, high body mass index, and thick subcutaneous adipose tissue.

This study had some limitations, including its retrospective and non-randomized design. The sample size was relatively smaller than that in previous

reports. Nevertheless, the researchers attempted to avoid bias in patient selection. Second, the distribution of the devices used for vascular closure was not homogenous because the Prostar device was more frequently used, particularly in early-stage TAVI implantations at our center, whereas the use of the ProGlide device was started later. Therefore, our surgeons had more experience with the Prostar device. Third, the sheath diameter was only altered in the Edwards Sapien valves, although it is known that different sheath sizes could lead to varying extents of vascular injury. Fourth, there was no significant difference between the groups with respect to the baseline characteristics. However, there was a trend toward male patients, which could influence the course of vascular complications and mortality.

Although vascular closure devices provide shorter operative times and allow local anesthesia, patients may require surgical re-exploration for vascular complications. There were no differences between the two devices in terms of complications. We suggest that the type of intervention should be

selected according to the risks posed by anesthesia and groin complications.

## ACKNOWLEDGMENTS

We would like to thank the Chief of Cardiology Department Prof. İlgin Karaca, the Chief of Cardiovascular Surgery, Prof. Oktay Burma, and Associate Professor Ayhan Uysal for their interest. We would also like to thank the employees of Editage Corporation who played a role in the design and translation of this study.

## FUNDING

This research was not funded by any public funding agency or by any commercial or nonprofit organizations.

## DECLARATION OF INTEREST

None of the academic staff members at the Cardiology Department of our hospital have any conflicts of interest to declare.

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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.217  
2021; 24(2): 212-219

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Received: Dec 10, 2020  
Accepted: Apr 07, 2021

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## RESEARCH

# FACTORS AFFECTING MORTALITY IN GERIATRIC PATIENTS DIAGNOSED WITH COMMUNITY-ACQUIRED PNEUMONIA TREATED IN INTENSIVE CARE UNITS

## ABSTRACT

**Introduction:** The aim of this study was to determine the factors affecting mortality in elderly patients with community-acquired pneumonia who were receiving intensive care unit.

**Materials and Methods:** The study was retrospective, cross-sectional, and descriptive. The medical records of patients over 65 years of age who were admitted to the intensive care unit with a diagnosis of community-acquired pneumonia between January 1, 2013 and February 29, 2020 were reviewed. The factors associated with mortality in the patients who had died were examined.

**Results:** A total of 208 patients with a mean age of  $75.11 \pm 5.59$  years, 78 of whom were women (37.5%), were included in the study. During the follow-up 35 (16.82%) of 208 patients had died from pneumonia or complications due to pneumonia. According to multiple linear regression analysis, the following parameters were found to be predictors of mortality: Charlson comorbidity index value (odds ratio: 1.44, 95% confidence interval: 1.132–1.1841,  $p=0.003$ ), chronic obstructive pulmonary disease (odds ratio: 0.292, 95% confidence interval: 0.094–1.149,  $p=0.038$ ), congestive heart failure (odds ratio: 0.199, 95% confidence interval: 0.051–0.782,  $p=0.021$ ), saturation value in arterial blood gas (odds ratio: 0.569, 95% confidence interval: 0.804–0.939,  $p<0.001$ ), intubation duration (odds ratio: 3.476, 95% confidence interval: 1.880–6.425,  $p<0.001$ ), hypertension (odds ratio: 3.449, 95% confidence interval: 0.941–12.649,  $p=0.042$ ), and the presence of diabetes mellitus (odds ratio: 3.116, 95% confidence interval: 2.673–59.021,  $p=0.046$ ).

**Conclusion:** Community-acquired pneumonia requiring intensive care unit is a clinical condition with high mortality in the elderly patient population. The presence of comorbid diseases and prolonged intubation time may be associated with higher mortality.

**Key words:** Pneumonia; Mortality; Geriatrics; Intensive Care Units



## INTRODUCTION

Community-acquired pneumonia (CAP) is a common disease among the elderly that has a high mortality rate. The estimated annual incidence of CAP in elderly patients is between 25 and 44 cases per 1000 people (1). The rate of hospitalization of elderly patients due to pneumonia is increasing, and CAP will be even more important in coming years, as 20% of the world population is expected to be elderly by 2050 (1). Compared to the population under 65 years, elderly patients over 65 have a higher incidence of CAP. This patient group almost always has some comorbid conditions, and mortality is higher than in the young population. The mortality rate in patients aged 65 years and over is between 10% and 30% (2). Many studies have been conducted on the relationship between pneumonia and short-term mortality in elderly patients. While in-hospital mortality was evaluated in some of these studies, others evaluated the 30-day mortality rate. Studies have shown that in-hospital mortality rates vary between 6% and 26% due to different inclusion and exclusion criteria (2–3).

Because of its atypical clinical presentation, varied epidemiology, and age-related changes in drug metabolism, CAP in the elderly is challenging for the clinician (1). Incorrect diagnosis of CAP may cause the patient to miss the best treatment opportunity and affect recovery and prognosis. Therefore, it is of great importance that we evaluate CAP progression in elderly patients in a timely and accurate manner.

Most studies investigating the factors affecting mortality in CAP have been conducted on under 65 years patients. Few studies have investigated these factors in elderly patients. The aim of this study was to determine the factors affecting mortality in elderly patients with CAP who were treated in an intensive care unit (ICU).

## MATERIALS AND METHODS

The medical records of patients over the age of 65 who were hospitalized with a diagnosis of CAP

between January 1, 2013, and February 29, 2020 at Baskent University, Faculty of Medicine, Adana Research Center, Turkey, were retrospectively reviewed. Patients with a clinical suspicion of respiratory tract infection (fever, cough, sputum, or dyspnea) and infiltration in the lung parenchyma detected in radiological imaging (direct radiography or computed tomography) were accepted as having a pneumonia diagnosis. Of the patients diagnosed with pneumonia, patients who were directly admitted to the ICU or hospitalized first and then admitted to ICU due to medical necessity were included in the study. The demographic data (age and gender) of the patients and their hemoglobin, white blood cell, thrombocyte, C-reactive protein, procalcitonin, arterial blood gas oxygen, carbon dioxide, saturation, and bicarbonate values were recorded. In addition, the pneumonia severity index, the Charlson comorbidity index (CCI) (4), the microbiology results (sputum, blood, and deep tracheal aspirate culture results), the CURB-65 score, the treatments they received, the length of stay in ICU, the duration of mechanical ventilation, the duration of hospitalization, and the proliferation of the infiltration on chest radiography were recorded. The records of patients who had died during their hospitalization and the patients who were discharged after completion of their treatment were compared, and the data related to mortality were determined. Additionally, by examining the records of patients who had died, the factors affecting mortality and the predictors of mortality were investigated.

Pneumonia occurring at least 48 hours after the patient was hospitalized or pneumonia developing within the first 48 hours after discharge were categorized as hospital-acquired pneumonia, and cases of pneumonia that emerged in the person's daily life other than for the reasons above were accepted as CAP (5). Acute respiratory failure was defined as the presence of severe respiratory distress accompanied by decreased oxygen saturation (<92%) in room air, hypoxemia (partial oxygen pressure <60

mm Hg), or the need for invasive/noninvasive mechanical ventilation. Blood cultures were taken from all patients. Sputum culture was obtained from the patients who could give sputum samples, while deep tracheal aspirate culture was obtained from the intubated patients. Antibiotic treatment was initiated empirically for all patients in accordance with the guidelines and antibiotic treatment was rearranged, if necessary, according to the culture results (6-7).

### Study exclusion criteria

Those who are under the age of 65, who develop pneumonia 48 hours after hospitalization, have a history of hospitalization within the last 48 hours when pneumonia is diagnosed, patients not treated in ICU during their hospitalization, bronchiectasis, chronic respiratory failure, renal failure requiring renal replacement therapy, use of immune suppressants, transplantation patients with end-stage chronic liver failure, those patients who did not have sufficient clinical information in their files, those who had another infection accompanying pneumonia during hospital admission, those who left the hospital voluntarily during the treatment, and patients who did not accept treatment, were excluded from the study.

### Statistical analyses

Continuous variables are expressed as mean  $\pm$  standard deviation or median (range, interquartile range [IQR]). Categorical data are presented as proportion. Chi-square test was used to analyze categorical parameters. Unpaired t-test was used to analyze continuous variables with normal distribution. Mann-Whitney U test was used to analyze continuous variables with non-normal distribution. Independent determinants of mortality were determined by standard multiple linear regression analysis. Continuous variables were checked with Kolmogorov-Smirnov test to assess whether they

were normally distributed. Values for  $p < 0.05$  were assessed statistically significant. The statistical software, SPSS was used for statistical analysis (SPSS version 21.0 for Windows; SPSS, Inc., Chicago, Illinois, US).

### RESULTS

A total of 208 patients (78 [37.5%] women) with a mean age of  $75.11 \pm 5.59$  years were included in the study. The patients' baseline demographic, clinical and laboratory characteristics are summarized in Table-1. The median duration of ICU stay was 3 (IQR = 2) days, and the median length of stay in the normal ward was 5.5 (IQR = 4) days. Blood cultures were taken from all patients, and 48 (23.07%) patients had a positive blood culture. Gram-positive cocci were found in the blood culture of 33 (68.75%) patients, Gram-negative bacilli were observed in the blood culture of 10 (20.83%) patients, and *Acinetobacter* growth was seen in the blood culture of 5 (10.41%) patients. Sputum culture was obtained from 93 (44.71%) patients; reproduction occurred in 72 (77.41%) of these patients. The sputum culture of 51 (70.83%) patients had Gram-positive cocci, 14 (19.44%) had Gram-negative bacilli, and 7 (9.72%) had *Acinetobacter* growth. Deep tracheal aspirate culture was obtained from 32 patients. *Acinetobacter* reproduced in 11 (34.37%) of these patients, while Gram-positive cocci growth in 9 (28.12%) patients and Gram-negative bacillus growth in 6 (18.75%) patients were observed. There was no growth in the deep tracheal aspirate culture of 6 (18.75%) patients. A total of 32 patients (15.3%) needed invasive mechanical ventilation. During the follow-up, 35 (16.82%) of 208 patients died from pneumonia and pneumonia-related complications.

The comparison of the baseline clinical, demographic, and laboratory data of surviving and non-surviving patients summarized in Table-2. According to the multiple linear regression analysis, the CCI score, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), ox-



**Table-1.** Baseline clinical and laboratory parameters in the study population

Age (year)	75.11±6.69
Female gender, n (%)	78 (37.5)
Charlson comorbidity index	4.69±1.50
CURB-65 score	2.28±0.57
Pneumonia severity index	3.89±0.68
Hypertension, n (%)	81 (38.9)
COPD, n (%)	59 (28.4)
Diabetes mellitus, n (%)	63 (30.3)
Asthma, n (%)	22 (10.6)
SVA, n (%)	37 (17.8)
Chronic liver disease, n (%)	4 (1.9)
Malignant, n (%)	12 (5.8)
Myasthenia gravis, n (%)	1 (0.5)
Dementia, n (%)	27 (13)
Heart failure, n (%)	29 (13.9)
Chronic kidney disease, n (%)	9 (4.3)
Hemoglobin (gr/dL)	12.29±1.86
White blood cell (/mm <sup>3</sup> )	13243±7387
Platelets (100/mm <sup>3</sup> )	247 (IQR=158)
Creatinine (mg/dL)	1.19±0.52
Sodium (mmol/L)	137.89±5.81
Potassium (mmol/L)	4.24±0.52
C-reactive protein (mg/L)	103 (IQR=137)
Procalcitonine (ng/mL)	0.6 IQR=1.3)
Arterial blood gas pH	7.42±0.06
Arterial blood gas oxygen saturation (%)	88.08±7.70
Arterial blood gas oxygen (mm Hg)	58.60±11.30
Arterial blood gas carbondioxide (mm Hg)	33.95±9.20
Arterial blood gas bicarbonate (mmol/L)	23.00±4.01

COPD: Chronic obstructive pulmonary disease, IQR: Inter quartile range, SVA: Serebro vascular accident

xygen saturation value in arterial blood gas at first admission, intubation time, hypertension, and diabetes mellitus were predictors of mortality. The regression analysis results are summarized in Table-3.

## DISCUSSION

According to the results of our study, the mortality from CAP in patients over 65 years old was 16.82%. The oxygen saturation value in arterial blood gas at first admission, COPD, CHF, hypertension, diabetes mellitus, intubation time, and the CCI score were predictors of mortality.

In elderly patients, both in- and out-of-hospital CAP mortality is higher than in non-elderly patients. In a study by Mangen et al., in which 562 patients with CAP over the age of 65 were examined, the annual mortality after discharge in elderly patients was found to be six times higher than in non-elderly patients. Their study also observed a 16% higher reduction in the quality of life of elderly patients after discharge (8). The increase in mortality in elderly patients may be due to comorbid conditions. It is well known that elderly patients with high comorbidity have low resistance to infections. In various studies, chronic respiratory disease, COPD, diabetes mellitus, chronic cardiovascular diseases, and chronic neurological diseases have been found to be the most common comorbid diseases observed in elderly patients during their pneumonia treatment (9-10). In addition, these comorbid conditions have been associated with prolonged hospitalization, prolonged ICU admission, sepsis, readmission, and mortality (10-11). The results of our study are consistent with the literature, and these comorbid conditions were observed with a higher incidence in the group that died in our study. Moreover, COPD, CHF, hypertension, and diabetes mellitus were factors that directly affected mortality in our study (9-11).

In elderly patients, the mortality of conditions requiring respiratory ICU admission may be high. In a recent study, the most common respiratory rea-

**Table-2.** Comparison of baseline clinical, demographic and laboratory values between groups with and without exitus

	No exitus (n=173)	Exitus (n=35)	p
Age (year)	75.27±6.91	74.31±5.54	0.445
Female gender, n (%)	69 (39.9)	9 (25.7)	0.114
Charlson comorbidity index	4.55±1.46	5.40±1.51	0.002
Pneumonia severity index	3.76±0.61	4.57±0.55	<0.001
CURB-65 score	2.08±0.26	3.29±0.62	<0.001
Hypertension, n (%)	63 (36.4)	18 (51.4)	0.097
COPD, n (%)	43 (24.9)	16 (45.7)	0.013
Diabetes mellitus, n (%)	50 (28.9)	13 (37.1)	0.333
Asthma, n (%)	18 (10.4)	4 (11.4)	0.77
SVA, n (%)	25 (14.5)	12 (34.3)	0.005
Chronic liver disease, n (%)	4 (2.3)	0 (0)	NA
Malignant, n (%)	11 (6.4)	1 (2.9)	0.695
Myasthenia gravis, n (%)	0 (0)	1 (2.9)	NA
Dementia, n (%)	18 (10.4)	9 (25.7)	0.014
Heart failure, n (%)	18 (10.4)	11(31.4)	0.001
Chronic kidney disease, n (%)	8 (4.6)	1 (2.9)	0.534
Hemoglobin (gr/dL)	12.33±1.89	12.06±1.73	0.442
White blood cell (/mm <sup>3</sup> )	13077±7543	14062±6610	0.473
Platelets (100/mm <sup>3</sup> )	238 (IQR=158)	284 (IQR=149)	0.172
Creatinine (mg/dL)	1.06±0.46	1.27±0.96	0.054
Sodium (mmol/L)	137.56±5.05	139.51±8.53	0.07
Potassium (mmol/L)	4.23±0.48	4.3±0.68	0.473
C-reactive protein(mg/L)	96 (IQR=132)	154 (IQR=118)	0.007
Procalcitonine (mg/L)	0.46 (IQR=1.1)	1.3 (IQR=1.4)	<0.001
Arterial blood gas pH	7.42±0.05	7.38±0.09	<0.001
Arterial blood gas oxygen saturation (%)	89.79±5.8	79.68±10.18	<0.001
Arterial blood gas oxygen (mm Hg)	60.62±10.54	48.65±9.6	<0.001
Arterial blood gas carbondioxide (mm Hg)	33.17±6.88	37.77±16.05	0.007
Arterial blood gas bicarbonate (mmol/L)	22.97±2.95	23.15±7.33	0.807

COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range, NA: Non-available, SVA: Serebro vascular accident



**Table-3.** Multiple linear regression analysis of mortality with clinical variables.

	Beta coefficient	OR	p	95% Confidence Interval	
				Lower	Upper
Charlson comorbidity index	0.367	1.444	0.003	1.132	1.841
COPD	-1.231	0.292	0.038	0.094	1.149
CHF	-1.615	0.199	0.021	0.051	0.782
Saturation in arterial blood gas*	-0.141	0.869	<0.001	0.804	0.939
Intubation duration time	1.246	3.476	<0.001	1.880	6.425
Hypertension	1.238	3.449	0.042	0.941	12.649
Diabetes mellitus	1.137	3.116	0.046	0.817	11.885
Dementia	2.531	12.560	0.001	2.673	59.021

\*First application blood gas, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, OR: Odds ratio

son for admission to ICU in patients over 65 years of age was pneumonia, with a 65% incidence. In the same study, albumin levels, APACHE II scores, and vasopressor requirements were the most important determinants of mortality (12). Some studies have investigated the predictors of mortality in CAP in elderly patients. In a retrospective study by Öcal et al. that included 186 patients (mean age  $63.7 \pm 20.5$  years; 114 patients > 65 years old), the determinants of mortality in geriatric patients hospitalized with a diagnosis of pneumonia were investigated. According to their results, age, prolonged ICU admission, anemia, hypoglycemia, hypoalbuminemia, and increased lactate dehydrogenase levels were risk factors for mortality. Furthermore, the mean length of ICU stay was longer for the geriatric patients (13).

According to another result of our study, the CCI score may be a predictor of mortality. Some studies have investigated mortality predictors in patients with CAP. Among these studies, the most frequently investigated were the pneumonia severity index and the CURB-65 score. Although there are conflicting results in different studies, the accuracy rate of these risk scoring systems decreases in elderly patients (1,14). In a study by Franzen et al. that included 108 patients with CAP, the CCI score was not associated with undesirable, poor results. The

reason why the results of this study differ from our study may be that it included patients from all age groups, and none of the patients required ICU hospitalization. Also, the pneumonia severity index was found to be a predictor of undesirable outcomes (15). In another study by Nguyen et al. (median age 79) with 565 patients with CAP, the CCI score was associated with high in-hospital mortality (Odds ratio [OR]:1.28; 95% Confidence interval [CI]: 1.07–1.53) (16). The fact that this study investigated an elderly patient group may account for the similar results to our study.

The strength of the study is that it is a clinical study and gives direct information about the factors affecting mortality in elderly patients on the other hand the weakness of our study is that it was a single center study.

**Limitations of the study:** The biggest limitation of our study is that it was conducted with a small number of patients. These results should be confirmed with multi-center studies including more patients. The retrospective study design is another limitation. The difference between the time of admission to the hospital after the onset of symptoms and the different treatment initiation times of the patients included in the study may also have affected the results.

**Conclusion:** According to the results of our study, the mortality of CAP in patients over 65 years old was 16.8%. The predictors of mortality may be the values of some parameters during initial admission to the hospital, such as blood gas saturation and CCI score, the intubation period and the presence of COPD, CHF, hypertension, and diabetes mellitus.

**Conflict of Interest, Disclosure Statement:** The authors declare that they have no conflicts of interest. The authors have indicated the have no finan-

cial relationships relevant to this article to disclose

**Ethical Approval:** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by Baskent University Institutional Review Board (Project no: KA20/39) and supported by Baskent University Research Fund.

**Acknowledgments:** None

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## RESEARCH

# CAN PERCUTANEOUS NEPHROLITHOTOMY BE SAFELY PERFORMED ON OCTOGENARIANS?

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.218  
2021; 24(2): 220-226

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## ABSTRACT

**Introduction:** This study aimed to analyze the efficacy and safety of the percutaneous nephrolithotomy procedure in octogenarians and compare them with the outcomes in a young patient group.

**Materials and Methods:** Patients older than 80 and younger than 90 were included in Group 1, and patients younger than 65 were assigned to Group 2. Group 1 included 45 patients, and Group 2 consisted of 90 patients recruited by one-to-two case-control matching based on gender, stone area, and the number of staghorn stones.

**Results:** The mean patient age was  $81.89 \pm 1.70$  and  $38.7 \pm 12.5$  years in Groups 1 and 2, respectively. The patients in Group 1 had a significantly higher rate of systemic hypertension. Pre-operative and post-operative serum creatinine levels were higher in Group 1 than in Group 2. The groups did not differ in terms of the preoperative serum hemoglobin level. However, the postoperative serum hemoglobin level was significantly lower in Group 1. There was no difference between the two groups in terms of the rate of blood transfusions. The duration of hospital stay was significantly longer in Group 1. However, the two groups were not different in terms of minor and major complications. The stone-free rates were calculated as 73.3% and 77.8% in Groups 1 and 2, respectively. There was no difference between the groups in terms of stone-free rates ( $p = 0.567$ ).

**Conclusion:** The percutaneous nephrolithotomy procedure is an effective and safe method for treating renal stone disease in octogenarians.

**Keywords:** Aged, 80 and over; Nephrolithotomy, Percutaneous; Nephrolithiasis



## INTRODUCTION

Percutaneous nephrolithotomy (PCNL) has a considerable role in the surgical treatment of renal stone disease (1). PCNL has been reported to be effective and safe in treating all renal stone patients, including those in their 70s (2). In accordance with the general population's increased life expectancy over the past decades, the incidence of urinary tract stone disease has also increased in the geriatric patient population. Therefore, the rates of PCNL and other surgical interventions performed for renal stone disease in this patient population have also increased. However, cardiovascular comorbidities and the associated high American Society of Anesthesiology scores of these patients are known to complicate both the preoperative and perioperative management of these patients (3,4).

Despite these reservations, the literature on the efficacy and safety of PCNL in octogenarians is scarce (5,6). In this study, we aimed to compare the outcomes and complication rates of PCNL in octogenarians with those in a relatively young control group.

## MATERIALS AND METHODS

The ethical review committee of our university approved this study, with approval number 200197. Data of the 450 patients who underwent PCNL at our department between January 2014 and January 2020 were retrospectively reviewed. Among these patients, those who were 80 or older constituted Group 1. The patients in Group 1 were reviewed in terms of gender, stone area, and the number of staghorn stones. These data were used to form the control group by one-to-two case-control matching among patients aged between 18 and 70. Thus, the groups were equated in terms of the mean stone area, the number of staghorn stones, and gender distribution.

Patients younger than 18, pregnant patients, patients with bleeding diathesis, and those with con-

genital renal anomalies were not included.

The PCNL procedure was performed for renal stones larger than 20 mm. All patients underwent PCNL, provided that their urine culture was sterile. Three experienced endourologists performed all PCNL procedures. A 6F ureteral catheter was inserted into the ipsilateral ureter through rigid cystoscopy, and the renal calyceal system was punctured in a prone position by an 18G diamond-tipped needle under fluoroscopy guidance. The percutaneous access tract was dilated by Amplatz (Cook Medical LLC, Bloomington IN, US) dilators, with diameters ranging from 8F to 30F. The renal stones were fragmented by a pneumatic lithotripter, and the stone fragments were removed by a stone grasper. A percutaneous nephrostomy tube was inserted in all PCNL cases. The ipsilateral urinary tract was scanned using flexible nephroscopy, antegrade nephrostogram, and fluoroscopy to detect residual stones immediately before the completion of the procedure. Non-contrast abdominopelvic tomography was performed if there was suspicion of clinically significant residual stone fragments postoperatively. A repeat PCNL procedure or ureteroscopy was performed for the treatment of these residual stones. In cases without clinically significant residual fragments, the nephrostomy tube and the ureter catheter were simultaneously removed after confirming the tract's patency through an antegrade nephrostogram. All patients underwent renal ultrasound or non-contrast abdominopelvic tomography at the 6<sup>th</sup> and 12<sup>th</sup> weeks of follow-up after discharge.

The demographic parameters and data on comorbidities, preoperative and postoperative complete blood count and blood biochemistry results, duration of hospital stay, blood transfusion, and stone-free rates and stone characteristics of the study patients were retrieved from patient folders. Moreover, the complications encountered within the postoperative 30 days were reviewed and graded as per the modified Clavien-Dindo classification

system. The patients who did not have any clinically significant residual stone fragments during the postoperative sixth-week follow-up visit were considered "stone-free."

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 22.0 software (SPSS Inc., Chicago, IL, USA). The student's t-test was used to compare the continuous variables with a normal distribution, and the chi-square test was utilized to compare the categorical variables. The differences were considered significant when the p-value was less than 0.05.

