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3-Books

BG Katzung. Special Aspects of Geriatric Pharmacology, In:Bertram G. Katzung,Susan B. Masters, Anthony J. Trevor (Eds). Basic and Clinical Pharmacology. 10th edition, Lange, Mc Graw Hill, USA 2007, pp 983-90.

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From The Editor In Chief

Researches conducted in the field of Geriatrics and Gerontology (on a population of 65 years and older) is published in Turkish Journal of Geriatrics.

The Journal specifically invites submission of Original Articles based on clinical and laboratory studies. 906 studies have been published in the Turkish Journal of Geriatrics since it started to be published in 1998.

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Review Articles are published only after the invitation from the Editorial Board, and 168 review articles have been published so far.

The most commonly used keywords in review articles are: Aged 35, Old age 31, Aging 26, Geriatrics 18, Osteoarthritis 14, Treatment 12 times.

The Editorial Board of the journal expects authors to submit higher standard researches that will guide the future, especially with an innovative approach.

Yeşim GÖKÇE KUTSAL

RESEARCH

FACTORS AFFECTING DRUG INTERACTIONS AND THEIR CLINICAL IMPORTANCE IN GERIATRIC OUTPATIENTS

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Abstract

Introduction: Polypharmacy can lead to drug-drug interactions. The aim of this study was to determine the possible factors affecting the prevalence and clinical importance, and interrater reliability of clinical significance of drug interactions in geriatric outpatients.

Materials and Method: Potential drug-drug interactions in 228 patients treated in an outpatient geriatric clinic were evaluated in this cross-sectional, retrospective study. The potential significance of the interactions was reviewed separately by a geriatrician and a clinical pharmacist.

Results: A total of 1342 drugs were prescribed (median 6 [2-14], per patient). Mean age of the patients was 78±0.5 (65-96). Polypharmacy was present in 64.0% of the patients. A weak positive correlation was found between patient age and the number of drugs used (Rs =.205; p=.002). No drug interaction was detected in 18.0% of the patients. In the prescriptions of the remaining 187 patients 760 category C, 70 category D, and 18 category X interactions (Lexicomp®) were detected. A strong positive correlation was found between the number of drugs per patient and the number of drug interactions (Rs =.734; p<.001). There was a strong correlation between the number of interactions and the presence of polypharmacy (r_{pb}=.702, p<.001). The measure of agreement between the clinicians was more pronounced for category D and X interactions (Cohen's κ=.714 and 1, p<.001).

Conclusion: Advanced age, a higher frequency of concomitant use of drugs, and polypharmacy are factors that require clinicians to be aware of drug-drug interactions. Clinical pharmacists can work with geriatricians in outpatient clinics to prevent drug interactions.

Keywords: Drug Interactions; Polypharmacy; Health Services for the Aged; Pharmacist.

INTRODUCTION

Although drugs are one of the key elements of many treatment protocols, the use of multiple drugs introduces the risk of possible drug-drug interactions (pDDIs) that may result in harm. In fact, drug-drug interactions are leading cause of hospitalization (1,2). While many adverse drug reactions are unpredictable, the consequences of pDDIs are predictable and preventable (3,4). Hence, when geriatric patients attend outpatient clinics, this is an important opportunity for recognizing pDDIs and optimizing their treatment.

In a research conducted in a university hospital's geriatric inpatient unit, we previously determined that the main reason for possible drug-related problems was pDDIs (5). As a result of the development of electronic databases in the field of medicine, the use of systems that automatically perform drug interaction analyses has increased. While the use of such tools to assist clinical decision-making increases the quality of healthcare, it can also cause "alert fatigue" when physicians encounter numerous pDDI warnings (6). Therefore, to optimize drug prescription and better predict the interactions that may result in harm to the patient, it is important to determine which pDDIs may be clinically significant. Various studies have shown that the patient's age and gender, as well as the presence of polypharmacy, a high number of chronic diseases or certain diseases, may increase the clinical importance of drug interactions (3). In a study that evaluated the frequency of geriatric syndromes in patients presenting to a geriatric outpatient clinic in Turkey, polypharmacy was observed in 54.5% of the patients (7). Polypharmacy not only leads to negative clinical outcomes (8), but also the incidence of drug interactions and adverse reactions increases exponentially with the increase in polypharmacy (8,9).

Additionally, the geriatric population is subject to significant changes in body composition and, physiological and organ functions, which in turn affect all aspects of pharmacokinetics, including drug absorption, distribution, metabolism, and excretion. Alterations in receptor number and sensitivity in older adults also impact pharmacodynamics (10,11). Consequently, there are considerable differences in the effects of drugs on this population compared to younger people. To address this issue, several standardized tools are available for the planning of pharmacotherapy based on the individual needs and abilities of geriatric patients. It is also worth noting that when geriatric patients have certain diseases, the use of particular drugs may be inappropriate (12,13). A drug-drug interaction may become clinically more significant if one of the drugs causing the interaction is potentially inappropriate for use in the elderly (14). Thus, determining the relationship between inappropriate drug use and the clinical significance of pDDIs is important in terms of reducing the vulnerability of patients.

The prevalence of pDDIs in community-dwelling elderly people ranges from 4 to 46% and, depends on the setting (e.g., hospital, outpatient clinic, pharmacy) and the method of determining the interaction (4). An accurate assessment of the clinical significance of pDDIs is essential to reduce patient vulnerability, regardless of the healthcare practitioner involved in optimizing the patient's treatment. It should be determined whether physicians and pharmacists evaluate the severity of the interaction differently, particularly in cases where they have equal access to patient information.