## RESULTS

The mean patient age was  $81.89 \pm 1.70$  and  $38.7 \pm 12.5$  in Groups 1 and 2, respectively. Group 1 consisted of 45 patients aged 80 and 87, and Group 2 included 90 patients aged between 21 and 65. No significant difference was found between the groups in terms of gender distribution ( $p = 0.624$ ) (Table 1). A comparison of the groups in comorbidity status revealed that the rate of systemic hypertension (HT) was significantly higher in Group 1 ( $p = 0.038$ ). No difference was observed between the two groups in terms of the rate of other systemic

**Table 1.** Demographics and comparison of preop values between groups.

	Octogenarian Group-1	Young Group-2	p-Value
Number of Patients (n)	45	90	
<b>Gender</b>			
Female (%)	21 (46.7)	38 (42.2)	
Male (%)	24 (53.3)	52 (57.8)	0.624
Age (mean±SD)	81.89±1.70	38.7±12.5	<b>0.001</b>
<b>Comorbidity</b>			
Diabetes Mellitus (%)	10 (22.2)	23 (25.6)	0.671
Hypertension (%)	20 (44.4)	24 (26.7)	<b>0.038</b>
Coronary Artery Disease (%)	11 (24.4)	13 (14.4)	0.152
<b>Medications</b>			
Aspirin (%)	20 (44.4)	14 (15.6)	
Coumadin (%)	8 (17.8)	2 (2.2)	
Clopidogel (%)	13 (28.9)	2 (2.2)	
Combination (%)	4 (8.9)	0 (0)	<b>0.001</b>
<b>Preop Laboratory</b>			
Mean Serum Creatinin (mg/dl±SD)	1.11±0.42	0.86±0.25	<b>0.001</b>
Mean Serum Hemoglobin (g/dl±SD)	12.16±1.86	12.63±2.12	0.204
<b>Stone Characteristic</b>			
Mean Stone Area (mm <sup>2</sup> )	385.17±51.47	387.94±45.9	0.752
Staghorn Stone (%)	12(26.7)	21(23.6)	0.697
<b>Laterality</b>			
Left (%)	24 (53.3)	56 (62.2)	
Right (%)	21 (46.7)	34 (37.8)	0.322



comorbid diseases. The ratio of patients on anticoagulant or antiplatelet medications was significantly higher in Group 1 than in Group 2 ( $p = 0.001$ ) (Table 1).

Whereas the preoperative mean serum creatinine level was significantly higher in Group 1 than in Group 2, there was no difference between the groups in terms of the preoperative mean serum hemoglobin levels ( $p = 0.001$  and  $p = 0.204$ , respectively) (Table 1).

The two groups were similar in terms of the total stone area and the number of staghorn stones due to the study cohort's case-control matched design. The postoperative mean serum creatinine level was significantly higher in Group 1 than in Group 2, whereas the postoperative mean hemoglobin level was lower in Group 1 than in Group 2 ( $p = 0.007$  and  $p = 0.029$ , respectively). The number of patients that required blood transfusion was 4 (8.9%) in Group 1 and 6 (6.7%) in Group 2. The mean operative times of Group 1 and Group 2 were  $66.12 \pm 11.47$  and  $62.61 \pm 12.81$  minutes, respective-

ly. No significant difference was found between the two groups in terms of blood transfusion rates and operative time ( $p = 0.642$  and  $p = 0.124$ , respectively). However, hospital stay duration was significantly longer in Group 1 than in Group 2 ( $p = 0.03$ ). The comparison in complications revealed no difference between the two groups in terms of the minor (Clavien-Dindo grades 1 and 2) and major (Clavien-Dindo grades 3 and 4) complication rates ( $p = 0.81$ ) (Table 2). Among the six patients in Group 1 who had major complications, four required retrograde double J stent (DJS) insertion because of persistent urine leakage from the nephrostomy tract, and one underwent retrograde DJS insertion because of renal colic associated with clot retention. The other patient had to undergo retrograde intrarenal stone surgery with DJS insertion because of a clinically significant residual lower pole stone. The stone-free rates were determined to be 73.3% and 77.8%, respectively. A comparison of the stone-free rates revealed no statistically significant difference between the groups ( $p = 0.567$ ) (Table 2).

**Table 2.** Comparison of postop values and complications between groups.

Variable	Octogenarian Group-1	Young Group-2	p-Value
<b>Postop Laboratory</b>			
Mean Serum Creatinin (mg/dl $\pm$ SD)	1.048 $\pm$ 0.45	0.88 $\pm$ 0.23	<b>0.007</b>
Mean Serum Hemoglobin (g/dl $\pm$ SD)	11.2 $\pm$ 1.59	11.9 $\pm$ 1.99	<b>0.029</b>
Transfusion (%)	4 (8.9)	6 (6.7)	0.642
Operative Time (mean, minutes)	66.12 $\pm$ 11.47	62.61 $\pm$ 12.81	0.124
Length of Stay (mean, day)	2.91 $\pm$ 1.8	2.32 $\pm$ 1.2	<b>0.03</b>
<b>Complication Rate</b>			
Clavien 1-2 (%)	11 (24.4)	25 (27.8)	
Clavien 3-4 (%)	6 (13.4)	13 (13.3)	
Clavien 5 (%)	0	0	0.081
Stone Free Rate (%)	33 (73.3)	70 (77.8)	0.567

## DISCUSSION

The incidence of nephrolithiasis is higher in octogenarians than in the general population (7). This relatively high incidence paves the way for increased urinary tract infection and renal dysfunction rates (8)  $p = 0.46$ . Although some of these cases benefit from conservative treatments, some mandate surgical interventions for definitive treatment. During the decision-making process, it should be considered that these patients may have impaired functional reserve with increased sensitization to complications, such as bleeding and urosepsis (9).

The potential complications of PCNL are renal hemorrhage requiring intervention (0.6%–1.4%), urosepsis (0.9%–4.7%), pulmonary complications (3.1%–23%), adjacent organ injury (0.2%), and the requirement of a second intervention that brings additional anesthesia-related risks (10). The risk of these complications is higher in octogenarians because of the higher age of these patients and their increased rate of comorbid conditions (11). In studies investigating the data of PCNL patients older than 60, the rate of comorbidities, such as HT, diabetes mellitus (DM), or chronic obstructive pulmonary disorder, was 66%–88% (12,13). In a study conducted by the Endourological Society PCNL study group that compared the outcomes of patients older than 70 with those of patients younger than 70 (i.e., 18–70 years), the rates of DM, cardiovascular diseases, and anticoagulant and prednisone use were significantly higher in the former group than in the latter (2). Thus, Morganstern et al., who compared octogenarians with young patients undergoing PCNL procedures, observed that comorbid conditions were significantly more prevalent in octogenarians (5). Consistent with our study, these authors also reported that the rate of systemic HT was significantly higher in octogenarians. In accordance with the studies that determined higher rates of antiplatelet or anticoagulant medication use, all the patients in Group 1 (i.e., octogenarians) of our study were on anticoagulant medications (5,14).

The prevalence of end-stage renal disease (ESRD) was calculated as 31% in octogenarians (15). This level is significantly higher than the rate of ESRD in the general patient population (i.e., 14%). In our study, we found a significant difference between the two groups in terms of both preoperative and postoperative serum creatinine levels. In another study, the researchers found similar results and reported that the mean serum creatinine levels were higher in octogenarians than in young patients, both preoperatively and postoperatively (2,6,14).

Some studies showed no statistically significant difference between old and young PCNL patients in terms of the postoperative decrease in hemoglobin levels and blood transfusion rates (4,5). Conversely, octogenarians had lower preoperative and postoperative hemoglobin levels and a higher risk of requiring blood transfusions than younger patients (6). These findings are consistent with ours.

The rate of blood transfusion increases with aging in the PCNL patient population (6). In our study, the higher blood transfusion ratio in octogenarians can be due to both older age and frequent use of anticoagulant medications.

Morganstern et al. reported that hospital stay duration was longer for octogenarians than for young patients, but the difference was not statistically significant (5). Conversely, some studies found a significantly longer mean post-PCNL hospital stay in octogenarians than in young patients (6).

Studies evaluating the success of PCNL in patients older than 65 years reported complication rates of 13% or 14% (4,10,16). Nevertheless, studies conducted on octogenarians reported complication rates of 25%–36% (5,6). In accordance with these reports, the complication rate was calculated as 37% in our series. Our analysis of the classification of the complications as per the modified Clavien-Dindo classification system revealed that the complication rate of octogenarians was similar to that of the young patient group. This finding is also in accordance with previous reports (5).



Conversely, some studies reported different results (6). Abedali et al. found that Clavien-Dindo grade 2 and grade 3 complications were higher in octogenarians than in younger patients (6). These differences need to be explained by more extensive clinical trials.

Studies comparing patients older than 65 with young patients in terms of PCNL success reported stone-free rates of 70%–72% in both patient groups (2,4). Some trials, including octogenarians undergoing PCNL, reported stone-free rates of 72%–78%, and the comparison of stone-free rates between octogenarians and young patients did not reveal any significant difference (5,6) In our study, the octogenarians' stone-free rate was similar to that in the literature but lower than that in our young patients. However, the difference was not statistically significant.

This study has some limitations that need to be considered when evaluating its findings. First, it is a retrospective study, as a result the surgeries were not performed by the same surgeon. Second, data on the stone analysis results and the Charlson comorbidity index scores of the patients were not available. In addition, the sample size was relatively

small, more cases might have revealed further significant results. The fact that the study was carried out at a single center restricts its ability to reflect the results of the general practice. Nevertheless, considering that some urology centers hesitate to perform PCNL on octogenarians, we believe that our findings on the safety of this procedure in octogenarians are encouraging.

## CONCLUSIONS

Despite the weaknesses of this study, we conclude that octogenarians may have cardiovascular or other types of comorbidities that can be challenging to both the urologists who will perform the PCNL procedure and the anesthesiologists. Nevertheless, PCNL can be safely performed in octogenarians with success and complication rates comparable with those of the young patient population.

## ACKNOWLEDGMENTS: -

**Conflicts of interest:** The authors declare no conflicts of interest.

**Financial support:** None. The authors have no industrial links.

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## RESEARCH

# EVALUATION OF PATIENTS FOLLOWED IN A PALLIATIVE CARE UNIT IN TURKEY

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.219  
2021; 24(2): 227-234

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## ABSTRACT

**Introduction:** The need for palliative care services is increasing day by day, but we think that these services are not sufficiently recognized by the society and health professionals. In this study, by presenting sociodemographic and clinical characteristics of the patients hospitalized in the palliative care unit together, we seek to raise awareness of palliative care services, which are still developing in Turkey.

**Materials and Method:** In this descriptive and retrospective study, 316 patients hospitalized in Palliative Care Unit of Harran University Research and Practice Hospital between April 2017- February 2019 were included. Sociodemographic characteristics and clinical data of the patients were evaluated. Falling risk is evaluated according to the Itaki Fall Risk Scale, Pressure Ulcers according to the guidelines published jointly by the National and European Pressure Ulcer Advisory Panels. The data were analyzed using frequency and percentage tests.

**Results:** Of 316 patients, 54.43%(n=172) were female, 45.57%(n=144) male; mean age was 66.23±19.66 years (18-111). The most common reason for hospitalization was cerebrovascular disease with a rate of 22.15%(n=70), then respectively malignancy was at 20.89%(n=66), cardiovascular disease at 15.19%(n=48), asthma/chronic obstructive pulmonary disease and Alzheimer's disease at 5.70%(n=18). Comorbidity was found at 88.61%(n=280) and majority of the patients (67.72%) were fed orally. The rate of patients with tracheostomy was 3.80%(n=12) and pressure ulcer at 23.70%(n=75).

**Conclusion:** Symptoms, pressure ulcers and nutritional support treatments in patients hospitalized in palliative care unit were presented with sociodemographic data. We believe that this study can help contribute to the awareness of palliative care and service scope, which is still developing in Turkey and around the world.

**Keywords:** Palliative Care; Pressure Ulcer; Nutritional Support; Aged.

## INTRODUCTION

Palliative care is a multidisciplinary approach that focuses on preventing and alleviating pain and promoting the best possible quality of life through early diagnosis, evaluation, and treatment of physical, mental, psychological and social problems of patients facing a terminal disease and those patient's families. It aims to relieve distress in all stages of the disease. Palliative care can be given at the same time with curative or life-extending treatments (1, 2). Palliative care is a set of services from birth to death that also includes the management of the family's mourning process after a patient's death (3).

The need for palliative care is increasing due to aging populations in Turkey and around the world (4). Cancers, central and peripheral neuronal diseases, muscle diseases, organ failures, irreversible trauma damages, infectious diseases such as HIV/AIDS, progressive genetic congenital diseases in children can be counted among the diseases followed in palliative care (5). One of the basic principles of palliative care is symptom management. Common symptoms include pain, fatigue, anorexia, constipation, dyspnea, cough, nausea, diarrhea, and anxiety (6). In a systematic review, it was stated that early integration of palliative care enables better symptom management, longer survival and better quality of life (7). According to the World Health Organization (WHO), 40 million people need palliative care every year, and 78% of these people live in low- and middle-income countries (2). Palliative care should be developed at the primary care level, including home and community-based care. Providing palliative care should be seen as an ethical duty for healthcare professionals (2,8).

The need for palliative care services is increasing day by day, but we think that these services are not sufficiently recognized by the society and health professionals. In this study, in which we evaluated data from a palliative care unit (PCU), we seek to increase the awareness about palliative care services that are still developing in Turkey by sharing nearly two years of experience.

## MATERIALS AND METHOD

This retrospective study was carried out by examining the data of patients hospitalized in the PCU at Harran University Research and Application Hospital in Sanliurfa, a city of over two million residents in southeastern Turkey. The study universe consisted of 316 patients hospitalized in that PCU between April 2017 and February 2019. For patients with repeated hospitalizations, data from first hospitalizations were evaluated. This study was undertaken with the approval of the Ethics Committee of Harran University Medical Faculty.

Patient data such as sociodemographic characteristics, general conditions, duration of hospital stay, activity status, falling risks, comorbidities, feeding patterns, pressure ulcers, tracheostomy status, reasons for receiving caregiver support, and status upon leaving PCU were evaluated. The falling risks of the patients were evaluated according to the Itaki Fall Risk Scale scores developed by the Ministry of Health, which was developed specifically for our country to prevent patients from falling (9). The results obtained by evaluating the patients with the Fall Risk Scale were divided into two groups; if the total score is below 5, it is considered as low risk and if the total score is above 5, it is considered as high risk. For pressure ulcer staging, the stages published by the European Pressure Ulcer Advisory Panel (EPUAP) and the National Pressure Ulcer Advisory Panel (NPUAP) were used (10).

The data were analyzed using the IBM Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). Descriptive analytical methods (means for continuous variables and percentages for categorical variables) were used in evaluating the data. The results were evaluated at a 95% confidence interval, and the significance level was  $p < 0.05$ .

Ethical approval was obtained from the local Ethics Committee (approval number: HRÜ/19.03.37-11.03.2019-03)



## RESULTS

Of the 316 patients hospitalized in the PCU and included in the study, 54.43% (n=172) were female and 45.57% (n=144) male; the mean age was  $66.23 \pm 19.66$  (18-111). From a demographic perspective, 66.54% (n=171) were married, 53.48% (n=169) lived in the city, and 44.30% (n=140) were illiterate. The complete sociodemographic characteristics of the patients included in the study are presented in Table 1.

It was found that 62.00% of the patients' (n=196) general status was moderate, and 50% (n=158) were dependent when their activity status was examined. Fall risk scores placed 76.58% (n=242) of patients in the high-risk, the average fall risk score was  $10.62 \pm 6.87$  (0-40). When feeding status was examined, 67.72% (n=214) of patients were fed orally. 3.80% (n=12) of the patients had tracheostomy.

Pressure ulcers were present in 23.70% (n=75) of patients and the majority of them were stage-2 ulcers in 40.00% (n=30). More detailed information about the patients' health characteristics is presented in Table 2.

The most common reason for hospitalization was cerebrovascular disease. Other most common reasons for hospitalization were malignancy at 20.89% (n=66), cardiovascular disease at 15.19% (n=48), asthma/ chronic obstructive pulmonary disease (COPD) at 5.70% (n=18), Alzheimer's disease at %5.70 (n=18). The detailed information on reasons for hospitalization is presented in Table 3.

Comorbidity was found in 88.61% of the patients (n=280), involving diseases such as hypertension, diabetes mellitus, cardiovascular disease, asthma, COPD, hepatitis, cerebrovascular disease, cancer, Alzheimer's, and Parkinson's. The most common

**Table 1.** Sociodemographic characteristics of the patients

	Mean $\pm$ SD (Min- Max)	
Age (year)	66.23 $\pm$ 19.66 (18- 111)	
		n (%)
Gender	Female Male	172 (54.43) 144 (45.57)
Marital status	Single Married Widow Unknown <sup>a</sup>	22 (8.56) 171 (66.54) 64 (24.90) 59 (18.70)
Working status	Not working Working Unknown <sup>a</sup>	233 (73.73) 51 (16.14) 32 (10.13)
Residential area	Rural Town Urban Unknown <sup>a</sup>	35 (11.08) 23 (7.28) 169 (53.48) 89 (28.16)
Education status	illiterate Literate/ Primary education High school/ University Unknown <sup>a</sup>	140 (44.30) 91 (28.79) 12 (3.79) 73 (23.12)

<sup>a</sup>Refers to those whose information cannot be reached from the files

**Table 2.** Clinical features of the patients

		n (%)
<b>General status</b>	Good	24 (7.60)
	Middle	196 (62.00)
	Bad	67 (21.20)
	Unknown <sup>a</sup>	29 (9.20)
<b>Activity status</b>	Dependent	158 (50.00)
	Semi dependent	106 (33.54)
	Independent	52 (16.46)
<b>Falling risk</b>	Low risk	74 (23.42)
	High risk	242 (76.58)
<b>Comorbid disease</b>	Yes	280 (88.61)
	No	36 (11.39)
<b>Feeding style</b>	Oral	214 (67.72)
	Nasogastric	41 (12.97)
	Percutaneous endoscopic gastrostomy	23 (7.28)
	Parenteral	38 (12.03)
<b>Tracheostomy</b>	Yes	12 (3.80)
	No	304 (96.20)
<b>Pressure ulcer</b>	Yes	75 (23.70)
	No	241 (76.30)
<b>Stage of the pressure ulcer</b>	Stage-1	9 (12.00)
	Stage-2	30 (40.00)
	Stage-3	19 (25.33)
	Stage-4	17 (22.67)

<sup>a</sup> Refers to those whose information cannot be reached from the files.

complaints reported by patients or their relatives were malnutrition with a rate of 38.30% (n=167), pressure ulcer 20.41% (n=89), cough or respiratory distress 14.45% (n=63), weakness or fatigue 9.40% (n=41), nausea or vomiting 4.13% (n=18), abdominal pain 4.13% (n=18), urinary tract problems 3.21% (n=14), dizziness or headache 2.52% (n=11), syncope or convulsions 2.29% (n=10), and fever 1.15% (n=5). In some patients, there was more than one complaint at the time of application.

All patients had caregiver support; 53.48% (n=169) of caregivers were spouses, 8.23% (n=26) fathers, 1.58% (n=5) mothers, 1.90% (n=6) brides, 12.34% (n=39) daughters, 3.16% (n=10) sons, and

3.80% (n=12) other relatives. Information about caregivers was not available for 15.51% (n=49) patients.

It was observed that 62.34% (n=197) of patients were transferred from another service, 23.42% (n=74) from the emergency service, and 14.24% (n=45) from the polyclinic. The mean duration of hospitalization of patients in the PCU was 13.92±20.35 days (1-250). According to the analysis of the patients' manner of leaving the PCU, 63.92% (n=202) were discharged, 18.35% (n=58) were referred to the intensive care unit, and 13.92% (n=44) to other wards. 3.80% of the patients (n=12) died in the PCU.

**Table 3.** Reasons for hospitalization

Diagnosis	n (%)
Cerebrovascular disease	70 (22.15)
Malignancy	66 (20.89)
Cardiovascular disease	48 (15.19)
Asthma / COPD	18 (5.70)
Alzheimer's	18 (5.70)
Paraplegia / tetraplegia	16 (5.06)
Diabetes and its complications	13 (4.11)
Trauma	10 (3.16)
Pulmonary thromboembolism	9 (2.85)
Parkinson's	7 (2.22)
Psychiatric illness	7 (2.22)
Pre / post-op	7 (2.22)
Others	27 (8.53)

## DISCUSSION

Medical and technological developments observed worldwide have brought about many improvements in living conditions. Thus, the life span has been extended, and survival times for chronic and deadly diseases have increased. Palliative care, which has been developing rapidly in recent years in Turkey, is a care system aimed at increasing the quality of life in progressive, incurable, and fatal diseases. Palliative care is a multidisciplinary practice that requires the coordinated work of different clinical specialties and professional groups. It is an important service step for physicians and for patients and their relatives (11). In this study, there was a heterogeneous patient population with a predominantly female population, including young patients. Cerebrovascular diseases were the leading cause of patients'

need for palliative care and pressure ulcer rates were low.

In a study conducted by Dinçer et al. with patients hospitalized at a palliative care in Turkey, 54.1% of 111 patients were male and 45.9% female. They reported a median duration for in-patient care of 24 days (range, 6–212) (12). In a study conducted by Yürüyen et al. with 319 patients hospitalized in a palliative care center, the mean age was  $71 \pm 15.8$  years, and the mean hospitalization period was  $15.4 \pm 15.7$  days (13). Dinçer et al. followed 435 patients in a palliative care center; 58.60% of the participants were male, 41.40% were female, the mean age was  $70.6 \pm 17.2$  years, and the duration of hospitalization was  $27.2 \pm 30.9$  days (14). In a study by Komaç et al. that retrospectively examined the clinical files of 258 patients hospitalized in the PCU of an internal diseases' clinic, the mean age of patients was 61.4 years (19-93), and the average length of stay was 9.4 days (1-68) (15).

In a study conducted by Dinçer et al., 52.2% of patients received nutritional support treatment; 40.5% had pressure ulcers, 42.3% neurological disease, 23.4% cancer, 41.4% chronic systemic conditions (diabetes mellitus and chronic pulmonary, cardiac, and renal disease), and 10.8% infections (12). The most common comorbid diseases reported by Yürüyen et al. were malnutrition (59%), malignancy (44%), infectious disease (33%), pressure ulcer (33%), and cerebrovascular disease (9.7%). The most common admissions complaints were oral intake disorder (35%), general condition disorder (19%), fever (17%), anorexia and weight loss (15%), and fatigue (13%) (13). The most common complaints of patients or their relatives in the present study were malnutrition, pressure ulcer, cough or respiratory distress, weakness or fatigue, nausea or vomiting, abdominal pain, urinary tract problems, dizziness or headache, syncope or convulsion, and fever. In a study by Komaç et al., 33.30% of patients were followed up for malignancy and complications related to malignancy, 17% for the completion of prolonged

antibiotic treatment initiated for reasons such as pneumonia, urinary tract infection, pancreatitis, and 17% for complications due to diabetes (15). Palliative care focuses on symptom control regardless of the cause of the disease and should not be associated with purely terminal care. It provides additional support in patient care, especially with cancer (16). In the present study, the five most common reasons for hospitalization were cerebrovascular disease, malignancy, cardiovascular disease, asthma/COPD, and Alzheimer's and related complications.

It has been reported in the literature that the lifetime risk of stroke is approximately 25% (17). In present study, the rate of hospitalization due to cerebrovascular disease was 22.15%. Miniksar et al. reported that 12.77% of patients in their study had cerebrovascular disease (18), while Dinçer et al. reported a neurological disease rate of 42.3% (12). In present study, the majority of the patients suffered from cerebrovascular disease. These palliative care patients can benefit from a structured approach to their needs and easing symptom burden. In addition, a holistic approach can improve their overall quality of life (19).

An evaluation of the mobilization status of patients in Yürüyen et al. showed that 75% were inactive, 15.30% semi-mobile, and 9.70% mobile (13). As to the activity status of the patients in the present study, the percentage of dependent patients is lower, but the proportions of semi-dependent and independent patients are higher. Studies have shown that immobility is an important risk factor in the development of pressure ulcers (20-22).

Yürüyen et al. observed that 71.90% of the patients were fed enterally and 28.10% parenterally. Of patients fed enterally, 75.90% were fed orally, 11.80% with nasogastric tube, and 12.20% with percutaneous endoscopic gastrostomy. Pressure ulcers were present in 33.50% of the patients; stage-2 pressure ulcers were most commonly seen (13). Similar to Yürüyen et al., most of the patients in present

study were fed orally and the majority of those with pressure ulcers were also stage-2, but pressure ulcer rates were lower.

Dinçer et al. reported that 46.20% of the patients they followed up in the palliative care center lost their lives (14). In Yürüyen et al., 52% of patients were discharged, 15.30% were transferred to advanced intensive care, and 33.60% died (13). Roldi et al. reported that 6% of patients died, while 92.3% were discharged (23). The mortality rate in Sargin et al. was reported as 21.5% (24). In the present study, 3.80% of the patients lost their lives in the PCU.

Most of the patients hospitalized in the PCU were elderly patients with comorbidities whose general health status ranged from moderate to poor. Evaluation of their activity status showed that more than half of patients were dependent and at high risk of falling. Nutrition support, wound care, pain palliation, and rehabilitation services were planned for these patients; they were treated for their infectious and chronic diseases.

## CONCLUSION

Palliative care includes multidisciplinary practices that require strong coordination and cooperation. In this study, in which we shared clinical experiences with PCU, it was seen that majority of patients were elderly dependent individuals who needed support in matters such as nutrition and wound care due to problems such as cerebrovascular disease and malignancy. Palliative care services are handled within the scope of human rights and it is suggested to be developed and expanded also at the level of primary health care services. We believe that this study will increase the awareness about palliative care services which still developing in Turkey and around the world. Sharing the data of palliative care services across the country will be an important step.

**Conflict of interest:** The authors declare no conflicts of interest.



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## RESEARCH

# COENZYME Q10 EFFECTIVELY PREVENTS AGE-RELATED HEARING LOSS IN C57BL/6 MICE

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.220  
2021; 24(2): 235-243

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Received: Mar 27, 2021  
Accepted: May 16, 2021

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## ABSTRACT

**Introduction:** Presbycusis is characterized by gradual, progressive sensorineural hearing loss. The aim of this study is to evaluate the effects of coenzyme Q10 in the prevention and treatment of age-related hearing loss.

**Materials and Method:** Thirty-two C57BL/6 mice were assigned into four groups as early treatment, late treatment, control and sham control. Treatment was started at three months of age in the early treatment group and at six months in the late treatment group. The auditory brainstem test was performed once every three months. At the end of the study period, the cochleae of the animals were harvested, and Bcl-2, Bcl-xL, iNOS, COX-2, NF- $\kappa$ B, Bax, and Bak levels were analyzed with real-time polymerase chain reaction.

**Results:** The hearing thresholds of the mice in the early treatment group were better than those of the other groups ( $p < 0.001$ ). Hearing levels were also better in the late treatment group than control groups, but the difference was not significant ( $p > 0.05$ ). The threshold shift in the early treatment group was significantly lower than the control groups ( $p < 0.001$ ). The mRNA expression levels of proapoptotic genes Bax and Bak were lower ( $p < 0.05$ ), antiapoptotic genes Bcl-2 and Bcl-xL were higher ( $p < 0.05$ ), and the NF- $\kappa$ B, COX-2, and iNOS genes, which play a role in inflammation, were lower ( $p < 0.05$ ) in the early treatment group.

**Conclusion:** These results suggest that coenzyme Q10 effectively attenuates the presentation of age-related hearing loss, especially when started before the onset of hearing loss.

**Key Words:** Presbycusis; Evoked Potentials, Auditory, Brain Stem; Oxidative Stress; Antioxidants

## INTRODUCTION

Age-related sensorineural hearing loss or presbycusis is a slow, progressive hearing loss that develops with age. Presbycusis is characterized by decreased hearing, difficulty in distinguishing speech in noisy environments, the slowing of acoustic stimuli in the brain, and the deterioration of sound localization. Hearing loss typically occurs at high frequencies (1, 2).

Oxidative damage, which is the cause of free radical damage, is perhaps the most fundamental cause of age-related pathologies in the biological aging of cells. Oxidative damage is also an important intrinsic factor in the pathogenesis of presbycusis. Free radicals, which occur as a by-product during the normal activities of cells, cause mitochondrial genome deletions. Considering the contribution of oxidative damage in the pathogenesis of presbycusis, an age-related condition, it can be thought that antioxidants may prevent the onset or progression of the disease. Therefore, the role of many antioxidants, including folate, melatonin, ascorbic acid, alpha lipoic acid, and carnitine, have been investigated for the prevention or treatment of presbycusis, as it has been suggested that various antioxidants may play a role in the prevention and treatment of age-related hearing loss (3, 4).

During inflammation, an increase in the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) genes was observed in monocytes, macrophages, synovial cells, fibroblasts, chondrocytes, and endothelial cells, which are stimulated by different cytokines, growth factors, or mitogens. In hearing loss, studies have shown that there is an increase in various inflammatory mediators, especially COX-2 and iNOS, and coenzyme Q10 (CoQ10), which causes a significant decrease in the amount of these mediators (5, 6).

Apoptotic cell death, which is an important mechanism for maintaining the balance between the life and death of cells, is stimulated or suppressively regulated by various proteins. Some cellular

molecules, such as caspase enzymes and intracellular Bcl-2 gene family proteins (Bcl-2, Bcl-xL, Bak, and Bax), are involved in the regulation of apoptosis. In mouse experiments, it has been shown that apoptotic cell death occurs earlier in mice with sensorineural hearing loss (7).

The aim of this study was to evaluate the possible protective, retarding and/or therapeutic effects of CoQ10 on presbycusis in C57BL/6 mice. In addition, after presbycusis development and CoQ10 administration, real-time polymerase chain reaction (PCR) examination of the cochlear tissues obtained from mice was conducted to determine the changes in mRNA expression levels of the iNOS, COX-2, and nuclear factor kappa B (NF- $\kappa$ B) genes, which are effective in inflammation, Bcl 2, Bcl-xL, Bax, and Bak genes, which play a role in the formation of apoptosis.

## MATERIALS AND METHODS

### *Laboratory animals*

The study sample comprised 32 C57BL/6 healthy male mice, each weighing 20–25 gr and aged three months. The mice were procured from Bilkent University Laboratory Animal Breeding and Experimental Research Center and brought to Gazi University Laboratory Animal Breeding and Experimental Research Center, where the experiment was conducted. The animals were housed in plastic cages at a temperature of  $23^{\circ} \pm 2^{\circ}\text{C}$ , with a 12 hours light/dark cycle, and had free access to food and water before and during the experiment. Ethics committee approval was obtained for the study from Animal Experiments Local Ethics Committee (G.Ü.ET-18.067, Number: 66332047-604.01.02).

The mice were separated into four experimental groups of eight animals in each group: 1) Control Group, 2) Sham Control Group, 3) Early Treatment Group, and 4) Late Treatment Group. The CoQ10 and Dimethyl Sulfoxide (DMSO) used in the exper-



iment were supplied by Sigma-Aldrich (Darmstadt, Germany).

### **Anesthesia**

The mice were anesthetized with an intraperitoneal injection of ketamine (45 mg/kg) and xylazine (2.5 mg/kg) during the ABR measurements. The depth of anesthesia was measured with pedal reflex, and to maintain anesthesia, a half dose of this cocktail was administered as required. At the end of the study, the animals were sacrificed under the same anesthetic protocol.

### **Study protocol**

Sample size was determined based on a desired power of 0.8, a desired alpha of 0.05, and an estimated size effect delta of approximately 1.4, based on preliminary data. The mice were randomly separated into four groups and treated as follows: Group 1 ( $n = 8$ ) as the control group received no drugs; Group 2 ( $n = 8$ ) as the sham control group was administered dimethyl sulfoxide (DMSO) at three months of age to evaluate the possible effects on hearing of DMSO, the substance in which CoQ10 was dissolved; Group 3 ( $n = 8$ ) as the early treatment group was administered CoQ10 starting at three months of age; and Group 4 ( $n = 8$ ) as the late treatment group received CoQ10 starting at six months of age.

CoQ10 was purchased from Sigma Aldrich (St. Louis, MO), dissolved in 30% DMSO (20 mg/ml) (Sigma Aldrich, St. Louis, MO), and added to the drinking water of the mice so that an approximate daily dosage of 500  $\mu\text{g}/\text{kg}$  for each mouse was maintained. A new solution was prepared weekly during the study period to ensure the stability of CoQ10. The mice were weighed every week, and the dose of the CoQ10 was adjusted according to the weight of the mice, if necessary. Additionally, 30% DMSO was freshly prepared on a weekly basis and added to the drinking water of the sham control group.

### **Auditory Brain Stem Response**

The auditory brainstem response (ABR) measure-

ments were taken using a two channel Neuro-audio® ABR device (Neurosoft, Ivanova, Russia). Body temperature was maintained at 37°C by placing the animal on a thermal blanket. After anesthesia, ABR measurements were taken from both the right and left ears of each mouse; two traces were registered for each ear to control the repeatability of the response. Frequency-specific tone bursts (TB) at 4000 Hz, 8000 Hz, 12000 Hz, and 16000 Hz were used as the auditory stimulus. The analysis time for the ABR recording was 20 ms, 100–2000 Hz for TB stimuli, 30–3000 Hz for click stimuli, and a band-pass filter and alternating polarity were selected. The repetition rate was set as 21/sec, and the average was 1024 sweeps. Thresholds were determined starting from the maximum outputs (110–118 dB SPL) and decreasing the stimuli by 5 dB; stimulus intensity was reduced until waves in reproducible morphology could not be detected.

### **Gene Analysis in Cochlea Homogenates**

To examine the effect of CoQ10 following the termination of the experiment at the end of 12 months, cochlear tissue was taken from the inner ear of each mouse to determine the expression levels of iNOS, COX-2, NF- $\kappa$ B, Bcl-2, Bcl-xL, Bax, and Bak genes, which are effective in inflammation and apoptosis, using real-time PCR analysis. The cochleae of both ears were removed under a dissecting microscope and crushed.

Total RNA was isolated from fresh cochlear tissues using Trizol reagent (Life Technologies, CA, USA) and stored at -80°C until use. RNA concentration was measured using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific). One microgram of total RNA was used for gene-specific reverse transcription polymerase chain reaction (RT-PCR) using a Transcriptor High Fidelity cDNA Synthesis Kit (Roche, Mannheim, Germany). The cDNA samples were kept at -80°C until PCR analysis. Gene expression level studies were determined using the quantitative real-time PCR (qRT-PCR) method using a Light Cycler-480™ (LC) device

(Roche, Germany).

### Statistical Analysis

From the real-time PCR analysis results of RNA obtained after RNA isolation from the cochlea tissue at the end of the experiment, differences in iNOS, COX-2, NF-kB, Bcl-2, Bcl-xL, Bak, and Bax mRNA expression levels were compared with the REST (2009 V2.0.13) statistics program (8). For the statistical evaluation of hearing loss between treated and untreated mice, SPSS V. 22 software was used (SPSS Inc., Chicago, IL, USA). The ABR results were compared with the Kruskal-Wallis analysis of variance (ANOVA) to determine the significance of the difference between the groups. The post hoc Tukey method of analysis was used to verify statistical significance; a value of  $p < 0.05$  was considered statistically significant.

### RESULTS

All 32 mice included in the study completed the study period of 12 months. There was no significant difference with respect to the pre- and post-study weights of the mice ( $p = 0.520$ ).

The ABR results of the mice at the beginning of the study, when the mice were three months old, were evaluated using Kruskal-Wallis ANOVA, and there was no statistically significant difference between the experimental groups in terms of ABR

results at all frequencies ( $p = 0.810$ ). There was no significant difference between the groups with respect to the ABR results in the third month of the experiment (mice at six months of age) ( $p = 0.635$ , **Table 1**).

In the tests performed in the sixth month of the experiment, the ABR thresholds of the early treatment group were significantly lower than those of the control, sham control, and late treatment groups ( $p = 0.007$ ). However, there was no significant difference in the ABR thresholds between the late treatment, control, and sham control groups ( $p = 0.354$ , **Table 2**). In comparison of the ABR thresholds between the third and sixth months of the experiment, no significant difference was determined in the ABR thresholds in the early treatment group ( $p = 0.264$ ). In the late treatment, control, and sham control groups, the ABR thresholds were found to be significantly higher at six months than at three months ( $p = 0.004$  for the late treatment group,  $p = 0.008$  for the control group, and  $p = 0.007$  for the sham control group).

In the tests performed in the ninth month of the experiment (when the mice were 12 months old), the mean ABR thresholds of the early treatment group were determined to be lower than those of the control and sham control groups at all frequencies ( $p < 0.001$ ). The ABR thresholds of the late treatment group were lower than those of the

**Table 1.** Mean ABR thresholds of the mice according to stimulus frequencies in the third month of the study (values in dB SPL).

Frequency (kHz)	Control (mean ± SD)	Sham Control (mean ± SD)	Early (mean ± SD)	Late (mean ± SD)	p
4	44,375 ± 4,973	43,75 ± 5,313	40 ± 5,212	41,875 ± 4,892	0,613
8	18,125 ± 3,323	20,625 ± 3,967	17,5 ± 4,112	18,125 ± 4,033	0,512
12	16,875 ± 3,612	17,5 ± 3,453	16,875 ± 3,834	19,375 ± 3,673	0,472
16	27,5 ± 4,345	28,125 ± 5,173	26,25 ± 4,873	28,75 ± 4,364	0,520

**Table 2.** Mean ABR thresholds of the mice at the sixth month of the study by frequency of stimulus (values in dB SPL)

Frequency (kHz)	Control (mean ± SD)	Sham Control (mean ± SD)	Early (mean ± SD)	Late (mean ± SD)	p*	p**
4	51,25 ± 8,873	51,875 ± 9,412	42,5 ± 10, 112	49,375 ± 10,883	0,005	0,312
8	24,375 ± 3,323	26,25 ± 3,967	20 ± 4,112	25,625 ± 4,033	0,007	0,245
12	23,75 ± 3,612	23,125 ± 3,453	19,375 ± 3,834	25 ± 3,673	0,008	0,564
16	34,375 ± 4,345	35 ± 5,173	30 ± 4,873	35,625 ± 4,364	0,004	0,320

p\*: Comparison of early treatment group with other groups

p\*\*: Comparison of late treatment. control and sham control groups

control and sham control groups, but the difference was not statistically significant ( $p > 0.05$ ). The ABR thresholds of the early treatment group were lower than those of the late treatment group. This difference was significant at 12 kHz and 16 kHz ( $p = 0.004$  and  $p = 0.006$ , respectively), and not significant at 4 kHz and 8 kHz (**Table 3**).

The last ABR threshold data obtained at the end of the study, just before the mice were sacrificed, are presented in **Table 4**. The ABR thresholds in the early treatment group were significantly better than those of the late treatment, control, and sham control groups ( $p = 0.000$ ). The mean difference in ABR thresholds between the early and late treat-

ment groups was 12.5 dB to 21.25 dB, the mean difference of ABR thresholds between the early treatment and the control group was 18.75 dB to 30 dB, and the mean difference in ABR thresholds between the early treatment and sham control groups ranged from 20.625 dB to 28.75 dB. When the mean ABR thresholds of the late treatment and the control group were compared, although the ABR thresholds of the late treatment group were better than those of the control group at all frequencies, the difference was not statistically significant ( $p = 0.102$ ).

The ABR threshold changes that occurred from the beginning of the study to the 15th month were

**Table 3.** Mean ABR thresholds of the mice at the 12th month of the study by frequency of stimulus (values in dB SPL)

Frequency (kHz)	Control (mean ± SD)	Sham Control (mean ± SD)	Early (mean ± SD)	Late (mean ± SD)	p*	p**	p***
4	61,875 ± 9,673	63,125 ± 9,412	47,5 ± 8,122	55 ± 6,883	<b>0,000</b>	0,102	0,312
8	42,5 ± 8,323	41,25 ± 7,967	27,5 ± 6,112	35,625 ± 5,433	<b>0,000</b>	0,007	0,245
12	41,25 ± 8,612	42,5 ± 8,453	28,75 ± 7,834	38,75 ± 6,773	<b>0,000</b>	0,090	<b>0,004</b>
16	57,5 ± 7,435	56,25 ± 8,137	37,5 ± 8,873	48,125 ± 7,844	<b>0,000</b>	0,112	<b>0,006</b>

p\*: Comparison of early treatment group with control groups

p\*\*: Comparison of late treatment. control and sham control groups

p\*\*\*: Comparison of early treatment group with late treatment group

**Table 4.** Mean ABR thresholds of the mice at the end of the study by frequency of stimulus (values in dB SPL)

Frequency (kHz)	Control (mean ± SD)	Sham Control (mean ± SD)	Early (mean ± SD)	Late (mean ± SD)	p*	p**
4	75 ± 9,563	76,875 ± 10,112	56,25 ± 9,132	68,75 ± 8,963	<b>0,000</b>	0,070
8	61,25 ± 8,432	60 ± 10,067	31,25 ± 9,012	52,5 ± 7,542	<b>0,001</b>	0,011
12	58,75 ± 8,723	57,5 ± 9,344	32,5 ± 8,123	48,75 ± 8,463	<b>0,000</b>	0,090
16	63,75 ± 9,324	63 ± 9,248	41,25 ± 9,762	55 ± 8,732	<b>0,000</b>	0,112

p\*: Comparison of early treatment group with late treatment and control groups

p\*\*: Comparison of late treatment group with control and sham control groups

also evaluated. The mean ABR threshold change in the control and sham control groups ranged from 34.375 dB to 46.25 dB ( $p = 0.935$ ). The threshold change ranged between 14.375 dB and 16.875 dB in the early treatment group and between 28.75 dB and 37.5 dB in the late treatment group. The ABR threshold changes in the early treatment group were lower than those of the control groups at all frequencies ( $p = 0.000$ ). The final threshold change differences of the early and late treatment groups varied between 11.875 dB and 23.125 dB. This difference was not significant at 4 kHz ( $p = 0.823$ ), and the threshold change at 8, 12, and 16 kHz was significantly lower in the early treatment group ( $p = 0.000$ ).

In the age-related hearing loss model, the mRNA expression levels of proapoptotic genes such as Bax and Bak, which may be responsible for increased apoptosis in cells, were determined to be significantly reduced ( $p < 0.05$ ) in the early treatment group compared to the control and sham control groups. The mRNA expression levels of anti-apoptotic genes such as Bcl-2 and Bcl-xL increased significantly ( $p < 0.05$ ) while the mRNA expression levels of iNOS, COX-2, and Nf-kB genes, which are the inflammatory mediators involved in inflammation, were statistically decreased ( $p < 0.05$ ). In the late treatment group, it was determined that the mRNA expression levels of proapoptotic genes

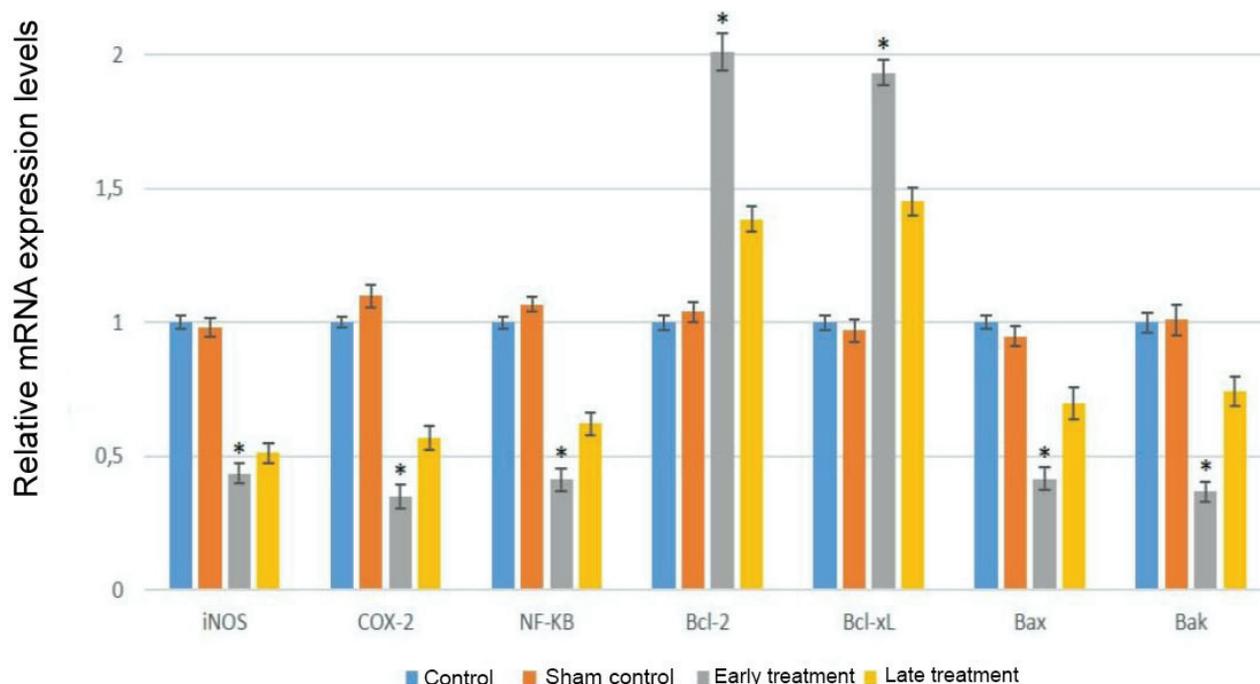
such as Bax and Bak decreased while the mRNA expression levels of antiapoptotic genes such as Bcl-2 and Bcl-xL increased; however, these increases and decreases were not statistically significant ( $p > 0.05$ ). In the late treatment group, it was observed that the mRNA expression levels of the inflammatory mediator's iNOS, COX-2, and Nf-kB decreased, which was similar to the early treatment group, but this decrease was not statistically significant ( $p > 0.05$ , **Figure 1**).

## DISCUSSION

Age-related hearing loss is a degenerative disease that affects millions of people around the world and can lead to isolation and depression by distancing people from their environment (9). Furthermore, once it has developed, age-related hearing loss rehabilitation is a highly expensive process requiring the use of rehabilitation centers, devices (hearing aids and cochlear implants), and other technologies (10). This places a heavy burden on social security institutions, and in countries such as Turkey, where such rehabilitation and devices are not fully covered by these institutions, the financial cost to the patient is also quite high (11). Therefore, the high prevalence, serious impact on the general health status and quality of life of elderly people, and the cost of rehabilitation to individuals or social security



**Figure 1.** The effect of coenzyme Q10 on the relative mRNA expression levels of the target genes in the age-related hearing loss model.



institutions make age-related hearing loss an important public health problem.

In cell aging, the most basic age-related pathology is oxidative damage caused by free radicals. It is now widely accepted that mitochondria are an important source of free radicals (ROS and RNS) and the main center of ROS/RNS-derived oxidative damage (12).

The current study findings, when evaluated in light of previous studies, show that antioxidant supplementation is more effective when initiated before the development of the genotypic changes responsible for age-related hearing loss. CoQ10 may have been less effective when treatment was initiated after the occurrence of age-related hearing loss, as the apoptotic process and inflammation had already begun at the molecular level. These re-

sults are in line with those of previous studies (13, 14), which have demonstrated that antioxidants are effective in preventing but not treating age-related hearing loss. This is due to the inability of hair cells and spiral ganglion neurons to regenerate in mammals, so hearing cannot recover after damage. These findings are consistent with the current study hypothesis that CoQ10 would be effective in preventing the development of age-related hearing loss.

Someya et al. showed that age-related hearing loss in C57BL/6J mice is mediated by Bak-dependent mitochondrial apoptosis and that oral supportive therapies containing mitochondrial antioxidants reduce cochlear cell death and prevent age-related hearing loss by lowering Bak expression in the cochlea (15). Similarly, in the current study, the ex-

pression levels of proapoptotic genes in cochlear tissue, such as Bak and Bax, which play an important role in the pathway of mitochondrial apoptosis, were found to be significantly lower in mice that were given CoQ10 before the damage that caused hearing loss had developed in the inner ear, when compared to the late treatment and control groups. In parallel with this, the mRNA expression levels in the cochlear tissue of the Bcl-2 and Bcl-Xl genes, which are antiapoptotic genes suppressing apoptosis, were also significantly higher when compared to the control and late treatment groups. These findings demonstrate that CoQ10 reduces age-related changes by suppressing mitochondrial apoptosis-mediated cell death.

It has been clearly demonstrated that chronic inflammation plays a role in age-related intracellular damage in mammalian cells (16). In the current study, the expression levels of the iNOS, COX-2, and Nf- $\kappa$ B genes, which are mediators with important roles at different levels in the inflammatory process, were determined to be significantly lower in the cochlear tissues of the mice that received CoQ10 treatment in the early period compared to the other groups. In the late treatment group, although the expression levels of these genes were lower than in the control groups, the difference was not statistically significant. This shows that the administration of CoQ10 slows down the emergence of these processes before the development of chronic inflammatory processes that are responsible for age-related changes. Although the use of CoQ10 after these processes began to suppress the inflammatory processes to some extent, it could not cause a change at the clinical or molecular level.

The results of the current study showed that CoQ10 has a protective effect against age-related hearing loss even when used alone, which is in accordance with the findings of previous studies (17, 18). This effect was particularly pronounced when CoQ10 was used before the onset of hearing loss. This protective effect of CoQ10 is due to the anti-

oxidant properties revealed by its anti-inflammatory and antiapoptotic properties, as demonstrated by molecular studies. CoQ10 reduces the mRNA expression levels of the proapoptotic genes Bax and Bak, as well as the inflammatory mediators NF- $\kappa$ B, COX-2, and iNOS, while increasing the mRNA expression levels of antiapoptotic genes such as Bcl-2 and Bcl-xL. These changes caused by CoQ10 slow down the aging process in the cochlea, thereby delaying the age-related changes.

In this study, functional and molecular studies revealed that CoQ10 treatment, which has antioxidant properties acting on many points in oxidative metabolism, can delay the emergence and reduce the severity of age-related hearing loss in C57BL/6 mice. This benefit was particularly evident in the early treatment group, where treatment was initiated before hearing loss developed. Furthermore, although the ABR results in the late treatment group were also better than those of the control groups, neither the changes at the molecular level nor the ABR thresholds were significantly better compared to the control groups.

The most important limitation of this study was that an ABR device covering 32 kHz could not be used due to technical limitations. Age-related hearing loss starts at high frequencies, so most, if not all, previous animal studies on this topic have included 32 kHz ABR measurements. In addition, the expression levels of the genes examined in this study were investigated only in the cochlear tissue, which, although this is the first study in this scope in the literature, resulted in the examination of only the peripheral component of hearing loss at the molecular level. To be able to reveal the effects of CoQ10 on the changes that occur in the central pathways of hearing with regard to aging, there is a need for different histopathological and molecular studies of central hearing centers.

In conclusion, the results of this study demonstrated that starting CoQ10 treatment before the mechanisms leading to presbycusis development



are effective in preserving hearing in mice. In the light of these findings, further studies are needed to determine the optimal dose and duration of treatment in humans. Human studies with a large num-

ber of participants should be conducted, together with animal experiments with ABR studies involving higher frequencies, where different doses are tested.

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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.221  
2021; 24(2): 244-254

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Received: Mar 26, 2021  
Accepted: May 16, 2021

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## RESEARCH

# THE EFFECT OF FRAILTY LEVEL ON ACCEPTANCE OF ILLNESS IN OLDER PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

## ABSTRACT

**Introduction:** The aim of this study is to examine the effect of frailty level on acceptance of illness in older people with Chronic Obstructive Pulmonary Disease. A descriptive and correlational design was used.

**Materials and Methods:** The sample comprised 311 Chronic Obstructive Pulmonary Disease patients aged 65 years and older who applied to the Chest Diseases outpatient clinics of the Chest Diseases and Surgery Hospital between February-April 2018. The Individual Diagnostic Form, the Edmonton Frailty Scale, and the Acceptance of Illness Scale were used. The Statistical Package for Social Science 23.0 was used for analysing the data.

**Results:** The mean age of the patients included in the study was 71.7 ± 6.0, and 74% of the patients were male. The mean score of frailty of the patients was found to be 5.00±3.36, and 49.8% were not frail. The mean score of acceptance of illness was 26.99±8.44. According to the results of the study, there was a strong negative correlation between the level of frailty and the level of acceptance of illness in older people ( $p<0.05$ ;  $r=-0.747$ ); the explanatory power of the relationship between the level of frailty and acceptance of illness is 55.6% ( $R^2 = 0.556$ ,  $p<0.001$ ).

**Conclusion:** It is thought that the increase in the acceptance of illness level of the older people significantly associated with the decrease in frailty.

**Keywords:** Frailty; Geriatrics; Pulmonary Disease, Chronic Obstructive



## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) holds an important place among public health problems in the world and due to the heavy burden of the disease (1). According to data from the World Health Organization (WHO), 5.6% of all deaths in 2015 were due to COPD, which makes it the fourth most common cause of death. The Burden of Obstructive Lung Disease (BOLD) study and other epidemiological studies have reported that the number of COPD cases in 2010 was 384 million, which covered 11.7% of the global population (2). Likewise, the prevalence study conducted in Turkey in 2011 is 5.3%, COPD ranks as the third most common cause of death, and it is estimated that every year about 30 thousand people die a result of COPD (2,3). Apart from chronic diseases such as COPD, which are more common with increasing age, degenerations caused by aging lead to a decrease in the ability of the organs to adapt, which –in some cases – causes geriatric syndromes. Along with immobilization, incontinence, depression, delirium, falls, and osteoporosis – all common examples of geriatric syndromes and diseases – Frailty Syndrome is also commonly seen in older people (3,4).

Frailty Syndrome describes several negative health outcomes such as decrease in physiological reserve, stress intolerance, low physical activity, weakness, slowness, sarcopenia, and unwanted weight loss. While this syndrome is seen in 7% of people aged over 65, it is estimated to be present in 30-45% of people over 80 years of age; however, it is not possible to come to an exact prevalence rate, since many factors such as psychological-cognitive, physical, economic and social status of people have an impact on their frailty levels (5,6). Diagnosis of this syndrome at later ages is very difficult because it is associated with many chronic diseases that increase the patient's disability, hospitalization rates, health care costs, and mortality. On the other hand, a cause-effect relationship cannot be established

due to the presence of other geriatric syndromes along with Frailty Syndrome (4,7).

As with many other diseases, the patient lives in uncertainty until the diagnosis is made in COPD. This sometimes causes emotional trauma in patients and often leads to acute stress reactions such as fear of loss of control, concentration problems, hopelessness, and the feeling that the situation is unreal. Therefore, the most important way to learn to cope with the disease is to help the patient accept the disease (8). In this way, the individual will be capable of restricting his or her negative feelings and increasing beneficial behaviours that improve and protect his or her health (9,10). People who can accept their disease can make better choices about their daily activities, and cope better with the problems caused by the disease (9,11). Failure to accept the disease, however, leads to an increase in the sense of dependence and a decrease in self-efficacy and self-esteem (8).

Considering all aspects of COPD and frailty syndrome, the level of accepting the disease complicates the adaptation process of older people (6). Acceptance of the disease plays an important role in the adaptation to the disease as well as treatment, and it is associated with recognizing the limitations it causes. Two of the determinants of the acceptance of the disease are chronic diseases such as COPD and geriatric syndromes such as frailty. Acceptance of illness is an important factor that can contribute to improvement in the prognosis and treatment of Frailty Syndrome (12). Although there are not enough data in the literature, a few studies have shown that higher levels of frailty lead to lower acceptance of the disease (13). To the best of our knowledge, there has been no study in Turkey evaluating the effect of the level of frailty on the acceptance of the disease in older people with COPD. Therefore, the purpose of this study was to investigate the effect of frailty level on the acceptance of the disease in older people with COPD.

## MATERIALS and METHODS

After obtaining permission from the Medical Faculty Ethics Committee (17-12.1 / 30) of a university, the approval of the Provincial Health Directorate was also obtained. The authors of the Turkish versions of the scales were contacted by e-mail and their approval was obtained.

### Sample

G-Power statistical analysis was performed to determine the sample size. When the sample size is calculated, the minimum number of samples that should be reached for Cohen's effect size  $\rho = 0.2$  with  $\alpha = 0.05$ , 0.80 power is determined as 197 patients.

The data of the study were collected from İzmir Dr. Suat Seren Chest Diseases and Surgery Hospital Chest Diseases Polyclinics between February and April 2018. The aim of the study was explained by the researcher to the patients included in the study and data were collected after they signed written and oral informed consent. To collect data, 10-15 minute one-to-one interviews were conducted with 311 COPD patients 65 years and older. Questionnaire questions were asked to the patient and the answers were recorded by the researcher. Inclusion criteria were set as follows: being diagnosed with COPD at least one year prior to the study; being 65 years and over; being literate; having access to the results of the Respiratory Function Test; voluntary participation in the study; and signing the informed consent form. Exclusion criteria were as follows: coexistence of other chronic lung diseases such as asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, pulmonary fibrosis, primary pulmonary hypertension, interstitial lung disease or any other active lung disease; presence of hemodynamic instability caused by chronic diseases other than COPD; presence of severe exacerbations of diseases other than COPD; and presence of a se-

rious psychiatric disorder requiring treatment (13).

### Materials Used

#### *Individual Diagnostic Form*

Based on the information collected from the literature, this form was composed by the researchers and consisted of four sections including socio-demographic characteristics, health and disease characteristics, mMRC dyspnea scale and forced expiratory volume in 1st second (FEV<sub>1</sub>) value measured in the last 3 months.

### NRS-2002 Nutritional Risk Screening

This tool aims to identify malnutrition and malnutrition risk, as well as to identify patients who may be in need of nutritional support. A score between 0-3 is allocated for each section, and one point is added to the total score for patients above 70 years of age. Patients with a total score of  $\geq 3$  are considered to be at nutritional risk (14).

#### *Edmonton Frailty Scale (EFS)*

In the validity and reliability study of the scale conducted by Eskiizmirli Aygör et al. In 2013, the scale consists of 11 items and the total score is used for evaluation. The lowest and highest total scores from the scale are 0 and 17, respectively. Higher total scores represent an increase in severity of vulnerability (15).

### Acceptance of Illness Scale (AIS)

The validity and reliability of the Turkish version was confirmed by Besen in 2009, and the total score range of the scale consisting of eight main headings is between 8-40. This Likert-type scale is rated by 5 points on participation/non-participation of the individual. Higher scores indicate higher levels of acceptance of the illness, which in return, indicate the patient's less negative reactions to the adverse outcomes of the illness (8).



## Assessment of Data

The analysis of the study data was carried out using the SPSS (Statistical Package for Social Sciences v.23, IBM Corp., Armonk, NY, USA) statistical analysis software.

Mean values and standard deviations were calculated for the variables. Independent Sample t test, Paired Sample t test, Mann Whitney U, One Way ANOVA, and Kruskal Wallis H were used to evaluate differences between variables (depending on whether or not they were normally distributed); Pearson Correlation Analysis was used to evaluate relationship (because dependent variables are normally distributed); and Tukey's HSD Test for normally distributed variables and Bonferroni (Dunn) Test for abnormally distributed variables were used for further analysis. Multivariate linear regression analysis was used to evaluate the existing significant relationship; Adjust  $R^2$  was used to compare the explanatory power of each linear regression model.

## RESULTS

The mean age of the patients included in the study was  $71.7 \pm 6.0$  and the mean duration of COPD was  $6.27 \text{ years} \pm 4.55$ . The mean score of mMRC was  $1.71 \pm 1$  and 44.4% had an mMRC score of "one". While the mean  $FEV_1$  value of the patients was  $51.61 \pm 17.46$ , 43.4% of these patients were GOLD II. The mean NRS-2002 score of the sample was  $2.00 \pm 0.83$  and 65.6% were not at risk ( $<3$ ). The mean score of the Acceptance of Illness Scale was  $26.99 \pm 8.44$ . The Edmonton Frailty Scale mean score was  $5.00 \pm 3.36$  and 49.8% of the patients were not frail (Table 1).

Among all patients, 74% were male, 64.3% were married, and 66.2% were primary or secondary school graduates. 65.2% of the patients were retired and 68.2% reported that their incomes were equal to their expenses. According to the analysis, while the women's frailty score was higher than the men's ( $p < 0.05$ ); there was no difference between the ac-

ceptance of illness scores between the genders ( $p > 0.05$ ). Considering other socio-demographic characteristics, it was found that being single/widowed, having a low level of education, being unemployed, and having a low level of income were associated with higher levels of frailty and lower scores of acceptance of illness ( $p < 0.05$ ) (Table 2).

Of the 311 patients in this study, 55% stated that they had quit smoking, 72.7% indicated that they did not drink alcohol at all. In terms of smoking, there was no difference in the frailty and acceptance of illness scores of the patients ( $p > 0.05$ ). In terms of alcohol usage, while there was no difference in acceptance of illness scores ( $p > 0.05$ ), patients who used/quit alcohol had lower scores of frailty ( $p < 0.05$ ). It was reported that 53.7% of the patients had COPD for less than five years, 60.1% had not been hospitalized due to COPD exacerbation in the last year, and 74.9% did not use an oxygen device at home. It was indicated that 47.6% of the patients had comorbidities along with COPD, and 11.5% of the sample group used five or more medications daily. Patients who were hospitalized due to COPD exacerbation in the previous year and those who used oxygen devices at home had higher frailty and lower acceptance of illness scores ( $p < 0.001$ ). Similarly, patients with comorbidities along with COPD and those taking five or more drugs daily had higher frailty scores ( $p < 0.001$ ) and lower acceptance of illness scores ( $p < 0.05$ ) (Table 2).

The relationships between some variables of the patients and their frailty and acceptance of illness scores were provided in Table 3. While there was a moderate positive relationship between the frailty score and the patients' age ( $r = 0.573$ ), there was a negative relationship between age and acceptance of illness score ( $r = -0.447$ ) ( $p < 0.001$ ). In terms of disease-related parameters, frailty scores had a positive relationship with COPD years ( $r = 0.344$ ); a negative relationship with  $FEV_1$  values ( $r = -0.344$ ); and a positive relationship with mMRC scores ( $r = 0.569$ ) ( $p < 0.001$ ). However, acceptance of illness

**Table 1.** Disease characteristics of the study sample (n=311)

Characteristics	n	%
	Mean±SD	Min-Max
Age	71.7±6.0	65-89
Mean of COPD Years	6.27±4.55	1-20
mMRC	1.71±1.00	0-4
<b>mMRC Classification</b>		
0	22	7.1
1	138	44.4
2	71	22.8
3	69	22.2
4	11	3.5
FEV <sub>1</sub>	51.61±17.46	26-94
<b>GOLD Classification</b>		
GOLD I	22	7.1
GOLD II	135	43.4
GOLD III	131	42.1
GOLD IV	23	7.4
NRS-2002	2.00±0.83	1-5
<b>NRS-2002 Classification</b>		
No risk (Score <3)	204	65.6
At risk (Score ≥3)	107	34.4
Acceptance of Illness Scale	26.99±8.44	8-40
Edmonton Frailty Scale	5.00±3.36	0-17
<b>Frailty Classification</b>		
Not frailty (0-4)	155	49.8
Apparently vulnerable (5-6)	48	15.5
Slightly frailty (7-8)	49	15.8
Medium frailty (9-10)	43	13.8
Severe frailty (11-17)	16	5.1

scores had a negative relationship with COPD years ( $r=-0.383$ ); a positive relationship with FEV<sub>1</sub> values ( $r=0.467$ ); and a negative relationship with mMRC scores ( $r=-0.461$ ) ( $p<0.001$ ). NRS-2002 scores indicating malnutrition risk status had a moderate positive correlation with frailty ( $r=0.536$ ), and a weak negative correlation with acceptance of illness ( $r=-$

$-0.466$ ) ( $p<0.001$ ). A moderate level of positive correlation was found between the patients' frailty level and their ages ( $r=0.573$ ), mMRC scores ( $r=0.569$ ), and NRS-2002 scores ( $r=0.536$ ); between the frailty levels and the year of COPD, a low level of positive correlation was found between the year of COPD ( $r=0.344$ ) ( $p<0.001$ ). However, a low level of nega-



**Table 2.** Comparison of frailty and acceptance of illness scores based on demographic and other variables (n=311)

Characteristics	n	%	Edmonton Frailty Scale		Acceptance of Illness Scale	
			Mean ± SD= 5.00±3.36 (Min-Max: 0-17)		Mean ± SD= 26.99±8.44 (Min-Max: 8-40)	
<b>Gender</b>						
Female	81	26.0	6.00±3.25	t=3.162	25.72±8.36	t= 1.595
Male	230	74.0	4.65±3.33	<b>p=0.002**</b>	27.44±8.44	p=0.113
<b>Marital Status</b>						
Married	200	64.3	3.76±2.97	t= -10.111	29.52±7.79	t= 7.770
Single/Widowed	111	35.7	7.24±2.81	<b>p=0.000*</b>	22.44±7.65	<b>p=0.000*</b>
<b>Educational Level<sup>x</sup></b>						
Literate <sup>a</sup>	66	21.3	7.55±2.84	x <sup>2</sup> =58.510 <b>p=0.000*</b>	22.68±8.03	x <sup>2</sup> =37.024 <b>p=0.000*</b>
Primary/Secondary <sup>b</sup>	206	66.2	4.60±3.23		27.31±8.04	
High School <sup>c</sup>	28	9.0	3.18±2.23		31.54±7.47	
University <sup>d</sup>	11	3.5	1.91±2.07		35.36±7.38	
<b>Labor Status</b>						
Working	38	20.3	4.50±3.39	F=12.317	27.50±9.92	F=4.211
Not working	63	12.2	6.81±2.85	<b>p=0.000*</b>	24.27±7.81	<b>p=0.016**</b>
Retired	210	67.5	4.55±3.32		27.72±8.20	
<b>Income Level</b>						
High	84	27.0	3.79±3.23	x <sup>2</sup> =20.574 <b>p=0.000*</b>	30.99±8.24	x <sup>2</sup> =25.883 <b>p=0.000*</b>
Moderate	212	68.2	5.34±3.30		25.49±8.14	
Low	15	4.8	6.93±2.92		25.87±6.61	
<b>Status of Smoking</b>						
Smoker	83	26.7	5.29±3.55	F=0.969 p=0.381	27.58±9.04	F=0.271 p=0.763
No history of smoking	57	18.3	4.49±3.17		26.75±8.31	
Ex-smoker	171	55.0	5.03±3.32		26.79±8.22	
<b>Alcohol Consumption</b>						
Not drinking	226	72.7	5.33±3.45	t=3.090	26.49±8.31	t= -1.717
Drinking/Stopped drinking	85	27.3	4.12±2.94	<b>p=0.002**</b>	28.83±8.68	p=0.087
<b>Hospitalization due to exacerbation of COPD during the last 12 months</b>						
Yes	123	39.9	6.79±3.14	t= -8.312	24.31±8.06	t= -4.710
No	188	60.1	3.83±2.96	<b>p=0.000*</b>	28.75±8.24	<b>p=0.000*</b>
<b>The use of oxygen at home</b>						
Yes	78	25.1	7.64±2.72	t= -9.004	21.44±6.66	t= -7.258
No	233	74.9	4.12±3.08	<b>p=0.000*</b>	28.85±8.16	<b>p=0.000*</b>
<b>Comorbidities out of COPD</b>						
Yes	148	47.6	5.87±3.28	t= -4.494	25.75±7.73	t= -2.497
No	163	52.4	4.21±3.24	<b>p=0.000*</b>	28.12±8.91	<b>p=0.013**</b>
<b>Polypharmacy (≥5 drugs)</b>						
Yes	32	11.5	7.38±3.18	t= -4.447	23.25±6.76	t= -2.675
No	279	88.5	4.73±3.27	<b>p=0.000*</b>	27.42±8.52	<b>p=0.008**</b>

\*p<0,001; \*\*p<0,05 t: Independent Sample t test Z: Kruskal Wallis H F: One Way ANOVA

<sup>x</sup> Tukey's HSD Test <sup>y</sup> Bonferroni (Dunn) Test

a>b>c=d. Underlined groups that cause significant differences between groups.

tive correlation was found between FEV<sub>1</sub> values and frailty level ( $r = -0.344$ ;  $p < 0.001$ ). A low level of negative correlation was found between the patients' level of acceptance of illness and their ages ( $r = -0.447$ ), mMRC scores ( $r = -0.461$ ), years of COPD ( $r = -0.383$ ) and NRS-2002 scores ( $r = -0.466$ ) ( $p < 0.001$ ). Also a low level of positive correlation was found between FEV<sub>1</sub> values and level of acceptance of illness ( $r = 0.467$ ;  $p < 0.001$ ). A high level of negative correlation was found between the patients' frailty level and their level of acceptance of illness ( $p < 0.05$ ,  $r = -0.747$ ) (Table 3).

The explanatory power of the models developed by multivariate linear regression analysis (Adjust R<sup>2</sup>) varies between 55.6% and 61.6%. According to multiple linear regression analysis, the explanatory power of the relationship between fragility level and acceptance of illness was found to be 55.6% (Model 1;  $\beta = -0.747$ , Adjust R<sup>2</sup> = 0.556,  $p < 0.001$ ). The explanatory power of frailty level and FEV<sub>1</sub> values together on acceptance of illness was 60.5% (Model 2; Adjust R<sup>2</sup> = 0.605,  $p < 0.001$ ). The explanatory

power of frailty level, FEV<sub>1</sub>, and NRS-2002 values on acceptance of illness was 61.2% (Model 3; Adjust R<sup>2</sup> = 0.612,  $p < 0.001$ ). And frailty level, FEV<sub>1</sub>, NRS-2002, and mMRC values were found to be 61.6% (Model 4; Adjust R<sup>2</sup> = 0.616,  $p < 0.001$ ) (Table 4).

## DISCUSSION

To the best of our knowledge, this study is the first study to investigate the relationship and effect between frailty level and acceptance of illness level in older people with COPD. Older people with COPD included in this study had a very low score of frailty of 5.00 (SD 3.36). Almost half of the patients (49.8%) were not frail. However, based on similar studies, this rate is reported to be higher in other countries (16,17). Contrary to the level of frailty, the score of acceptance of illness in COPD patients included in our study was 26.99 (SD 8.44), which is above average. Although there are no studies investigating the level of acceptance of illness of patients with COPD in our country, our results were similar to the results found in other countries (18,19).

In this study, the women's frailty scores were higher than the men's. In the first large-scale frailty study conducted by Fried et al. (2001), women were reported to be frailer (20). Married older people had lower frailty and higher acceptance of illness scores than single or widowed patients. The presence of a spouse has a positive effect on the psychosocial sub-dimension of frailty syndrome; likewise, higher levels of acceptance of illness can be described in terms of social and psychological support of the spouse. A significant difference was also found between levels of frailty and acceptance of illness and level of education as another socio-demographic variable. According to our results, as the education level increased, the frailty scores decreased and the levels of acceptance of illness increased. In this context, the studies were also consistent with our results (18,21). In the present study, it was concluded that the unemployed patients had a higher frailty level and lower acceptance of illness level than those

**Table 3.** Correlation coefficients between some variables of the patients and their frailty and Acceptance of Illness Scale (AIS) Scores (n=311)

Characteristics	Edmonton Frailty Scale	Acceptance of Illness Scale
Age	$r = 0.573$ $p = 0.000^*$	$r = -0.447$ $p = 0.000^*$
Year of COPD	$r = 0.344$ $p = 0.000^*$	$r = -0.383$ $p = 0.000^*$
FEV <sub>1</sub>	$r = -0.344$ $p = 0.000^*$	$r = 0.467$ $p = 0.000^*$
mMRC	$r = 0.569$ $p = 0.000^*$	$r = -0.461$ $p = 0.000^*$
NRS-2002	$r = 0.536$ $p = 0.000^*$	$r = -0.466$ $p = 0.000^*$
Edmonton Frailty Scale	1	$r = -0.747$ $p = 0.000^*$

\* $p < 0.001$  r = Pearson's Correlation



**Table 4.** The relationship between some variables and acceptance of the disease level of frailty according to multiple linear regression analysis (n=311)

Models	B (95.0%CI for B)	$\beta$	t	p	Adjust R <sup>2</sup>	Model p
<b>Model 1. AIS</b>						
EFS	-1.877 (-2.064,-1.689)	-0.747	-19.723	<b>0.000</b>	0.556	<b>0.000</b>
<b>Model 2. AIS</b>						
EFS	-1.671 (-1.859,-1.483)	-0.665	-17.478	<b>0.000</b>	0.605	<b>0.000</b>
FEV <sub>1</sub>	0.115 (0.079,0.151)	0.238	6.259	<b>0.000</b>		
<b>Model 3. AIS</b>						
EFS	-1.518 (-1.737,-1.299)	-0.604	-13.633	<b>0.000</b>		
FEV <sub>1</sub>	0.118 (0.082,0.154)	0.244	6.468	<b>0.000</b>	0.612	<b>0.000</b>
NRS-2002	-1.119 (-1.959,-0.278)	-0.110	-2.618	<b>0.009</b>		
<b>Model 4. AIS</b>						
EFS	-1.627 (-1.867,-1.386)	-0.647	-13.321	<b>0.000</b>		
FEV <sub>1</sub>	0.139 (0.098,0.180)	0.288	6.714	<b>0.000</b>	0.616	<b>0.000</b>
NRS-2002	-1.125 (-1.961,-0.289)	-0.110	-2.648	<b>0.009</b>		
mMRC	0.869 (0.60, 1.677)	0.103	2.113	<b>0.035</b>		

AIS: Acceptance of Illness Scale EFS: Edmonton Frailty Scale; B: unstandardized coefficients; CI: confidence interval;  $\beta$ : standardized regression coefficient; R<sup>2</sup>: coefficient of determination.

who had retired or still continued to work. Similarly, in their study on diabetic patients in Turkey, Şireci and Yılmaz Karabulutlu (2017) reported that unemployed patients had a lower level of acceptance of illness (11). This situation can be explained by the fact that almost all of the unemployed people in our country are women, and they are "housewives" who live a sedentary life. In terms of income status, it was found that older COPD patients with a good income had lower levels of frailty and higher acceptance of illness scores than patients with moderate or low income. This can be explained by the fact that better socioeconomic conditions can provide easier access to adequate food, health services and medicines.

Older COPD patients who were using alcohol or those who had quit using it had lower frailty scores. This difference can be explained based on the fact that all of these patients in our study were male. Smoking, however, did not have any effect on the

frailty and acceptance of illness scores.

Patients who were hospitalized due to COPD exacerbation in the past year had higher frailty and lower acceptance of illness scores. This result can be explained by the fact that the dyspnoea and inactivity experienced by patients during COPD exacerbation contribute to the deterioration of their physical activity (reduction in walking speed, loss of muscle strength), which are common features of frailty syndrome. The mean acceptance of illness score of the hospitalized COPD patients reported by Uchmanowicz et al. (2016) was lower than the results in our study (13). Similarly, in our study, it was concluded that older people who used oxygen devices in their homes had higher frailty and lower acceptance of the disease than those who did not use these devices. This can be explained by the failure of the patients to comply with oxygen therapy on one hand, and deterioration of quality of life as a negative impact of the disease on the other; both

of these adversely affect the level of acceptance of illness.

Patients with comorbidities besides COPD, and with polypharmacy, had higher frailty and lower acceptance of illness scores. Although comorbidity is different from frailty and disability, they may aggravate each other and contribute to the progression of frailty (22). An increase in the amount of drugs used, which is in direct relationship with the number of comorbidities, may be a risk factor for frailty.

Age was positively related to frailty, and as it increased the level of frailty increased moderately. This result was consistent with studies conducted in other countries (20,23,24). Physiological and cognitive changes caused by aging which lead to frailty can explain this situation. In contrast to this, age was negatively correlated with the acceptance level of the disease. While Nowicki, Krzemkowska and Rhone (2015) found no correlation between age and acceptance of illness in their study on cancer patients, the results of Mroczek et al. (2015) and Jankowska-Polańska et al. (2015) in their study on the level of acceptance of illness in COPD patients were consistent with our study (18,19,23). The duration of COPD, FEV<sub>1</sub> values, and mMRC scores, which are all parameters of COPD, were correlated with the levels of frailty and acceptance of illness. Considering the fact that longer duration of COPD, lower FEV<sub>1</sub> values, and higher mMRC scores are all indicators of higher levels of severity and the burden of COPD, they all lead to an increased level of frailty and decreased level of acceptance of illness. Similar to our study, in their study on Polish patients, Jankowska-Polańska et al. (2016) reported that as the burden of COPD increases, older patients have difficulty in accepting their disease (21). Furthermore, Maddocks et al. (2016) found that COPD patients with low FEV<sub>1</sub> values and high mMRC scores were frailer due to reduced lung capacity and difficulties caused by dyspnoea (16). NRS-2002 scores had a positive correlation with the level of frailty and a negative correlation with the level of acceptance

of illness. Similar to our results, Machón et al. (2018) also reported that frail people were more prone to malnutrition risk. The fact that chronic malnutrition causes sarcopenia and indirectly leads to frailty can explain this situation (25).

In this study, there was a strong negative correlation between frailty level and acceptance of illness in patients older than 65 years. In this context, the increase in the vulnerability of older people may be due to a decrease in the level of acceptance as a strong factor. In contrast to our study, in their study on hospitalized COPD patients with a mean age of 63.2, Uchmanowicz et al. (2016) used a different measurement tool to evaluate frailty, and reported a weak negative correlation between the physical and social subscales of frailty and acceptance of illness level, yet they found no correlation between total frailty score and acceptance of illness level (13). It can be assumed that independent variables such as age and hospitalization can change the direction and strength of the relationship between the level of frailty and the level of acceptance of illness.

When the literature is examined, although there are studies examining the relationship between the level of frailty and acceptance of the disease, no study has been found that indicates the explanatory power of this relationship. In this respect, the explanatory power of other independent variables related to acceptance of the disease, as well as the level of frailty with a high level of negative correlation and acceptance of the disease, were examined. As a result, the combination of frailty level, FEV<sub>1</sub> value, NRS-2002 score and mMRC value according to statistically established models explained the acceptance of illness level at a rate of 61.6%; The level of frailty alone explains the acceptance of the disease at a rate of 55.6%. As a result, it is thought that attempts to increase the acceptance of the disease in older people with COPD will make a great contribution to reducing frailty, which is a biopsychosocial syndrome.



### Limitations

First, the study has a descriptive and correlated design; therefore, the results of the study cannot suggest causality. We evaluated only older people admitted to the outpatient clinics. Finally, the sample was small and the findings were limited to a single department of a single hospital in Turkey. These disadvantages, together with our non-random sam-

pling and data collection in only one centre, limit the generalizability of findings to all Turkish older people with COPD. Even with these limitations, this study provides a better understanding of the relationship between frailty and acceptance of illness in older people with COPD. This study provides instructions for future longitudinal or experimental studies.

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## RESEARCH

# ADAPTATION OF THE AGING SEMANTIC DIFFERENTIAL SCALE INTO TURKISH

Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.222  
2021; 24(2): 255-263

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Received: Jan 14, 2021  
Accepted: May 21, 2021

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## ABSTRACT

**Background:** The aim of this study was to adapt the Aging Semantic Differential Scale into Turkish. Rosencranz and McNevin (1969) first developed this scale to measure ageism and specific attitudes toward old people. Since then, this scale has been adapted into many languages, though not Turkish, and widely used in gerontology literature.

**Method:** This current study involved 204 volunteer Turkish undergraduate students registered at Hacettepe University (139 females, mean age 20.6). They completed the questionnaires in a test-retest format in their classrooms.

**Results:** Factor analyses revealed that the Turkish form had 26 items and 4 factors with an eigenvalue greater than 1 and explaining 46.8% of the total variance. The scale also highly correlated to two other scales on ageism, The Attitudes Toward Old People Scale and The Ageism Attitude Scale. Its internal reliability and two-week interval test-retest reliability scores were high.

**Conclusion:** In conclusion, the Turkish form of the Aging Semantic Differential Scale is a valid and reliable tool. By adapting a well-known ageism scale into Turkish, this study makes an important contribution to Turkish gerontology literature.

**Keywords:** Ageism; Semantic Differential

## INTRODUCTION

Ageism refers to negative attitudes toward an individual or group of people based on their biological age (1). These attitudes can emerge through thoughts, feelings, or actions as stereotypes, prejudice, or discrimination, respectively (2). Research shows that old people are more frequently exposed to these negative attitudes than young people (3).

Being subject to ageism harms individuals' physical and psychological wellbeing. The degree of these effects depends on several factors, such as age, the extent to which individuals associate these attitudes with themselves, and the life domains in which these attitudes are based (4). A recent study on old age ageism indicates that ageism negatively affects life satisfaction as people grow older (4). Specifically, elders who perceive old age positively report higher life satisfaction than their counterparts with negative perceptions of old age. However, this relationship is not significant among young people. Other studies reveal the long-term effects of ageism: for instance, two longitudinal studies demonstrate that internalized ageism negatively affects elders' cognitive performance and personality development over time (5, 6). While old people suffer from all of these aspects in their daily lives, ageism among healthcare workers also weakens the quality of healthcare elders receive. Therefore, ageism among healthcare professionals can worsen old people's health conditions (7). Overall, in addition to the physical and mental difficulties of old age, elders can also suffer from ageism.

Using both explicit and implicit measures, a considerable amount of literature has been published in the last few decades on the sources and consequences of ageism and possible precautions against it (4, 8, 9). The level of ageism people show is affected not only by demographic factors (i.e., age, gender), but also the life domains in which age groups are evaluated. For instance, Kornadt and Rothenmund (2011) asked approximately 700 volunteers to rate their attitudes toward old people based

on eight life domains. In general, the participants rated old people positively in the "religion and spirituality" and "family and partnership" domains but negatively in "physical and mental fitness" and "financial situation." (4). However, these results varied depending on the participants' age: old people reported high levels of ageism for some domains (e.g., "religion and spirituality") while young people showed a similar tendency in different domains (e.g., "physical and mental fitness"). Another study by Kornadt et al. (2013) stressed the importance of both age and gender. According to this study, young people demonstrate ageism more than old people and target old males more than old females (10). Even though the researchers could not find a gender effect among young participants, the level of ageism fluctuated depending on the target's gender among old and middle-aged participants. In the same study, these relationships depended on the life domains in which elders were evaluated, in parallel to previous findings. While female elders were rated more negatively in the "work" and "finances" domains, male elders were rated more negatively in the "religion" and "friends" domains.

This study aimed to adapt a well-known ageism scale, the Aging Semantic Differential Scale (ASD) into Turkish. This scale asks participants from various age groups to report their attitudes toward old people. This scale was first developed by Rosenzanz and McNevin (1969) as a semantic differential scale (11). Semantic differential scales are one form of forced-choice scales, which also include Likert scales, created by Osgood et al. in 1957 (12). While participants rate the degree of their agreement with a particular statement in Likert scales, in semantic differential scales, they rate their attitudes toward a situation or group of people based on a line scale between two opposite adjectives (13). To date, semantic differential scales have been widely used in various research areas from pain assessments (14) to self-concept evaluations (15). Research shows that these scales reveal statistically more valid results in



measuring psychological constructs compared to Likert scales (16) however only a few Turkish studies utilize them (17).

To sum up, ageism negatively affects people's psychological and physical wellbeing, cognitive and personality development. In addition, old people are subject to ageism more than young people. The ASD, the most widely used ageism scale in gerontology literature, has been adapted into various languages (3, 18). For these reasons, this study can make an important contribution to Turkish gerontology literature and consequently to old people's wellbeing by adapting the ASD into Turkish.

## MATERIALS AND METHOD

The academic ethics board at Hacettepe University approved this research. In total, 204 undergraduates registered at Hacettepe University participated in the study.

In this study we used three scales on ageism: The Aging Semantic Differential Scale (ASD), The Attitudes Toward Old People Scale, The Ageism Attitude Scale. Rosencranz and McNevin first developed the ASD in 1969, which asks participants to report their attitudes toward old people depending on line scales divided into seven degrees between 32 opposite adjective pairs as illustrated below:

Progressive \_\_X\_\_ \_\_ \_\_ \_\_ \_\_ Old-fashioned  
Generous \_\_ \_\_ \_\_ \_\_ \_\_ X\_\_ Selfish

Participants can score between 32 and 224 on the scale, with higher scores denoting a more negative attitude toward old people. The original scale had three factors: instrumentality, autonomy, and acceptability. However, later studies that reassessed the ASD's psychometric properties support a four-factor model with the original three factors and the new addition of integrity (3, 19).

The Attitudes Toward Old People Scale was developed by Kogan in 1961 to measure ageism to-

ward old people (20). It consists of 34 items, with 17 positive and 17 negative propositions rated on a 6-point Likert scale. The negative items are reverse-coded; therefore, high scores indicate more positive attitudes toward old people. In 2013, Duyan and Gelbal (21) adapted this scale into Turkish and note that the Turkish form has good reliability and validity scores.

The Ageism Attitude Scale was developed by Vefikulucay and Terzioglu to measure discrimination against old people in 2011 (22). Participants rate their agreement with 23 propositions on a 5-point Likert scale. The scale is composed of three factors: restrictions in elders' lives, negative ageism, and positive ageism. Participants can score between 23 and 115 on the scale. The first two factors are reverse-coded, meaning high scores represent less discrimination against old people. Vefikulucay and Terzioglu report that the scale has good psychometric properties (22).

The researcher and another academic who speaks both English and Turkish translated the ASD into Turkish via a back-translation technique. Afterwards, 15 graduate students with a mean age of 23 completed the scale for a pilot study. They reported that the items were easy to follow. The scale items in their original form and their Turkish translations are listed in Table 1.

The volunteers completed the demographics and three scales on ageism including the ASD in their classrooms via paper-pencil method. Two weeks later, all participants filled out the ASD again using the same method, to assess the test-retest validity.

We started psychometric analyses of the scale with factor analyses using the SPSS and the AMOS programs. After the analyses confirmed the structural validity of the scale, the SPSS program was used to run the remaining validity and reliability tests (i.e., convergent validity, internal reliability and test-retest reliability).

**Table 1.** Overview of the items of the Original Version and the Turkish Version of the Aging Semantic Differential Scale (ASD).

Original ASD (Rosencrantz & McNevin, 1969)	Turkish Translation of ASD
1. Progressive–Old-fashioned	Yenilikçi-Eski kafalı
2. Consistent–Inconsistent	Tutarlı-Tutarsız
3. Independent–Dependent	Bağımsız-Bağımlı
4. Rich–Poor	Zengin-Fakir
5. Generous–Selfish	Cömert-Bencil
6. Productive–Unproductive	Üretken-Üretken değil
7. Busy–Idle	Meşgul-Başboş
8. Secure–Insecure	Güvenli-Güvenli değil
9. Strong–Weak	Güçlü-Zayıf
10. Healthy–Unhealthy	Sağlıklı-Sağlıksız
11. Active–Passive	Aktif-Pasif
12. Handsome–Ugly	Güzel-Çirkin
13. Cooperative–Uncooperative	İşbirlikçi-İşbirlikçi değil
14. Optimistic–Pessimistic	İyimser-Kötümser
15. Satisfied–Dissatisfied	Tatminkar-Tatminsiz
16. Expectant–Resigned	Beklentisi olan-Kabullenmiş
17. Flexible–Inflexible	Esnek-Katı
18. Hopeful–Dejected	Umutlu-Umutlu değil
19. Organized–Disorganized	Düzenli-Düzensiz
20. Happy–Sad	Mutlu-Üzgün
21. Friendly–Unfriendly	Canayakın-Soğuk
22. Neat–Untidy	Tertipli-Dağınık
23. Trustful–Suspicious	Güvenilir-Şüphe uyandıran
24. Self-reliant–Dependent	Özgüvenli-Başkalarına bağımlı
25. Liberal–Conservative	Özgürlükçü-Muhafazakar
26. Certain–Uncertain	Kendinden emin-Emin değil
27. Tolerant–Intolerant	Hoşgörülü-Hoşgörüsüz
28. Pleasant–Unpleasant	Hoş-Nahoş
29. Ordinary–Eccentric	Sıradan-Alışılmamış
30. Aggressive–Defensive	Saldırgan-Savunucu
31. Exciting–Dull	Heyecan verici-Sıkıcı
32. Decisive–Indecisive	Kararlı-Kararsız

## RESULTS

The sample consisted of 139 females and 65 males. Their mean age was 20.62 and 63% were majoring in social sciences.

An exploratory factor analysis (EFA) with varimax rotation helped determine the number of factors in the Turkish ASD form. At first, we checked whether the Kaiser Meyer Olkin (KMO) value was higher

than .80 and if Bartlett's Test of Sphericity (BTS) was significant. The results showed that the KMO was .84 and BTS was significant ( $\chi^2(496) = 2698.71$ ,  $p < .001$ ), as expected (23). The EFA showed that a four-factor structure explained 46.8% of the total variance, with an eigenvalue greater than 1. We removed 7 items that were not represented by these factors from the Turkish ASD. The factor loadings for each item are listed in Table 2.

A confirmatory factor analysis (CFA) through AMOS showed that this initial model did not fit the data ( $\chi^2(318) = 701.285$ ,  $p = .00$ , CFI = .79, RMSEA = .07). Depending on the modification indices, we added covariances between error terms to the following items: items 8 and 23 in the acceptance domain; items 26 and 32 in the autonomy domain; items 2 and 32 in the autonomy domain; and items 10 and 11 in the instrumentality domain. In addition, item 15 was moved from the integrity domain to the acceptance domain depending on the modification indices. This change was acceptable for two reasons. First, as can be seen from Table 2, item 15 was represented in both dimensions with similar factor loadings (.50 vs. .46). Second, this adjective pair was represented in the acceptance dimension in previous studies (3). In the end, the final model showed a sufficient fit with the model ( $\chi^2(265) = 485.48$ ,  $p = .00$ , CFI = .87, RMSEA = .06). Figure 1 shows additional details of the final model.

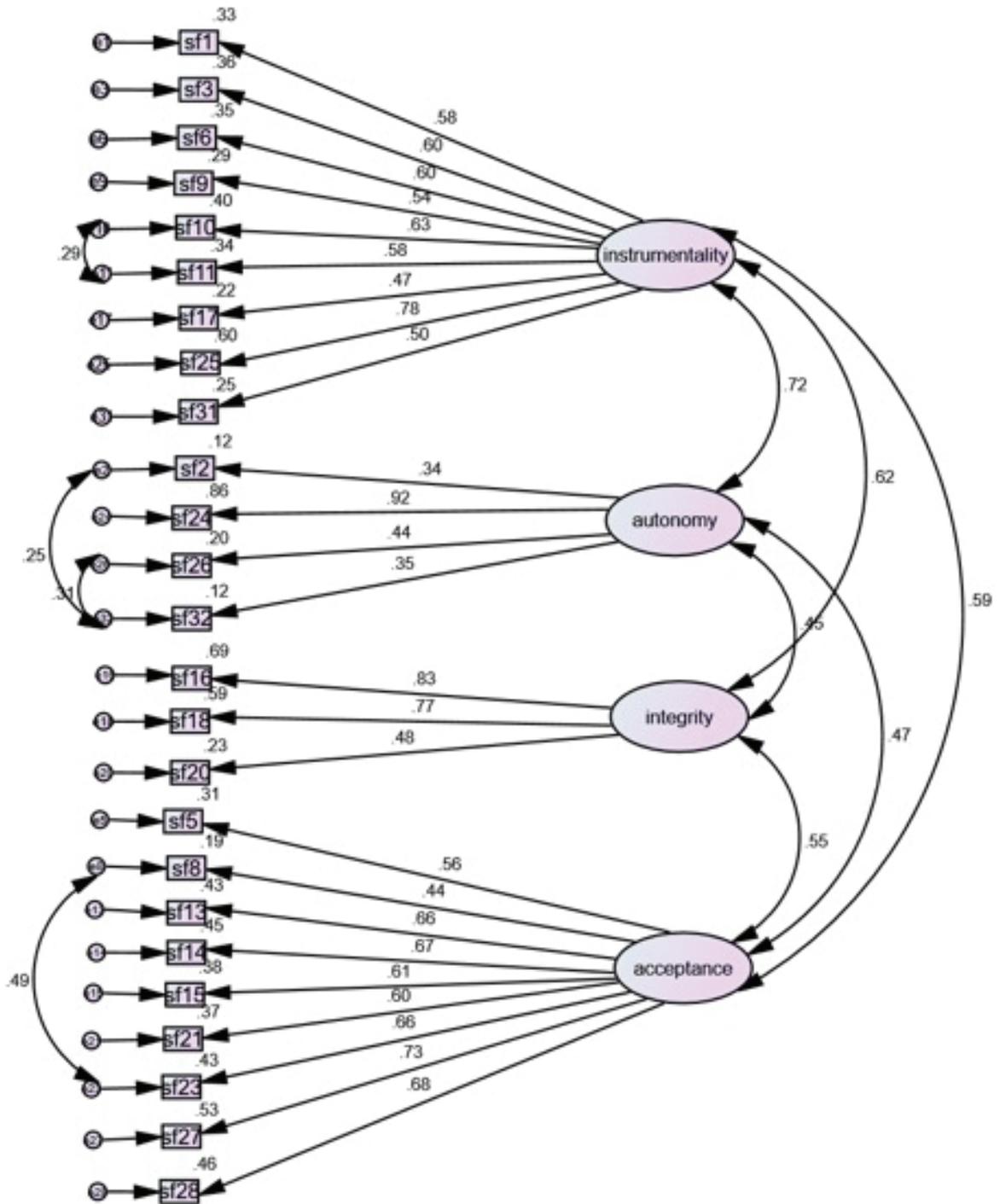
Lastly, we tested whether previous versions of the ASD better fit the data. Unfortunately, neither the original version with 32 items and three factors ( $\chi^2(461) = 1424.792$ ,  $p = .00$ , CFI = .59, RMSEA = .10) (11) nor the updated version of the scale with 25 items and four factors fit the data ( $\chi^2(293) = 819.88$ ,  $p = .00$ , CFI = .69, RMSEA = .09), (3).

To test the Turkish ASD's convergent validity, Pearson correlations were conducted for it, the Ageism Attitude Scale, and the Attitudes Toward Old People Scale. As anticipated, the ASD negatively correlated with the total scores of the Ageism Attitude Scale ( $r = -.58$ ;  $p < .01$ ) and the Atti-

**Table 2.** Factor Loadings of the Items in the Turkish Form of the ASD.

	Instrumentality	Autonomy	Integrity	Acceptance
1. Progressive–Old-fashioned	.55			
3. Independent–Dependent	.50			
6. Productive–Unproductive	.47			
9. Strong–Weak	.40			
10. Healthy–Unhealthy	.64			
11. Active–Passive	.73			
17. Flexible–Inflexible	.46			
25. Liberal–Conservative	.67			
31. Exciting–Dull	.49			
2. Consistent–Inconsistent		.55		
24. Self-reliant–Dependent		.55		
26. Certain–Uncertain		.69		
32. Decisive–Indecisive		.70		
16. Expectant–Resigned			.74	
18. Hopeful–Dejected			.81	
20. Happy–Sad			.54	
5. Generous–Selfish				.55
8. Secure–Insecure				.62
13. Cooperative–Uncooperative				.46
14. Optimistic–Pessimistic				.55
15. Satisfied–Dissatisfied			.50	.46
21. Friendly–Unfriendly				.63
23. Trustful–Suspicious				.73
27. Tolerant–Intolerant				.62
28. Pleasant–Unpleasant				.46

**Figure1.** Measurement Model Developed Depending on the Confirmatory Factor Analysis using AMOS.





tudes Toward Old People Scale ( $r = -.62; p < .01$ ). In addition, the ASD significantly correlated with the sub-domains of these scales in the expected directions. The correlation coefficients are listed in Table 3. Except for the restrictions sub-domain of the Ageism Attitude Scale which revealed a low correlation, the adapted form of the ASD was found to be highly correlated with other scales on ageism in general.

For the one-factor model, confirmatory factor analysis yielded a high internal reliability ( $\alpha = .90$ ). The Cronbach's alpha value was .83 for the instrumentality domain, .72 for the integrity domain, .66 for the autonomy domain, and .85 for the acceptance domain. The item-total correlations ranged between .35 and .66 in all sub-domains therefore all sub-items were sufficiently distinct, and the Turkish ASD's internal reliability was high.

Lastly, a Pearson correlation analysis showed that the ASD's two applications at a two-week interval were significantly correlated with a high degree ( $r = .67; p < .001, n = 204$ ).

## DISCUSSION

In this study, we adapted the ASD, which measures attitudes toward old people, into Turkish. This scale was first developed by Rosencranz and McNevin in 1969 and has been adapted into many other languages since then for wider use in gerontology literature (3, 18, 19). While the EFA revealed that the scale had 25 items represented by four factors, a CFA showed that the final model fits the data well. In terms of convergent validity, the 25-item ASD displayed high correlation with two other ageism scales in the expected direction. Further analyses showed that the scale's internal and test-retest reliability were high. In summary, the Turkish form of the ASD shows good psychometric characteristics.

The variety of measurement techniques provides researchers flexibility and makes it easier to reach more diverse and multiple groups. Similar to the development of visual analog scales for children and illiterate people, people with concentration problems can more easily complete semantic differential scales compared to Likert scales that may

**Table 3.** Bivariate Correlation Results Between the ASD and Other Ageism Scales.

Ageism Scales	Sub-Domains	Correlation with The ASD
Ageism Attitude Scale		-.58**
	Restrictions	.29**
	Negative Ageism	.43**
	Positive Ageism	-.49**
Attitudes Toward Old People Scale		-.62**
	Negative Attitudes	.48**
	Positive Attitudes	-.60**

Numbers indicate correlation coefficients, \*\* $p > 0.01$ .

have long propositions. Even though semantic differential scales are not prevalent in Turkish academic studies, they have several advantages compared to Likert scales (16). As such, the Turkish ASD will make an important contribution to Turkish gerontology literature.

Although ageism occurs almost everywhere, its frequency and characteristics can vary from one society to another (1, 24). For this reason, the contents of ageism scales used in different societies may also vary. In this study, the ASD's Turkish form was represented by four factors similar to the scale's adaptations into other languages. In addition, the ASD's model fit scores parallel the scores obtained by those scales (3, 25). Still, there were small differences between the Turkish and other forms of the ASD (e.g., item number). This situation may have arisen from the characteristics of the sample or as a cultural effect.

In this study, we recruited college students in Turkey which prevents us from generalizing our results to other groups. Therefore, these results should be

replicated on different age groups in different cultures. In addition, this scale mainly focuses on one aspect of ageism, specifically stereotypes (i.e., negative generalizations) about old people. Therefore, future studies on this area of research should also include scales on prejudice and discrimination aspect of ageism to comprehensively assess negative attitudes towards elders.

In conclusion, there are few studies using semantic differential scales in the Turkish literature despite their advantages over Likert scales. The ASD has a semantic differential format and it is the most widely used ageism scale in the gerontology literature. This study showed that the Turkish form has good psychometric properties. Because of these reasons, this scale will enrich Turkish gerontology literature. Since ageism has detrimental effects on old people's physical and psychological well-being, we hope that this important contribution in the literature will help us understand the antecedents and dynamics of ageism better and consequently improve elders' life standards.

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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.223  
2021; 24(2): 264-275

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Received: Jan 15, 2021  
Accepted: Apr 04, 2021

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## RESEARCH

# KNOWLEDGE, ATTITUDES AND BEHAVIOURS OF ELDERLY PEOPLE LIVING AT A NURSING HOME RELATED TO PNEUMOCOCCAL AND INFLUENZA VACCINES

## ABSTRACT

**Introduction:** The World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020; since then, protecting the elderly against infections through immunisation has become increasingly critical. This study aims to assess the knowledge level of individuals aged 65 years and above at a nursing home who are in the risk group for pneumococcal and influenza vaccines along with their attitudes and behaviours regarding immunisation.

**Materials and Methods:** The questionnaire prepared by the researcher was administered to the elderly residents aged 65 years and above who could perform their own self-care in the blocks designated for healthy residents at the Narlıdere Nursing Home Elderly Care and Rehabilitation Center after obtaining their oral consent.

**Results:** The average age of the 708 elderly residents who participated in the research was  $79.05 \pm 7.32$  years (range 62–98), and 63% were female. Of the residents, 75.1% had heard about the pneumococcal vaccine, and 97.2% were aware of the influenza vaccine. Only 24.6% had been administered the pneumococcal vaccine, and 29.9% expressed that they did not receive it because their physician did not recommend it. A significant relation was found between having received the pneumococcal vaccine and age group ( $p = 0.046$ ) and having received the pneumococcal vaccine and educational background ( $p = 0.025$ ).

**Conclusion:** Elderly people have more knowledge about influenza vaccine than pneumococcal vaccine. Their healthcare professionals mostly inform them about vaccinations. Therefore healthcare professionals should be trained about the pneumococcal vaccination procedures in elderly.

**Keywords:** Aged; Influenza Vaccines; Pneumococcal Vaccines; Nursing Homes



## INTRODUCTION

There is clear evidence that the average age of the world's population is rising. In Turkey, the number of individuals who are 65 years of age and above has increased by 21.9% over the past five years (1). Thus, healthy ageing of the population is increasingly important. The main factor contributing to healthy ageing is the practice of protection. Reports indicate that pneumococcal disease and influenza are the leading causes of mortality and morbidity associated with diseases that can be prevented by immunisation in the elderly (2). Immunisation is the easiest, most economical and most strategic method for infectious disease protection in both elderly individuals and children.

Aged people are vulnerable to diseases because of changes in the immune system, and even simple upper respiratory infections may have serious consequences (2). Immune system changes in the elderly include a decrease in immunological functions and the deterioration of immune regulation as a person ages (3). Accordingly, the incidence and mortality of pneumococcal disease in individuals 65 years of age and above have significantly increased (4). Analysis of data from the Turkish Statistical Institute reveals that respiratory system diseases were, with a rate of 14.8%, the third-highest cause of mortalities in individuals aged 65 years and above in 2018 (5).

Influenza viruses cause acute respiratory tract infections and vary in presentation from mild clinical symptoms to severe infections that may result in mortality (6). The elderly exhibit respiratory insufficiency with influenza at a rate that is 10–30 times higher than in young people (4). According to data from the Centers for Disease Control and Prevention (CDC), of the approximately 31,000 deaths due to COVID-19, pneumonia and influenza infections between February and September 2020, 79% involved patients aged 65 years and above (7, 8).

The World Health Organization (WHO) has identified "***Streptococcus pneumonia***" and seasonal

influenza amongst those respiratory tract infections that may be the most significant causes of hospitalisation and mortality in aged people which can be prevented by immunisation. At the global level, the medical community has reported a very high mortality rate of COVID-19, which emerged in December 2019, in the aged population. However, the clinical findings are unclear, atypical and not specific to the disease. The need to minimise other respiratory tract infections has become increasingly urgent in view of the mortality rate of COVID-19 pneumonia in the aged population. Accordingly, there has been an increase in the importance of pneumococcal and influenza vaccines as well as amplified social interest (9, 10). Living at a residential facility or nursing home and being 65 years of age or older are main risk factors for pneumococcal disease and influenza (11). Thus, the aim of this study is to determine the knowledge level of individuals aged 65 years and above at a nursing home who are in the risk group with respect to pneumococcal and influenza vaccines and to assess their attitudes and behaviours regarding immunisation.

## MATERIALS AND METHOD

The research design entails a cross-sectional questionnaire study. The questionnaire form was administered to individuals aged 65 years and above who were living in the blocks for healthy residents at the Izmir/Narlıdere Nursing Home Elderly Care and Rehabilitation Center. The respondents had to be able to manage their own care and daily life activities without assistance from others, and their participation was approved after the researchers obtained their oral consent via a face-to-face interview method between the dates of May 2016 and January 2017.

The researchers prepared a questionnaire form that contained 14 items covering the demographical characteristics of the participants, including their age, sex, educational background, and marital status, the presence of disease, their knowledge of

pneumococcal and influenza vaccines, whether they had been informed about the vaccines by health-care professionals, whether such information was sufficient, their immunisation status, information about payment for vaccines by the social security institution, and their reasons for not receiving the vaccines (Table 1). The study was conducted with consideration to the number of elderly residents who were on leave in the summer. As of January 2017, all elderly residents of the blocks for the healthy at the nursing home had been contacted.

### Statistical Analysis

The dependent variables were vaccination status and knowledge and attitudes of pneumococcal and influenza vaccines in the elderly, while the independent variables were sex, age group, marital status, educational background and presence of disease. The obtained data were processed on a computer and evaluated with the Statistical Package for Social Sciences (SPSS) version 18.00. Group comparisons were performed using the chi-squared test for categorical variables, and significance was defined as  $p < 0.05$ .

### Ethical Considerations

The study was initiated after securing approval from the ethical committee of Izmir Katip Celebi University (no. 110, dated 26.05.2016) along with the consent of the relevant ministries and institutions. All participants were literate, and they were informed about the study before they provided oral consent. The researchers distributed the questionnaires and monitored the process, and the participants filled out the questionnaire forms independently at the health offices, in common living spaces or in their rooms.

## RESULTS

Of the 746 elderly residents of the unsupported living blocks in the nursing home, 708 residents who

had not been diagnosed with dementia agreed to participate in the study. Of these 708 participants, 63.1% were female ( $n = 447$ ), and the average age was  $79.05 \pm 7.32$  years (range 62–98). The distribution of each age range was as follows: 190 (26.8%) participants were 65–74 years of age, 329 (46.5%) were 75–84 years of age and 189 (26.7%) were aged 85 or older. In addition, 218 (30.8%) participants had completed primary and secondary school, 263 (37.1%) were high school graduates and 227 (32.1%) held university degrees.

A chronic disease was reported by 81.6% of the participants. Specifically, 354 (50%) identified hypertension (HT), 169 (23.9%) reported diabetes mellitus (DM), 124 (17.5%) had coronary artery disease (CAD), 118 (16.7%) identified congestive heart failure, 77 (10.9%) experienced chronic obstructive pulmonary disease (COPD) and 51 (7.2%) reported obesity. Amongst the participants, 397 (56.1%) had been informed about the payment status of the vaccines by the social security institution.

A total of 532 (75.1%) participants had heard about the pneumococcal vaccine. Twenty-five (3.5%) elderly patients had contracted pneumonia in the most recent year, while 174 (24.6%) of the elderly residents had received the pneumococcal vaccine.

With regard to reasons for not receiving the pneumococcal vaccine, 212 (29.9%) of the elderly participants indicated that their physician did not recommend it, 148 (20.9%) stated that they had not heard about the vaccine, 68 (9.6%) reported that they were healthy, 63 (8.9%) did not believe that it was effective and 5 (0.7%) had been unable to find the vaccine. Of the elderly participants who had received the vaccine, 17 (10.2%) expressed that they had acquired pneumonia despite being vaccinated. No significant relation was found between the presence of chronic disease and having received the pneumococcal vaccine ( $p > 0.05$ ). Significant relations were found between the age group ( $p = 0.046$ ) and educational background ( $p = 0.025$ ) and having received the pneumococcal vaccine, but no



**Table 1.** Questionnaire form

Knowledge, behavior and attitudes of the individuals aged 65-year and above living at the nursing home related to the pneumococcal and influenza vaccine					
Line	Questionnaire questions				
1	Age				
2	Sex		<input type="checkbox"/> female	<input type="checkbox"/> male	
3	Marital status	<input type="checkbox"/> single	<input type="checkbox"/> married	<input type="checkbox"/> widow	<input type="checkbox"/> divorced
4	Educational background	<input type="checkbox"/> primary school	<input type="checkbox"/> secondary school	<input type="checkbox"/> high school	<input type="checkbox"/> university
		<input type="checkbox"/> higher education	<input type="checkbox"/> literate	<input type="checkbox"/> not literate	
5	Do you have any known disease?	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> if yes, indicate	
6	<input type="checkbox"/> DM <input type="checkbox"/> HT <input type="checkbox"/> CAD <input type="checkbox"/> CRD <input type="checkbox"/> COPD <input type="checkbox"/> CLD <input type="checkbox"/> Obesity <input type="checkbox"/> Other				
7	Did you hear about pneumococcal and influenza vaccine?	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> if yes, where?	
8	<input type="checkbox"/> tv <input type="checkbox"/> radio <input type="checkbox"/> internet <input type="checkbox"/> press <input type="checkbox"/> friends <input type="checkbox"/> family <input type="checkbox"/> healthcare professional				
6	Do you think that information is sufficient if you informed by the healthcare professional?	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> partly	
7	Did you get pneumococcal vaccine?	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> if yes, when	
8	Did you get influenza vaccine?	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> if yes, when	
9	Did you get another vaccine?	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> if yes, indicate	
20	Do you know that vaccine cost is covered by the social security institution for chronic diseases?	<input type="checkbox"/> no	<input type="checkbox"/> yes		
11	Have you had pneumonia or influenza in recent year?	<input type="checkbox"/> no	<input type="checkbox"/> yes		
12	Reason of not getting vaccine? (You may choose more than one options for the answers of these questions)				
12-A	Reason of not getting pneumococcal vaccine?				
12.A.1	I didn't hear about pneumococcal vaccine.	<input type="checkbox"/>			
12.A.2	I don't believe it is efficient	<input type="checkbox"/>			
12.A.3	I could not find the vaccine	<input type="checkbox"/>			
12.A.4	My physician did not recommend it	<input type="checkbox"/>			
12.A.5	I believe that it has side effects.	<input type="checkbox"/>			
12.A.6	I had problems when I had got it before.	<input type="checkbox"/>			
12.A.7	I have never had lung disease in my life	<input type="checkbox"/>			
12.A.8	I am a healthy person, therefore I don't get it	<input type="checkbox"/>			
12.B	Reason of not getting the influenza vaccine				
12.B.1	I didn't hear about influenza vaccine.	<input type="checkbox"/>			
12.B.2	I don't believe it is efficient	<input type="checkbox"/>			
12.B.3	I could not find the vaccine	<input type="checkbox"/>			
12.B.4	My physician did not recommend it	<input type="checkbox"/>			
12.B.5	I believe that it has side effects.	<input type="checkbox"/>			
12.B.6	I had problems when I had got it before.	<input type="checkbox"/>			
12.B.7	I have never had influenza in my life	<input type="checkbox"/>			
12.B.8	I am a healthy person, therefore I don't get it	<input type="checkbox"/>			
13	Did you have pneumonia even if you got pneumococcal vaccine?	<input type="checkbox"/> no	<input type="checkbox"/> yes		
14	Have you had influenza in recent year even if you got influenza vaccine?	<input type="checkbox"/> no	<input type="checkbox"/> yes		
Thank you for participating in our questionnaire.					

significant relation was identified for sex or marital status (Table 2).

Twenty (2.8%) participants indicated that they had not heard about the influenza vaccine. There was a statistically significant difference ( $p = 0.00$ ) between the rate of awareness of the influenza vaccine (97.2%) versus of the pneumococcal vaccine (75.1%) amongst the participants. While 281 (39.7%) participants reported that they had contracted influenza in the most recent year, 419 (59.2%) had received influenza vaccine. In terms of reasons for not receiving the influenza vaccine, 111 (15.7%) of the participants did not believe that it was effective, 76 (10.7%) indicated that their physician did not recommend it, 67 (9.5%) stated that they were healthy and 3 (0.4%) explained that they had not been able to find the vaccine. Of the individuals who had received the vaccine, 50.5% indicated that they had acquired influenza despite being vaccinated. No significant relation was found between sex, age group, marital status or educational status of the participants and having received a vaccination ( $p > 0.05$ ). (Table 2)

Of the participants, 149 (21.0%) had received both the pneumonia and the influenza vaccines, while 264 (37.3%) had not received both vaccines. No significant relation was found between sex, age group, marital status or educational status of the participants and having received the pneumococcal and influenza vaccines ( $p > 0.05$ ). Table 2 details the characteristics of the patients who had received both the pneumococcal and influenza vaccines.

Some of the participants had received other vaccines; for example, 25 (3.5%) had received the tetanus vaccine, and 11 (1.5%) had received the rabies vaccine. A total of 364 (51.4%) participants had been made aware of the pneumococcal vaccine by healthcare professionals, while 135 (19%) had heard about it from television. Likewise, 528 (74.5%) participants had been informed about the influenza vaccine by healthcare professionals, whereas 174 (24.5%) had heard about it from television. Figure 1 specifies the sources from which the participants

had heard about the pneumococcal and influenza vaccines.

## DISCUSSION

A few studies have investigated the knowledge, attitudes and behaviours of elderly residents in the community towards influenza and pneumococcal vaccines in Turkey. However, the present study is the first on this subject amongst elderly nursing home residents in our country. Notably, the data were obtained from the highest-capacity residential and nursing home and rehabilitation centre in the country, and almost all occupants of the blocks for healthy residents participated in the study.

Of the 708 elderly residents who participated in the study, 63% were female; however, 63% of the elderly residents of the state-affiliated institutional nursing home in Turkey are male. In addition, high school or equivalent graduates account for 5.9% of the population above the age of 65, and the rate of individuals with higher education is 5.8% (12). Although the average age of the participants was high at approximately 80, about 70% of them reported a high school or university education. A possible explanation for this finding is that they or their family members had retired from official duty for the state. These demographic data reflect that the study was carried out in an institutional nursing area amongst a female, age-weighted population with relatively high levels of education and socioeconomic status.

Chronic disease heightens the risk of infection for elderly residents of a nursing home. Of the 81.6% of participants who stated that they had a chronic disease, 50% identified the presence of HT, and 23.9% reported experiencing DM. In the literature, the most prevalent type of chronic disease is HT, which exhibits a rate of 38.5–48.4% in nursing homes, while the same rate is 18.2%–26.4% for DM (13).

In the present study, 75.1% of the elderly participants at the nursing home stated that they had



**Table 2.** Status of getting pneumococcal and influenza vaccine of the participants by the characteristics

Characteristics	n (%)	n (%)	n (%)	P
	Vaccinated	Unvaccinated	Total	
<b>Sex</b>				
<b>Pneumococcal vaccine</b>				
Female	119 (26,6)	328 (73,4)	447(100)	0.098
Male	55 (21,1)	206 (78,9)	261(100)	
<b>Influenza vaccine</b>				
Female	254 (56,8)	193(43,2)	447(100)	0.095
Male	165 (63,2)	96(36,8)	261(100)	
<b>Pneumococcal and Influenza vaccine</b>				
Female	98 (36,8)	172(63,7)	270(100)	
Male	51 (35,7)	92(64,3)	143(100)	0.952
<b>Age</b>				
<b>Pneumococcal vaccine</b>				
65-74	9 (20,5)	51(79,5)	190 (100)	
75-84	95 (28,9)	234 (71,1)	329 (100)	<b>0.046*</b>
85+	40 (21,2)	149 (78,8)	189 (100)	
<b>Influenza vaccine</b>				
65-74	107 (56,3)	83(43,7)	190 (100)	
75-84	197(59,9)	132(40,1)	329 (100)	0.628
85+	115 (60,8)	74(39,2)	189 (100)	
<b>Pneumococcal and Influenza vaccine</b>				
65-74	31(29,2)	75 (70,8)	106 (100)	
75-84	81 (40,7)	118 (59,3)	199 (100)	0.113
85+	37 (34,3)	71 (65,7)	108 (100)	
<b>Marital status</b>				
<b>Pneumococcal vaccine</b>				
Single	26 (32,1)	55 (67,9)	81 (100)	
Married	67 (24)	212 (76)	279 (100)	0.242
Widow/Divorced	81 (23,3)	267 (76,7)	348 (100)	
<b>Influenza vaccine</b>				
Single	48 (59,3)	33 (40,7)	81 (100)	
Married	175 (62,7)	104 (37,3)	279 (100)	0.269
Widow/Divorced	196 (56,3)	152 (43,7)	348 (100)	

<b>Pneumococcal and Influenza vaccine</b>				
Single	21 (42,9)	28 (57,1)	49 (100)	
Married	61 (38,4)	98 (61,6)	159 (100)	0.476
Widow/Divorced	67 (32,7)	138 (67,3)	205 (100)	
<b>Educational background</b>				
<b>Pneumococcal vaccine</b>				
Literate/not literate, primary school	25 (19,4)	104 (80,6)	129 (100)	
Secondary school	26 (29,2)	63 (70,8)	89 (100)	<b>0.025*</b>
High school	54(20,5)	209 (79,5)	263 (100)	
Higher education	69(30,4)	158 (69,6)	227 (100)	
<b>Influenza vaccine</b>				
Literate/not literate, primary school	70 (54,3)	59 (45,7)	129 (100)	
Secondary school	58 (65,2)	31 (34,8)	89 (100)	0.105
High school	146 (55,5)	117 (44,5)	263 (100)	
Higher education	145 (63,9)	82 (36,1)	227 (100)	
<b>Pneumococcal and Influenza vaccine</b>				
Literate/not literate, primary school	22 (28,2)	56 (71,8)	78 (100)	
Secondary school	24 (45,3)	29 (54,7)	53 (100)	0.014
High school	45 (29,4)	108 (70,6)	153 (100)	
Higher education	58 (45,0)	71 (55,0)	129 (100)	

heard about the pneumococcal vaccine, and 24.6% had received that vaccine. In a study by Erdogdu et al., which was conducted at an elderly living facility in Kars, 26.9% of the 543 participants were aware of the pneumococcal vaccine, but only five of them had received it. This study suggested that educational level and low economic income affected knowledge about the vaccine and immunisation (14). Additionally, in research by Baig et al., 79.5% of the elderly participants who recorded high socioeconomic and educational levels had heard about the pneumococcal vaccine, whereas this figure was only 28.8% amongst those with low socioeconomic and educational levels. In the same study, the immunisation rate was 16.5% for the former group but only 2.3% for the latter (15).

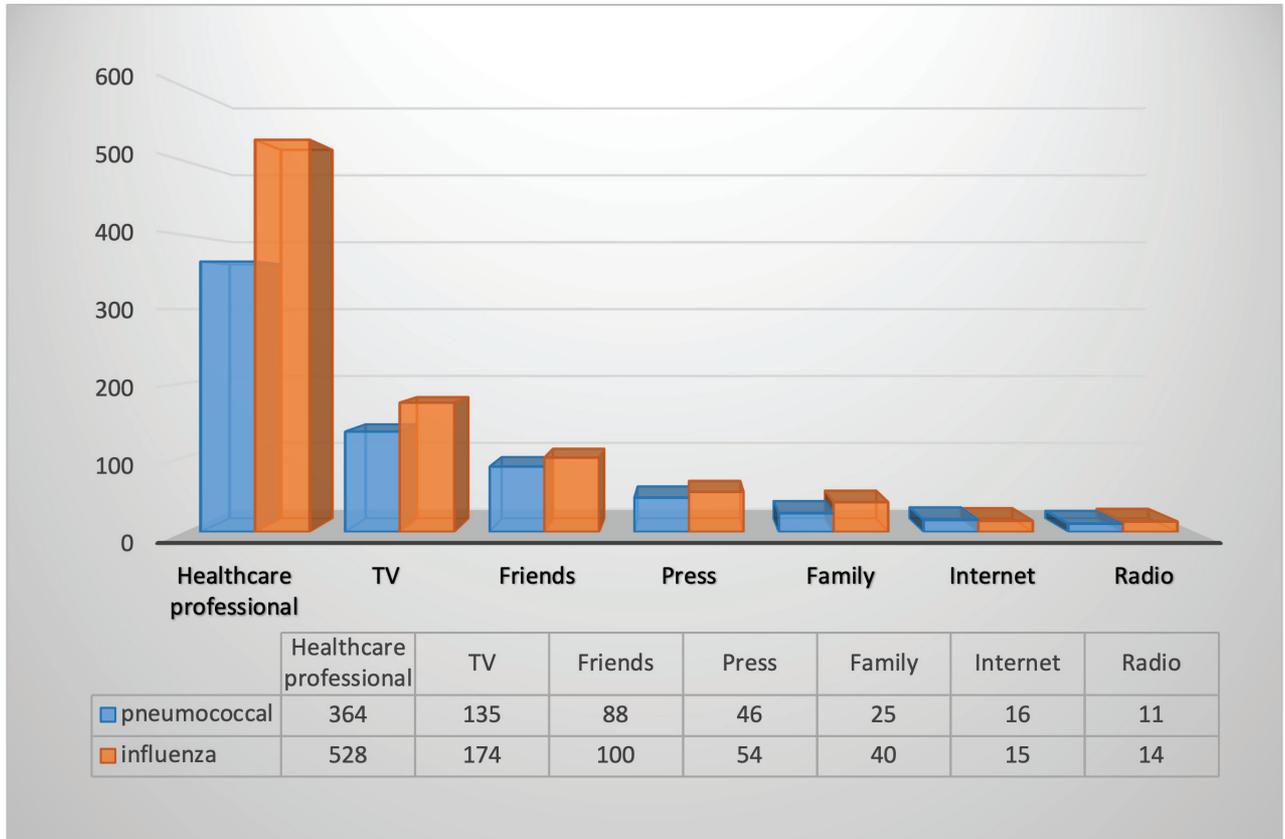
Participants had heard about and received the

pneumococcal vaccine at significantly higher rates in the present study compared to in other studies in the context of Turkey. While the rate of awareness of the pneumococcal vaccine was congruent with the rate in a study of a high socioeconomic group of elderly participants in Pakistan, the immunisation rates were slightly higher in our study. These results are supported by the statistically significant relations between the age groups and educational background of our research participants and having received the pneumococcal vaccine.

In a study by Kohlhammer et al., a recommendation from a physician and recognition of the pneumococcal vaccine were the main determinants of receiving the pneumococcal vaccine. Other reported determinants were chronic diseases, advanced age, high educational level and pneumonia (16).



**Figure 1.** Sources that participants heard about pneumococcal and influenza vaccine



While the present study has identified a significant relation between age group and educational level and the condition of immunisation, no relation with chronic diseases was found. According to research by Schneeberg et al., in Canada, the rate of pneumococcal vaccination was 58%, and the strongest factor for vaccination was a recommendation from a healthcare professional (17). In the present study, the most frequently cited reason for not receiving the pneumococcal vaccine was that 'my physician did not recommend it'. The other reasons were that 'I have not heard about the pneumococcal vaccine' and 'I am healthy'. In the study by Erdogdu et al., only 15.1% of the participants stated that they would not receive the vaccine even if it had

been recommended by a physician; other reasons for not receiving the vaccine included a fear of the side effects, good health, old age and not being old enough (14). Based on our study with the elderly residents of the nursing home, it is evident that the most important obstacle to receiving the pneumococcal vaccine can be overcome by encouraging physicians to recommend the vaccine. This conclusion is consistent with the implications of prior studies amongst elderly individuals who were living in the larger society.

Our study registered a statistically significant difference between the rate of awareness of the influenza vaccine versus of the pneumococcal vaccine. Although 97.9% of the participants had heard

about the influenza vaccine, only 59.2% had been vaccinated. The differences between the various sociodemographic factors and having received the influenza vaccine were not statistically significant. In the study by Erdogdu et al., which was performed with elderly individuals who were living in society, 52.7% of the participants had heard about the influenza vaccine, while approximately 12% had received it (14). In research by Gazibara et al., 92.4% of the participants recorded scores ranging from good to very good for their knowledge levels regarding influenza, yet the vaccination rate was found to be 47.7% (18). Research by Polat et al. in Antalya determined that 55.7% of the individuals aged 65 years and above who were living in society were aware of the influenza vaccine, but only 15% of them had received it (19). Finally, in a study by Ciblak et al. in Turkey, the rate of having received the influenza vaccine was 5.9% (6), and Yigitbas et al. similarly noted that 22% of elderly applicants to the hospital had been vaccinated against influenza (20). In our study, the rates of vaccination amongst the elderly were notably higher than those reported by numerous studies in other countries as well as in Turkey.

In the present study, reasons for not receiving the influenza vaccine included a belief that it was not effective, a lack of recommendation from a physician and a self-perception of good health that rendered the vaccine unnecessary. In the study by Gazibara et al., the participants cited similar reasons, such as being healthy, not needing the vaccine and not believing that it would provide protection against the flu (18). Ciblak et al. specified that the most frequent reason in their research was that 'the vaccine is not effective', though, similarly to in our study, other reasons included that 'the vaccine will cause influenza' and 'influenza can be treated' (6). In another study by Yigitbas et al., the first three reasons for not receiving the vaccine were that the participants had not been informed about the influenza vaccine, they did not feel that they needed it and they did not believe in its efficiency (10.9%). Those researchers also observed that the provision of advice to the

elderly by physicians had an influence on vaccination (20).

In a study of elderly people living in the community in Turkey, only 3 of the 543 participants had received both the pneumococcal and influenza vaccines (14). Meanwhile, in our study, 21% of the participants had received both the pneumococcal and influenza vaccines. It is noteworthy that this rate is remarkably high compared to data from the national level. In 2021, given the increase in awareness during the COVID-19 pandemic, vaccination rates are being considered throughout the country. Therefore, it is likely that new studies are needed.

In Europe as a whole, the WHO has achieved the goal of a 75% vaccination rate in only the Netherlands and the United Kingdom; in some countries, such as Lithuania, Estonia and Bosnia-Herzegovina, rates remain below 5% (21). Generally, apart from the most frequent reason (that a physician did not recommend it), all reasons for not receiving the vaccine concern individual attitudes and behaviours. However, these attitudes and behaviours can be changed by healthcare professionals (20). In a study by Unal et al., a one-day training was provided to family physicians in Denizli, Turkey; after eight months of administering the pneumococcal vaccine to individuals 65 years of age and above, the vaccination rate reached 60% (22). Thus, adult vaccination rates could be improved by providing training to family physicians in countries that have strong, widespread family physician practices.

In the National Vaccine Workshop that was held in Ankara in 2014, it was noted that, amongst adults, there is limited knowledge of diseases that could be prevented by vaccination as well as of the vaccines themselves. Furthermore, physicians possess limited knowledge of adult vaccination and, even if they have been informed about it, have not developed the habit of immunisation themselves. The workshop concluded that social fear and doubt must be eliminated to encourage the vaccination of adults, and communication problems may also require resolution (23).



Following healthcare professionals, media (mainly television) and friends were the most important sources of information for participants in our study. In addition to knowledge and training regarding the protection that vaccines can provide against seasonal influenza and pneumococcal infections, which may occur in winter, there has been intense interest in vaccines for COVID-19 in recent efforts to mitigate the pandemic. These expectations warrant careful consideration. It is assumed that, besides the guidance of healthcare professionals, media (mainly television) and communication with friends (digital or otherwise) have considerable effects, which the results of our study reflect. There is still scarce information available about potential interactions between pneumococcal and influenza vaccines and COVID-19, though it is known that the risk of pneumococcal infection increases, the pneumococcal vaccine can prevent both primary and secondary bacterial infections, and the unnecessary use of antibiotics may seasonally affect the clinical presentation of infection by occurring concomitantly with other viral infections. While countries with pneumococcal and influenza vaccination programmes for aged and high-risk individuals have taken action to combat the spread of COVID-19, the maintenance of these programmes for aged people is recommended. Hospitalisation for respiratory tract diseases caused by pneumococcus and influenza can be prevented through vaccination, which would increase the availability of ventilatory support equipment, medicines and healthcare professionals to treat COVID-19 patients.

## CONCLUSION

Primary care physicians have the crucial role of efficiently and adequately informing the elderly to ensure their vaccination within the scope of the programme. During the COVID-19 pandemic period, vaccination of the elderly needs to continue, and education and knowledge levels amongst this population are central in facilitating this process. Media

(especially television) appear to be highly influential in addition to the guidance of healthcare professionals, especially during the pandemic, and the demand for vaccines has increased in line with the conclusions of our study. Therefore, it is imperative to deliver accurate information through the media.

With respect to the data in the study, training sessions were conducted for the physicians and the elderly. The programme, which was realised between October 2017 and February 2018, was considered the first collective adult conjugated pneumococcal vaccine practice at a nursing home in Turkey. Within this period, free conjugated pneumococcal vaccines were supplied by the provincial public health directorate, and the vaccine was administered to the elderly residents of the nursing home, who consented based on the indications. This vaccination programme exemplifies practical use of the conclusions of scientific studies to improve societal conditions, and the introduction of this programme prior to the pandemic process was significant. The growing public interest in conjugated pneumococcal vaccines in addition to influenza vaccines during the pandemic is essential to the success of this practice, as is informing physicians about measures for making adult vaccines as accessible as paediatric vaccines (e.g. by offering them at no cost). Elderly people have more knowledge about influenza vaccine than pneumococcal vaccine. Their healthcare professionals mostly inform them about vaccinations. Therefore healthcare professionals should be trained about the pneumococcal vaccination procedures in elderly.

## LIMITATIONS

Our study presents the general limitations of a questionnaire study, and the conclusions are founded on the answers from the participants. The study was carried out at a nursing home amongst individuals with high levels of education and sociocultural status in the mid-upper income group. Thus, the findings do not reflect the entire elderly population.

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Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.224  
2021; 24(2): 276-286

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Received: Mar 24, 2021  
Accepted: May 21, 2021

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#### RESEARCH

## PSYCHOMETRIC PROPERTIES OF THE TURKISH VERSION OF THE REVISED SCALE FOR CAREGIVING SELF-EFFICACY

### ABSTRACT

**Introduction:** The self-efficacy of caregivers is an important matter that merits investigation, and this requires that the concept of self-efficacy be measured with a valid, reliable instrument.

**Materials and Methods:** This research examined the psychometric properties of the Turkish version of the Revised Scale for Caregiving Self-Efficacy. A sociodemographic form and the Revised Scale for Caregiving Self-Efficacy were employed to collect data from April through December 2019. A total of 250 family caregivers were included in the study, which assessed the content validity, construct validity and reliability of the Revised Scale for Caregiving Self-Efficacy.

**Results:** All 18 items had significant item-to-total correlations ( $p < 0.05$ ). The Cronbach's alpha coefficient was 0.82 for the total scale, 0.76 for the self-efficacy in obtaining respite subscale, 0.82 for the self-efficacy in responding to disruptive patient behaviours subscale and 0.96 for the self-efficacy in controlling upsetting thoughts about caregiving subscale.

**Conclusion:** The results of this study indicate that the Revised Scale for Caregiving Self-Efficacy is a valid, reliable measurement tool and suitable to the Turkish culture.

**Keywords:** Dementia; Caregivers; Self Efficacy; Reproducibility of Results



## INTRODUCTION

The elderly population has grown significantly worldwide, accompanied by a rapid increase in the incidence of the chronic disease of dementia. According to the World Health Organization approximately 50 million people have dementia globally, and 10 million new cases are detected each year (1). A global prevalence study investigating countries and regions in the years 1990–2016 found that 754,169 individuals had dementia in Turkey, 35,355 had lost their lives to the disease and 462,429 had suffered from disabilities associated with dementia (2). There were no current data from Turkey in the Global Dementia Observatory country profiles (2017–2019) in 2020.

Dementia is a chronic, progressive syndrome that causes deterioration in cognitive function beyond what is expected from normal aging, affecting memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment (1). As dementia progresses, the care needs of people with dementia (PwD) also gradually increase. The care of the individual and the management of the disease are mostly provided by families in a home setting. The Alzheimer's Association (AA) reports that most caregivers (66%) live with the person with dementia in the community (3).

It is well known that the care needs of dementia are complex, wide-ranging and extremely challenging (3-5). In caregiving, caregivers provide material, emotional, social and financial support to the person with dementia (6). Due to the challenges associated with caregiving, caregivers experience problems including the burden of care, emotional stress, depression, anxiety, negative family relationships, an increased risk of chronic diseases (such as hypertension and diabetes), sleep problems, smoking, dementia, job losses, financial difficulties and poor quality of life (6-9). The negative consequences of caregiving affect caregivers' own self-care behaviours and self-efficacy (10, 11).

The profiles of caregivers also affect their self-

care and self-efficacy. AA reports that approximately two-thirds of dementia caregivers are women. About 30% are aged 65 or older, and over 60% are married, living with a partner or in a long-term relationship. Over half provide assistance to a parent or in-law with dementia. Among primary caregivers of PwD (i.e., those who indicate having the greatest responsibility for helping their relatives), over half care for parents. Approximately one-quarter of dementia caregivers are 'sandwich generation' caregivers, meaning that they care not only for an aging parent but also for a child (3). These profile characteristics complicate caregivers' daily activities, causing them to neglect their own care and experience difficulties in managing the disease. Studies in the literature have identified the factors affecting the self-efficacy of family caregivers (4, 5, 12), confirming that their self-efficacy is a vital concern that merits evaluation to empower caregivers and reduce the negative consequences of care.

Self-efficacy is defined as people's desirable performance of their own activities and their management of situations encountered in daily life (13-15). The concept of self-efficacy, an element of Bandura's social cognitive theory, is frequently cited in studies (13-15). When caregivers face problems, their self-efficacy decreases, and negative thoughts increase. As this concept gains importance, studies of family caregivers' self-efficacy have proliferated (16, 17), and studies offering valid, reliable measurement tools to evaluate this concept are needed. The Revised Scale for Caregiving Self-Efficacy (RSCE), developed by Steffen et al. in 2002, is one scale used to examine the self-efficacy of caregivers of PwD (18). In 2018, Steffen et al. undertook a cross-national review and found that validity and reliability studies of this scale had been conducted in languages including Arabic, Chinese, English, French, Italian and Spanish) (17), but no psychometric analysis of the scale has been conducted in Turkish society. Accordingly, this research examined the psychometric properties of the Turkish version of the RSCE.

## MATERIALS AND METHODS

### Design and Sample

A methodological, descriptive and correlational study design was used. The sample size suggested for studies of scale validity and reliability is 5 times the number of items in the scale (19), and in this case an estimated sample size of 90–180 represented between 5 and 10 times the 18 items in the scale. In April–December 2019, 250 family caregivers of PwD were recruited from a neurology and geriatrics outpatient clinic by non-probability convenience sampling. Random sampling was used to select the participants, who voluntarily agreed to take part. In the collection of research data, 250 caregivers met the inclusion criteria and were included in the analyses. The inclusion criteria were as follows: primarily responsible for a PwD; responsible for providing care for at least 1 year; providing  $\geq 5$  hours of care per day; literate; can speak Turkish; willing to participate.

### Measures

#### *Sociodemographic Form*

The form was developed by the researchers to collect data on the sociodemographic characteristics of caregivers and patients. The form composed of two parts. The first part contained questions regarding the caregivers' age, gender, educational status, relationship with the patient, working status, economic status, and the length of time of care. The second part contained questions about the PwDs' age, gender, education status, length of illness, the type and stage of dementia, and their capability of performing daily life activities.

#### *The Revised Scale for Caregiving Self-Efficacy*

The scale, originally called the Self-Efficacy Scale for Care, was developed in 1999 by Zeiss et al. to evaluate caregivers' self-efficacy and problem-solving self-efficacy (20). In 2002, the RSCE was revised by Steffen et al. to include 18 items measuring the self-efficacy of those caring for PwD. Validity and

reliability analyses were conducted (18). All the scale's questions aim to evaluate how effectively the caregiver achieves a particular goal. The 18 items are each scored from 0 through 100 points, with high scores indicating high self-efficacy. The scoring is interpreted as follows: 0% confidence indicates that the caregiver has low self-efficacy for an item, 50% confidence indicates moderate self-efficacy and 100% confidence indicates high self-efficacy (18).

The 18-item scale contains three revised subscales: self-efficacy in obtaining respite (first subscale) (5 items), self-efficacy in responding to disruptive patient behaviours (second subscale) (8 items) and self-efficacy in controlling upsetting thoughts about caregiving (third subscale) (5 items). The Cronbach's alphas of the scale were 0.85 for the self-efficacy in obtaining respite subscale, 0.82 for the self-efficacy in responding to disruptive patient behaviour subscale and 0.85 for the self-efficacy in controlling upsetting thoughts about caregiving subscale (18). The current study tested the revised version of the RSCE. A researcher read the scale to the caregivers and recorded their answers. The validated scale questions in Turkish are provided in Appendix 1.

### Psychometric Analyses

The Statistical Package for the Social Sciences version 21.0 (SPSS Inc, Chicago, IL, USA) and AMOS 24.0 were used for statistical evaluation of the data.

### Validity Analysis

#### *Language and concept validity*

For language validity, the scale was independently translated from English to Turkish by two experts (an English language specialist and a subject matter expert whose native language is Turkish). Thereafter, the researchers collaborated to develop the Turkish version of the scale by determining the most appropriate translation for each item. The back translation of the scale from Turkish to English was done by a language expert who had



not read the English version before and who had a good understanding of both languages and cultures. The translated English form and the original form were compared by the researchers. No items were changed.

### **Content validity**

Content validity was confirmed by seven experts in dementia care (three psychiatric nurses, three internal medicine nurses and one psychologist), who were asked to evaluate the scale in terms of language and content. Their opinions were assessed using the Polit-Beck content validity index. The scale-level content validity index (S-CVI) and item-level content validity index (I-CVI) were calculated. The experts rated the items as 1 ('not appropriate'), 2 ('should be made more appropriate'), 3 ('appropriate but needs minor changes') or 4 ('highly appropriate'). The number of experts who score three or four is divided by the total number of experts to calculate the CVI. A CVI score above 80% indicates excellent agreement (21).

### **Pilot study**

To test the clarity and intelligibility of the items, the scale was given to a small representative group of the sample. In this pilot study, a sample of 25 family caregivers was selected in light of the number of items and the intended sample size. The pre-test sample data were not included in the study (19).

### **Construct validity**

Confirmatory factor analysis (CFA) determined the construct validity. In the CFA, the authors analysed Pearson's  $\chi^2$ , degree of freedom, root mean square error of approximation (RMSEA), goodness-of-fit index (GFI), comparative fit index (CFI) and normal fit index as the GFIs.

### **Reliability Analysis**

Reliability was determined using Cronbach's alpha, item-total correlations, test-retest, ceiling and floor effects and Hotelling's T-squared test for response bias (22).

### **Ethical Consideration**

Written permission of RSCE was obtained via e-mail from Ann M. Steffen, who revised the scale in 2002, to perform the adaptation. Written permission was received from the Neurology and Geriatrics Department of X University Hospital and Ethics Committee of X University (approval number: 2019/01-04). Individuals were informed about the aim and design of the study, and their oral and written consents were obtained.

### **RESULTS**

Family caregivers were mostly female (70%), with age at the range of 26–78 years old with a mean of 54.29 years (standard deviation: 8.64). Of the caregivers, 54% were children of PwD.

### **Validity**

#### **Content and language validity**

The opinions of seven experts were sought for language and concept validity. For all the items, the concordance of the experts' opinions was 0.94 for the whole scale.

#### **Confirmatory factor analysis**

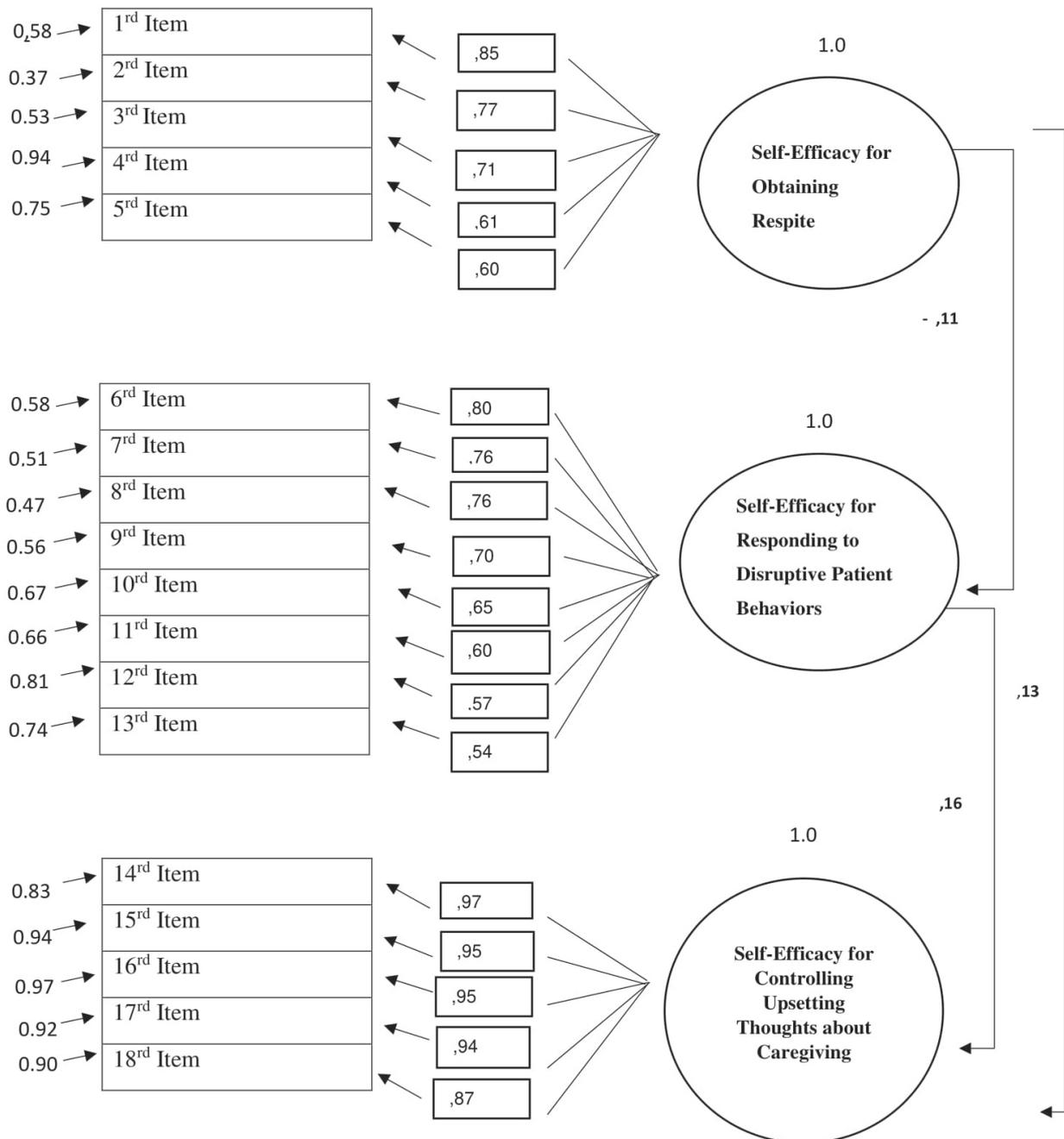
The CFA identified the factor loadings of all the items in the scale. The factor loads in the first subscale ranged from 0.37 to 0.94, those in the second subscale from 0.47 to 0.81 and those in the third subscale from 0.83 to 0.97. The model fit indicators were determined as: CFI = 0.93, incremental fit index (IFI) = 0.93, GFI = 0.92, root mean square residual (RMR) <0.01, chi-square/degree of freedom ( $\chi^2/df$ ) = 2.90 ( $p < 0.001$ ) and 90% confidence interval of RMSEA = 0.07 (Figure 1, Table 1).

### **Reliability**

#### **Test-retest reliability**

Before the data collection, the scale was provided to 25 randomly selected family caregivers, and a 2- to 6-week period passed between the two

**Figure 1.** Confirmatory Factor Analysis Results of the Revised Scale for Caregiving Self Efficacy



Chi-Square: 2.90 p-value: 0.01, RMSEA: 0.07 GFI:0.92, CFI:0.93, IFI:0.93



**Table 1.** Model fit indices of confirmatory factor analysis of the RSCE

Model fit indices of CFA	Reference values <sup>a</sup>	Values in the current study
$\chi^2_{/df}$ (Chi-Square/Degree of Freedom)	<5	2.90
GFI (Goodness of Fit Index)	>0.90	0.92
IFI (Incremental Fit Index)	>0.90	0.93
CFI (Comparative Fit Index)	>0.90	0.93
RMSEA (Root Mean Square Error of Approximation)	<0.08	0.07
RMR (Root Mean Square Residual)	<0.08	<0.01

<sup>a</sup> Peñacobá C, Losada A, López J, Márquez-González M. Confirmatory factor analysis of the Revised Scale for Caregiving Self-Efficacy in a sample of dementia caregivers. *International Psychogeriatrics* 2008;20: 1291–1293. (PMID: 18620625).

data collections. A statistically significant positive relationship was observed between the test-retest scores of the scale's three subscales. The first subscale had an  $r = 0.99$  and a  $p < 0.001$ , the second had an  $r = 0.96$  and a  $p < 0.001$  and the third had an  $r = 0.98$  and a  $p < 0.001$ .

### Internal consistency analysis

The total Cronbach's alpha internal consistency reliability coefficient was 0.82, and the Cronbach's alpha coefficient was 0.76 for the first subscale, 0.82 for the second and 0.96 for the third. The item-total correlations were statistically significant ( $p < 0.05$ ) and varied from 0.46 to 0.68 for the first subscale, 0.42 to 0.67 for the second and 0.81 to 0.95 for the third.

### Floor and ceiling effect analysis

When the data were evaluated, the floor and ceiling effect of the scale was less than 15%. Response bias was evaluated to test whether the participants answered in line with their own opinions or with the expectations of the community or researcher while completing the scale. The Hotelling T2 value was 29.823 and was significant ( $p < 0.001$ ).

## DISCUSSION

### Validity

In the current study, a Turkish version of the RSCE was prepared, and the language validity criterion was fulfilled (the first step in scale adaptation studies). The CFA yielded factor loads from 0.37 to 0.94 in the first subscale and 0.47–0.81 and 0.83–0.97 in the second and third subscales, respectively. The CFA determined that the factor loads of all the subscales were above 0.30. The Turkish version of the scale is structurally similar to the original, so the structural validity of the Turkish version was confirmed. The results of the CFA in this study support the construct validity of the scale, confirming its validity. The present study also supports two CFA studies (23, 24) that confirmed the three-factor structure identified in the original development article.

An RMSEA value of 0.08 or less is considered an adequate fit, with RMSEA = 0 indicating a perfect fit. When the model fit indicators were examined in the current study, the RMSEA value of the scale was found to be 0.07, indicating that the model ad-

equately agrees with the sample. When the GFI is  $>0.90$ , the factor model well explains the original variability, and the model is usable, with GFI values close to 1 indicating a good fit. In the current study, the GFI value was above 0.92, indicating that our scale has good fit-index values. IFI and CFI values of  $>0.90$  indicate an acceptable fit, and those values in this study were found to be 0.93.

A high correlation between the observed variables causes the chi-square value to increase. The ratio of the degrees of freedom to the chi-square, an important criterion of the chi-square test, can be used as a fit criterion. A ratio of less than 5 is considered to indicate a good fit (25). In this study, the  $\chi^2/df$  ratio was 2.90, and the RMR value, an absolute index, was 0.01, indicating strong fitness. The RSCE confirmed its construct validity by providing five fit indexes, and these results agree with those of other language adaptations (23, 24). The CFA results of the Chinese version of the scale were  $\chi^2 = 29.09$ ,  $df = 23$  and  $RMSEA = 0.05$  (23). The CFA of the Spanish version of the scale supported the three-factor model ( $\chi^2 = 120.86$ ,  $df = 87$ ,  $GFI = 0.93$ ,  $IFI = 0.97$ ,  $CFI = 0.97$ ,  $RMSEA = 0.04$ ; the factor loadings ranged from 0.45 to 0.94) (24).

### Reliability

The test-retest reliability analysis of the RSCE was evaluated by Pearson correlation analysis, which yielded a correlation coefficient of 0.70–1.00. This value is sufficient to confirm a high reliability. The test-retest reliability analysis results of this study are compatible with those of the original scale, which were above 0.70 for all the subscales (18).

A statistically significant positive relationship was observed between the test-retest scores of the scale's three subscales ( $r = 0.99$  and  $p < 0.001$  for first subscale,  $r = 0.96$  and  $p < 0.001$  for the second and  $r = 0.98$  and  $p < 0.001$  for third). A T-test was conducted on the dependent groups to determine whether a difference exists between the mean scores obtained after repeated measurements of the scale. No statistically significant difference was observed between the mean scores ( $p > 0.05$ ).

To confirm a scale's reliability, all its subscales should be used to measure the same property. Therefore, the reliability coefficient of the scale should be calculated. Cronbach's alpha values between 0.60 and 0.80 indicate that a scale is fairly reliable, and values between 0.80 and 1.00 indicate that a scale is highly reliable (22). The first subscale's Cronbach's alpha was  $a = 0.76$ , the second's  $a = 0.82$  and the third's  $a = 0.96$ ; the whole-scale alpha was  $a = 0.82$ . These results indicate that the full scale and its subscales are highly reliable and have a strong internal consistency. Furthermore, in the original study, the Cronbach's alphas were above 0.80 (18). Our results agree with those of the English as well as those of the Chinese version (in which the Cronbach's alphas of the first, second and third subscales were 0.92, 0.86 and 0.75, respectively) (23).

Regarding item reliability, an item-total analysis was conducted to confirm that the items in the subscales measure the concepts they are intended to measure. An item-total analysis score should be greater than 0.25 for each item (22). The item-total analysis yielded item-total scores above 0.40 for all the subscales, indicating that all the scale items had a high correlation with the total score and with the total scores of the subscales. The item reliability of the Turkish version of the scale, with factor loadings of 0.42–0.95, agrees with those of the English (factor loadings of 0.30–0.94) and Spanish (factor loadings of 0.45–0.94) versions of the scale (24).

On the basis of the total score, the lowest total score obtainable from a scale indicates the floor effect, and the highest total score indicates the ceiling effect. The floor and ceiling effects should not exceed 15% (22). The analysis demonstrated the homogeneity of the scale. Hotelling's T-squared test was used to determine response bias. This test also indicates whether the average of the whole is normally distributed. The test's score is expected to be statistically significant to avoid response bias ( $p < 0.05$ ) (22). In this test, the Hotelling's  $T^2$  of the RSCE was 29.823 and determined as  $p < 0.001$ , confirming



the absence of reaction bias in the scale. The original study was evaluated as lacking information on the floor and ceiling effects and on responsiveness measurement domains.

## CONCLUSION

The results of this study confirm that the RSCE is a valid, reliable measurement tool to assess the self-efficacy of family caregivers of PwD in the Turk-

ish culture. Given the importance of family caregiver interventions in the global community, the use of this scale should benefit family caregivers.

## Acknowledgements

The authors thank the caregivers of PwD who participated in this study.

## Declaration of Interest Statement

No conflict of interest has been declared by the authors.

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## Appendix 1. Revize Edilmiş Bakıma Yönelik Öz Yeterlilik Ölçeği

### Appendix 1 Revize Edilmiş Bakıma Yönelik Öz Yeterlilik Ölçeği

Bu ölçek, bakım veren bireyin, bakım verme sürecinde, kendi aktivitelerini nasıl devam ettirdiğini ve bakıma yönelik tepkilerini değerlendirmektedir. Lütfen size okuyacağım soruları dikkatli bir şekilde düşünün ve gerçekten yapabildiğinizi düşündüğünüz şey hakkında elinizden geldiği kadar dürüst ve samimi olun. Bakım veren olarak yaşayabileceğiniz olay ve düşünceleri içeren maddeler okuyacağım. Lütfen her bir maddeyi düşünün, bunları ne kadar yapabildiğinizi ve kendinize ne kadar güvendiğinizi söyleyin. Her bir maddeyi 0'dan 100'e kadar derecelendirin, burada % 0 güven, okuyacağım maddeleri hiç yapamayacağımız, % 50 güven, okuyacağım maddeleri orta derece yapabileceğiniz, %100 güven ise, okuyacağım maddeleri kesinlikle yapabileceğiniz anlamına gelmektedir. Size okuyacağım maddelere 0 ile 100 arasında herhangi bir derecelendirme yapabilirsiniz (10, 20, 30..vb). Örneğin %20 derecelendirme okuyacağım maddeyi tamamen olmasa da düşük düzeyde yapabileceğiniz anlamına gelir.

0	10	20	30	40	50	60	70	80	90	100
Hiç				Orta derecede						Kesinlikle
yapamam				yapabilirim						yapabilirim

Lütfen derecelendirmelerinizi geçmiş zaman göre değil şu an içinde bulunduğunuz süreci değerlendirerek yapınız. Sorularınız var mı? Anlaşılır olduğundan emin olmak için hızlı bir uygulama derecelendirmesi yapacağız. Şu anda farklı ağırlıktaki nesnelere kaldırmamız istense, bunu yapabileceğinizden ne kadar emin olabilirsiniz:

#### FİZİKSEL DAYANIKLIK

#### GÜVEN (0-100)

1. 10 kilo ağırlığındaki bir nesneyi kaldırın \_\_\_\_\_
2. 20 kilo ağırlığındaki bir nesneyi kaldırın \_\_\_\_\_
3. 50 kilo ağırlığındaki bir nesneyi kaldırın \_\_\_\_\_
4. 100 kilo ağırlığındaki bir nesneyi kaldırın \_\_\_\_\_

Lütfen okuyacağım maddeleri yaparken kendinizden ne kadar emin olduğunuzu söyleyin. ("Durumunuz için uygun olmayan maddeleri lütfen bildiriniz").

#### KENDİNE ZAMAN, ÖZ YETERLİLİĞİ

- \_\_\_ 1. Doktora gitmeniz gerektiğinde bir arkadaşınızdan/aile üyenizden bir gün için hastanız ile kalmasını isteyebileceğinizden ne kadar eminsiniz?
- \_\_\_ 2. Yapılacak işleriniz olduğunda bir arkadaşınızdan/aile üyenizden bir gün için hastanız ile kalmasını isteyebileceğinizden ne kadar eminsiniz?
- \_\_\_ 3. Bir arkadaşınızdan/aile üyenizden sizin işlerinizi yapmasını isteyebileceğinizden ne kadar eminsiniz?
- \_\_\_ 4. Yalnız kalmaya ihtiyaç duyduğunuzda bir arkadaşınızdan/aile üyenizden bir gün için hastanız ile kalmasını isteyebileceğinizden ne kadar eminsiniz?
- \_\_\_ 5. Kendinize zaman ayırmanız gerektiğinde bir arkadaşınızdan/aile üyenizden bir hafta için hastanız ile kalmasını isteyebileceğinizden ne kadar eminsiniz?

#### RAHATSIZ EDİCİ HASTA DAVRANIŞLARINA KARŞI YANIT

#### ÖZ YETERLİLİĞİ

- \_\_\_ 6. Hastanız günlük rutinleri unuttuğunda ve siz öğle yemeğini yedirdikten hemen sonra öğle yemeğinin ne zaman hazır olacağını sorduğunda, ona sesinizi yükseltmeden cevap verebileceğinizden ne kadar eminsiniz?
- \_\_\_ 7. Hastanız aynı soruyu defalarca tekrarladığı için sınırlendiğinizde kendinizi sakinleştiren şeyleri söyleyebileceğinizden ne kadar eminsiniz?

**Appendix 1 (continued)**

\_\_\_8. Hastanız, sizin kendisine davranış şeklinizden dolayı şikayet ettiğinde, onunla tartışmadan cevap verebileceğinizden ne kadar eminsiniz? (ör. kendisini rahatlatmak veya oyalamak gibi?)

\_\_\_9. Hastanız, öğle yemeğinin ne zaman hazır olacağını, öğle yemeğinden sonraki bir saat içinde 4 kez sorduğunda, kendisine sesinizi yükseltmeden cevap verebileceğinizden ne kadar eminsiniz?

\_\_\_10. Akşam yemeğini hazırlarken hastanız işinizi dördüncü kez yarıda bıraktığında, sesinizi yükseltmeden cevap verebileceğinizden ne kadar eminsiniz?

\_\_\_11. Hastanız oturma odasını dağıttığında bu dağınıklığı sessizce temizleyebileceğinizden ve yarıda bıraktığınız işe tekrar geri dönebileceğinizden ne kadar eminsiniz?

\_\_\_12. Hastanız evde sizi takip ediyorsa, kendinizi rahat hissedebileceğinizden ve işlerinize devam edebileceğinizden ne kadar eminsiniz?

\_\_\_13. Hastanız evde sizi takip ediyorsa, en azından kısa bir süre bunu yapmasını engelleyebilecek bir yol bulabileceğinizden ne kadar eminsiniz?

"Tüm bakım verenlerin bazen durumlarıyla ilgili olumsuz düşünceleri vardır. Bazı düşünceler kısa süreli akılda kalır. Diğer zamanlarda ise tıpkı saçma bir melodinin akıldan çıkarılmasının zor olması gibi düşüncelerin de zihinden çıkarılması zor olabilir. Aşağıdaki düşüncelerden herhangi birinden ne kadar iyi kurtulabildiğinizi bilmek istiyoruz. Lütfen aynı derecelendirmeyi kullanın. Düşüncelerin ne sıklıkta ortaya çıktığı konusunda endişe etmeyin. Aklınıza geldiğinde düşüncelerden kurtulabilme veya düşünceleri aklınızdan çıkarabilme konusunda kendinize olan güveninizi derecelendirmenizi istiyoruz." (Uygulayıcı: Bakıcılar, maddelerden birindeki düşüncelere kesinlikle hiç sahip olmadıklarını belirttiğinde, güven derecelendirmesi için çizgi üzerine "uygun değil" yazın.)

**BAKIM HAKKINDAKİ ÜZÜCÜ DÜŞÜNCELERİN KONTROLÜ ÖZ YETERLİLİĞİ**

\_\_\_14. Hastanızın bakımının hoş olmayan yönleri hakkındaki düşüncelerinizi kontrol edebileceğinizden ne kadar eminsiniz?

\_\_\_15. Bu duruma katlanmak (hastanızın bakımı) zorunda olmanızın ne kadar adaletsiz olduğu düşüncesini kontrol edebildiğinizden ne kadar eminsiniz?

\_\_\_16. Hastanızın hastalığından önce ne kadar iyi bir hayat geçirdiğinizi ve daha sonra ne kadar kaybınız olduğu düşüncesini kontrol edebildiğinizden ne kadar eminsiniz?

\_\_\_17. Hastanız nedeniyle neler kaybettiğinize ya da nelerden vazgeçtiğinize ilişkin düşüncelerinizi kontrol edebildiğinizden ne kadar eminsiniz?

\_\_\_18. Hastanız ile ilgili ileride ortaya çıkabilecek sorunlar hakkındaki endişelerinizi kontrol edebileceğinizden ne kadar eminsiniz?



Turkish Journal of Geriatrics  
DOI: 10.31086/tjgeri.2021.225  
2021; 24(2): 287-295

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Received: Dec 17, 2020  
Accepted: Apr 24, 2021

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## RESEARCH

# ASSESSMENT OF THE BURDEN AMONG FAMILY CAREGIVERS OF PATIENTS WITH ALZHEIMER'S DISEASE

## ABSTRACT

**Introduction:** The objective of this study was to examine the caregiving burden and identify the predictors of burden among family caregivers of patients with Alzheimer's disease.

**Materials and Method:** The sample consisted of 154 family caregivers of community-dwelling Alzheimer patients. Zarit Burden Inventory was used to measure caregiver burden. Depending on the total score, the level of burden is classified as absent to little burden (0 to  $\leq 20$ ), mild to moderate burden (21 to 40), moderate to severe burden (41 to 60), and very severe burden ( $\geq 61$ ). The cutoff point for the clinical depression was taken as 24.

**Results:** The caregivers were mainly women (78.6%), the patient's daughters (56.5%), living with the patient (79.1%), and they were not receiving any support from other family members for patient care (54.5%). The average time spent on caregiving tasks was 4.8 hours a day. The mean Zarit Burden Inventory score was 22.4. The burden scores of 39.6% of the caregivers were significant for clinical depression. The most pronounced predictors of higher burden were the absence of someone supporting the care, social isolation, the length of time spent daily for caregiving, and the patient's age, comorbidities, and functional impairment in daily activities. Receiving psychological counselling was a protective factor against the development of burden.

**Conclusion:** The results suggest that burden is high among the caregivers of patients with Alzheimer's disease. Strategies should be developed to support family members in countries such as Turkey, where the care is undertaken by informal caregivers.

**Key Words:** Alzheimer Disease; Cost of Illness; Family Caregivers; Patient Care; Long-term Care

## INTRODUCTION

There are approximately 50 million people with dementia in the world today, with around 10 million new cases being diagnosed every year. The number of people with dementia is predicted to exceed 131 million by 2050 (1). Although it is not a natural part of the aging process, dementia primarily affects older people and about 7% of the individuals over the age of 65 have dementia. The most common type of dementia is Alzheimer's disease (AD), which accounts for 60 to 70% of the cases (2).

The care needs of people with dementia are relatively complex (3). It has been shown that family members generally care for individuals with dementia for 10 or more years prior to either the institutionalization or the death of the patient (1, 3). Family caregivers are obliged to meet all of the physical, psychological, and social care needs of these patients. Caregivers are compelled to adjust their lives according to the patients' needs, with the resulting shortage of time for their own lives, along with increased social isolation and financial difficulties, leading to caregiving burden (CB) (3).

Currently, more than 600,000 people suffer from dementia in Turkey and 400,000 of them have AD (4). Individuals with AD frequently live with their family, and institutionalization is extremely low (4). The lifespan in Turkey has increased, and the percentage of people with ages >65 years increased from 8% in 2014 to 9.1% in 2019. The percentage of the elderly population is projected to increase to 10.2% in 2023, to 12.9% in 2030, and to 16.3% in 2040. The number of elderly people who died from AD increased from 10,236 in 2014 (3.9%) to 13,767 (4.6%) in 2018 (5).

In examining these figures, it can be predicted that the number of cases of AD will increase in parallel with the increase in the elderly population. Consequently, in the future, we will need more family caregivers and more people will have CB as well. To our knowledge, there have only been two studies on CB among the family caregivers of patients with

dementia in Turkey (6-7). More research with a larger sample is still needed. Moreover, little is known about some of the independent predictors of CB. Considering the dramatically increasing number of patients with Alzheimer in Turkey, assessing the family's CB and independent predictors of CB will guide us in developing, implementing, and assessment strategies to support family members. In this study, we aimed to examine the CB and the affecting factors among the family members of patients with AD in Turkey.

### Study Questions

- What is the level of CB of family members caring for Alzheimer's patients?
- What are the factors affecting CB in family members caring for Alzheimer's patients?

## MATERIALS AND METHOD

### Research design

A cross-sectional research design was used in this study.

### Participants and setting

The study was conducted between May 2 and November 29, 2019 in Istanbul, Turkey in the day nursing home of the Turkish Alzheimer Association. Serving since 2011, the day nursing home provides Alzheimer's patients and family caregivers with free education, social support and psychological support on various subjects in cooperation with specialist physicians, nurses, social workers, psychologists and volunteers. The family caregivers who came to the day nursing home between the study dates and met the inclusion criteria were explained the purpose of the study and invited to take part. The caregivers were included in the study if they were 18 years of age or over, had been performing the care of the patient for at least 6 months, and agreed to participate in the study. The study participants included 154 primary informal family caregivers of community-dwelling patients with AD. Only one



caregiver per patient was included in the study.

### Measures

The data were collected using the Information Sheet and Zarit Burden Interview (ZBI).

The Information Sheet was prepared by the researchers using the relevant literature and includes questions for caregivers and patients in two parts. The first part includes questions about socio-demographic variables such as age, gender, and marital status of the caregivers, as well as health status, providing care and difficulties in providing care. The second part includes questions about the patients' age, gender, years since diagnosis, health status, and ability to perform daily life activities (DLAs) including walking and moving around, eating and drinking, toileting, dressing, and body hygiene as well as presence of any speaking and sleep problems.

ZBI was used to measure caregiver burden. It includes 22 items scored over a 5-point Likert-type scale ranging from 0, "never" to 4, "almost always". Responses to the items in the ZBI are added together to calculate a total burden score ranging from 0 to 88. Higher scores indicate greater burden. Depending on the total score, the level of burden is classified as absent to little burden (0 to  $\leq 20$ ), mild to moderate burden (21 to 40), moderate to severe burden (41 to 60), and very severe burden ( $\geq 61$ ). The cutoff point for the ZBI was reported as 24, meaning that individuals with more than 24 points are at risk for clinical depression (8). The internal consistency for the original ZBI was 0.89 (9). In the current study, Cronbach's alpha value of the ZBI was 0.95.

### Data collection

Data collection tools were distributed to family caregivers who came to the day nursing home for various activities and they were asked to complete the forms by themselves. The ability of the patient to perform daily life activities (DLAs) was also evaluated by family caregivers. The patients were classified as *independent* if they were able to perform

DLAs with no assistance, *semi-dependent* if they were able to DLAs with assistance or supervision, and *dependent* if they were entirely dependent on others to meet their basic needs. The family caregivers answered two questions, i.e. "Does your patient has speech problem?" and "does your patient has sleep problem" as yes or no. Each participant took about 20 minutes to fill out the data collection tools.

Before collecting the data, ethical approval was obtained from the University Ethics Committee in accordance with the Helsinki Declaration (2019/27). Written informed consent was obtained from each participant.

### Statistical analyses

Normality tests (histogram, skewness, kurtosis, Shapiro-Wilk) were performed to determine whether the ZBI mean score was suitable for normal distribution. Pearson's correlation coefficients were calculated to examine the relationships between two continuous variables. Independent unpaired t-tests were used for two-group comparisons of continuous variables. The one-way ANOVA was used to compare the scores for three-group comparisons of the continuous variables. Homogeneity was examined using the Levene test. Data was presented as numbers and mean  $\pm$  standard deviations (SD), where appropriate. The effects of the independent variables on the CB were examined using linear regression analysis.

The significance level was taken as  $P < 0.05$ . Data analyses were conducted using SPSS, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA).

## RESULTS

### The characteristics of the caregivers

The descriptive characteristics of the family caregivers are provided in Table 1. The majority of the caregivers were women (78.6%). They had a mean age of 45.1 years; 69.5% were married, 66.2% had children, 59.7% were unemployed, and 46.1% were

**Table 1.** Characteristics of the caregivers (N=154)

Characteristics	Number (%)
Gender (Female)	121 (78.6)
Age (Mean±SD years) (Min-max)	45.1±13.30 (Min-max: 23-77)
Marital status (Married)	107 (69.5)
Having children (Yes)	102 (66.2)
Education Primary school Secondary school / High school University	37 (24.0) 46 (29.9) 71 (46.1)
Employment (unemployed)	92 (59.7)
Financial status Poor / Moderate	36 (23.4) / 118 (76.6)
Relationship to the patient Daughter / Spouse Daughter in law / Second degree relatives	87 (56.5) / 11 (7.1) 34 (22.1) / 22 (14.3)
Living with patient (Yes)	122 (79.1)
Length of time spent on caregiving tasks during the day (Mean±SD) (Min-max)	4.83±2.2 (Min-max: 1-11)
Presence of someone else to help patient care (No)	84 (54.5)
Having a chronic disease (Yes)	61 (39.6)
Problems related to caregiving reported by caregivers	
Physical and/or psychological health problems (Yes)	132 (64.7)
Feeling exhausted (Yes)	76 (49.4)
Economic burden Always / Sometimes / Never	17 (11.0) / 86 (55.8) / 51 (33.1)
Negative impact on social life (being unable to spend time in personal social life etc.) Always / Sometimes / Never	39 (25.3) / 60 (39.0) / 55 (35.7)
Negative impact on family relationship Always / Sometimes / Never	59 (38.3) / 53 (34.4) / 42 (27.3)
Feeling insufficient in caregiving tasks Always / Sometimes / Never	27 (17.5) / 78 (50.6) / 49 (31.8)
Getting psychological support related to caregiving (Yes)	41 (26.6)
Attending an education programme on patient care with AD (Yes)	122 (79.2)



university graduates. Most of them described their financial status as moderate (76.6%). The majority of the caregivers (56.5%) were the daughters of the patient and they lived with them (79.1%), and 54.5% did not receive any support from other family members for patient care. The average time spent on caregiving tasks was 4.8 hours a day.

A significant proportion of the participants stated that providing care caused some physical and mental problems (64.7%), tiredness and exhaustion (49.4%), and economic burden (always, 25.3%; sometimes, 39%). In addition, 39.6% had a chronic disease. The caregivers also stated that providing care affected both their social life (always, 25.3%; sometimes, 39%) and their family relationships negatively (always, 38.3%; sometimes, 34.4%). Some caregivers stated that they felt inadequate in caregiving tasks (always, 17.5%; sometimes, 50.6%); 26.6% of them received psychological support to

solve problems related to caregiving, and most of them (79.2%) attended an education program on the care of a patient with AD.

### The characteristics of the patients

The characteristics of the patients are shown in Table 2. The mean age of the patients was 76 years, 50.6% were male, the mean time since the diagnosis of AD was 4.8 years, and 92.2% of the patients had a comorbidity. When the ability to perform daily life activities was examined, the percentage of the patients who could walk/move around, eat and drink, manage toilet needs, dress and maintain body hygiene independently was found to be 53.9, 55.2, 53.9, 41.6, and 37%, respectively. The remaining patients were fully- or semi-dependent in varying degrees on others in performing these activities. Approximately 4 (39%) of 10 patients had speaking difficulties, and 7 (71.4%) had sleep problems.

**Table 2.** Characteristics of the patients (N=154)

Characteristics	Number (%)
Gender (Male)	78 (50.6)
Age (Mean±SD years) (Min-max)	75.92±9.50 (Min-max: 55-91)
Time since diagnosis (Mean±SD years) (Min-max)	4.81±2.3 (Min-max: 1-15)
Having a chronic disease (Yes)	142 (92.2)
Ability to perform daily life activities	
Walking / moving around Independent / Semi-dependent / Dependent	83 (53.9) / 40 (26.0) / 31 (20.1)
Eating/drinking Independent / Semi-dependent / Dependent	85 (55.2) / 52 (33.8) / 17 (11.0)
Toileting Independent / Semi-dependent / Dependent	83 (53.9) / 40 (26.0) / 31 (20.1)
Dressing Independent / Semi-dependent / Dependent	64 (41.6) / 60 (39.0) / 30 (19.5)
Body hygiene Independent / Semi-dependent / Dependent	57 (37.0) / 38 (24.7) / 59 (38.3)
Speaking problems (Yes)	60 (39.0)
Sleep problems (Yes)	110 (71.4)

### Caregiving burden and related factors

The mean ZBI score was 22.4, and 27.3% of the caregivers reported mild to moderate burden (ZBI 21–40), 18.8% reported moderate to severe burden (ZBI 41–60), and 53.9% reported absent to little burden (ZBI ≤ 20). According to the cutoff point, 39.6% of the caregivers had CB scores that were clinically significant.

### Factors affecting the caregiving burden

In the initial analysis, it was determined that some of the variables related to the caregiver and the patient affected CB.

These variables were examined using a multiple regression analysis. The results of this analysis are presented in Table 3. As seen in the table, the effect of the independent variables included in the analysis on the CB was determined to be 81.3%. According to the results of the *F*-test, the linear

relationship between the CB and the set of independent variables belonging to the caregivers and the patients was found to be statistically significant ( $F = 62.33, P < 0.001$ ). When the partial regression coefficients (*b*) determining the effect of each independent variable were examined, it was seen that the contribution of all of the independent variables to the change in the CB mean score was statistically significant, except for living with the patient.

### DISCUSSION

Studies have shown that a significant number of factors affect CB. In some studies, the functional impairment in daily living activities was reported to pose a higher risk for CB (10–14). In others, being a woman, being a partner, not receiving support from family members, and lack of knowledge on dementia were predictors of CB. In comparison, receiving

**Table 3.** Results of regression analysis (N=154)

	ZBI			
	B	Beta	t	P
Caregivers' characteristics				
Living with the patient	-1.180	-0.031	0.73	0.468
Absence of someone else supporting care	-4.857	-0.159	4.12	0.000***
Negative impact of caregiving on social life	-3.472	-0.181	4.063	0.000***
Receiving psychological counselling related to caregiving	6.373	0.185	4.420	0.000***
Length of the time spent on caregiving tasks during the day	-3.950	-0.576	12.25	0.000***
Patients' characteristics				
Age	-0.154	-0.096	-2.546	0.012*
Comorbidity	-7.844	-0.138	3.146	0.002**
Walking / moving around	-2.590	-0.145	3.074	0.003**
Toileting	-2.999	-0.168	3.549	0.001**
Body hygiene	-3.768	-0.192	-3.664	0.000***
R=0.902, R <sup>2</sup> = 0.813, F=62.33, P=0.000***				

\*P<0.05; \*\*P<0.01; \*\*\*P<0.001



support from informal sources, such as friends and neighbors, and having adequate knowledge regarding dementia were protective factors (15–17).

We found that approximately 40% of the caregivers perceived significant CB at the clinical level. Explaining 81.3% of the total variance, the most important predictors of CB were the absence of someone else supporting the care, limitations on social life, receiving no psychological counselling, the length of time spent daily for caregiving, caring for a relatively younger patient, the patient's comorbidities, and the patient's functional impairment in daily activities—including walking/-moving around, toileting, and body hygiene. These findings indicate that the CB shows both the influence of some variables and the cumulative effect of caregiving work on the family member.

In the current study, patients' dependence or semi-dependence in walking and moving around, toileting, and body hygiene activities were important predictors of CB. In addition, the absence of a second person to support the care had a negative impact on the CB. Since walking/moving around, toileting, and maintaining body hygiene are both time-consuming and tiring activities that require significant strength and attention, it was anticipated that these variables would be predictive of CB. It is not difficult to predict that the absence of a second person to help support the care will be a predictor of CB. Previous studies have shown that functional impairment, dependence in daily life activities (11–15), and the absence of a second caregiver (15) all increase the CB. Our results are consistent with the literature.

Different studies have shown contradictory results on the impact on the burden of being a short- or a long-term caregiver. Some studies suggested that the CB increases (18–20), and one reported that the CB decreases over time (21). In our study, being a short- or a long-term caregiver did not have an influence on the ZBI scores although the burden

increased as the time allocated for caring increased during the day. We feel that the time that the caregiver actively spends on caregiving tasks affects the CB, rather than the days, months, and years spent with the patient.

In our study, a negative correlation was found between the patient's age and the CB, and a relatively younger age was an independent predictor of higher CB. Although previous investigations have shown similar results (12, 18), a positive correlation was found between the CB and the patient's age in some studies (7-8). The possible explanation for our finding is as follows: The current life experiences and the life expectancies of family members who provide care for young patients are different. Since the care demands of the young patients are higher, it might be possible that the caregivers of younger patients perceive a higher burden. As the patients get older, hospital admissions due to comorbidities increase, which may slightly reduce the burden of family members (17). Nevertheless, future research needs to determine the relationship between the patient's age and the CB.

Most patients with dementia lose their ability to understand and communicate and over time, they become almost dependent on others to maintain life (22). As a result, the caregivers of AD patients provide fulltime caregiving support to these patients. Both the physical burden of direct caregiving and the consequent restrictions on social life cause the caregiving individual to perceive more burden (22). In the current study, 64.3% of the caregivers reported that providing care negatively affected their social life. Consistent with the literature, the negative impact on social life appears to be an important predictive variable for increased CB.

It has been reported that psychosocial well-being is associated with CB (23) and that psychosocial interventions will reduce the CB and improve the quality of life for the caregiver (24). In the current study, the ZBI mean scores were lower among

caregivers who received psychological counselling (26.6%). Our results are consistent with the literature.

The present study has some limitations to be considered. The main ones include the convenience sampling of the family caregivers and the limited data collected on the participants. The data did not contain some important information such as the neuropsychiatric symptoms of the patients, the severity of the dementia, or the coping strategies of the caregivers.

Previous research has found that the levels of burden may be moderated by the patient's symptoms and the severity of the dementia (12, 14). Previous research has also shown that positive feelings are associated with a decreased burden level (25). The current study was also limited by the fact that it did not specifically assess the positive effects of caregiving (such as feeling useful or the increased closeness with the patient) that are not indexed in the ZBI. Therefore, the results of the present study should be interpreted cautiously.

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## CONCLUSION

In conclusion, despite the limitations, our data confirms that the CB was very common among our sample, and the most pronounced predictors for burden were the absence of someone else supporting the care, social isolation, the length of time spent daily for caregiving, and the patient's age, comorbidities, and functional impairment in daily activities. Receiving psychological counselling was a protective factor against the development of burden.

We believe that it may be possible to minimize the burden by providing occasional care support from formal or volunteer caregivers, thereby reducing the length of time spent per day in caregiving and decreasing the negative impact of caregiving on the caregiver's life. Psychological counselling should be provided as much as possible to reduce and prevent the CB. Caregivers of patients with advanced age, with comorbidities, and with functional impairments should be especially supported.

## Conflict of Interest

No conflict of interest to disclosure.

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