Although geriatric outpatients are at high risk for drug-related adverse effects, the number of studies investigating the types and severity of potential drug-drug interactions in Turkey is limited. Therefore, the aims of this study were to determine i) the prevalence and predictors of pDDIs that may be clinically important in community-dwelling geriatric patients and ii) whether the clinical significance of pDDIs varies depending on the evaluator (physician vs. pharmacist).

MATERIALS AND METHOD

Study population and data collection

This study was conducted between November 2019 and November 2020 in the geriatric outpatient clinic of a tertiary university hospital in İzmir, Turkey. The incidence of clinically important drug-drug interactions has been reported as 16% in ambulatory geriatric patients (1,4). According to the Turkish Statistical Institute (TUIK), the number of elderly people living in İzmir was 493,673 in 2019 (15). The smallest sample size with a 5% margin of error and 95% confidence interval was calculated as 207 people, and it was decided to include 228 patients (+ 10%). A total of 676 patients applied to the outpatient clinic in the study period. The first 228 patients who met the inclusion criteria (aged ≥65 years, being treated with at least 2 drugs) and did not have missing information in their electronic medical files were included in this observational, cross-sectional, retrospective study.

The patients' age, gender, chronic diseases, and clinical data (vitals and biochemical markers), medications, drug administration routes, and complaints, were extracted from the patients' electronic medical files. The presence of polypharmacy was defined as the use of five or more drugs per patient. The active ingredients of the drugs were classified according to the Anatomical Therapeutic Chemical (ATC) code recommended by the WHO for drug utilization monitoring (WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2023. Oslo, Norway, 2022. Available address: https://www.whocc.no/filearchive/publications/2023_guidelines_web.pdf), and the pharmaceutical forms were classified using the New Form Codes (NFC) (EMA New Form Code Classification Guidelines, Version 2023, Publication date: January 2023, Available address: https://www.ephmra.org/sites/default/files/2023-01/2023%20EPHMRA%20NFC%20Guidelines.pdf). Each patient's prescription was analyzed for pDDIs using the Lexi-Interact Online database (Lexicomp®) by one pharmacist (İZY). In this database, drug interactions are classified as A, B, C, D, and X. Category A represents no known interactions, Category B represents the specified agents can interact but there is no need for action. Category C interactions are between drugs that interact with each other, and the combination can usually be used with a monitoring plan. Category D interactions are more serious interactions that may need therapy modification. Lastly, in category X, concurrent use of the interacting members should generally be avoided because of significant risks. The interacting drugs, definition, and severity of the interaction were recorded.

During the drug interaction review, the drug interactions of each patient were examined separately by both of one geriatrician (ET) and one clinical pharmacist (EE). The possible interactions were classified as clinically significant/important or insignificant. The following factors were taken into consideration when determining the clinical importance of the pDDIs: interaction severity; potentially inappropriate medication (PIM) criteria (12,13); and patient factors, such as complaints, chronic diseases, vital values (arterial pressure, heart rate), and laboratory findings (serum creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, fasting blood glucose, hemoglobin A1c, international normalized ratio, activated prothrombin time, serum sodium, potassium, and calcium levels).

Ethics

The authors complied with Good Clinical Practice standards throughout the study. This study was approved by the Ethics Committee for Medical Research of the Faculty of Medicine at Ege University (20-12T/3; 08.12.2020) and was conducted according to the World Medical Association Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

The database was constructed using Microsoft Excel. Continuous variables are expressed as means ± standard error of mean (SEM). Categorical data are presented in terms of frequencies. Normality testing was performed using the Shapiro-Wilk test. The correlation statistics of data that did not show normal distribution were calculated using the Spearman's test. The Mann-Whitney-U test was used for comparisons between the subgroups of continuous variables with non-parametric distribution. Categorical data were evaluated using Chi-Square test. Point-biserial analysis was performed for correlation statistics between categorical and continuous variables. Inter-rater reliability was measured using Cohen's kappa (κ). All statistical tests were performed using SPSS version 25.0 (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp., Armonk, NY, USA). A p value ≤ .05 was considered statistically significant.

RESULTS

Demographic characteristics of patients

The average age of the 228 patients included in this study was 78 ± 0.5 years. The minimum and maximum ages of the patients were 65 and 96, respectively. Among the patients, 139 (61%) were female, and 89 (39%) were male (Table 1). There was no difference between the average age of the male and female patients (female = 78 ± 0.7 years and male = 78 ± 0.7 years).

The median number of chronic diseases per patient was 3 (min-max: 0 - 7). The estimated glomerular filtration rate (eGFR) was considered normal in 61.35% of the patients, while 80 patients had varying degrees of renal disease (Table 1). Serum creatinine or eGFR values were not found in the electronic files of 21 patients. Most of the patients (n = 165, 72.37%) presented to the outpatient clinic due to active complaints, while the remainder presented for routine check-up or prescription refill.

Prescription and drug use patterns

There were 1342 prescribed drugs (Table 1). There was a weak positive correlation between patient age and the number of drugs used (Rs = .205; p = .002). Female patients used fewer drugs compared to male patients (p = .030; female = 5.69 ± 0.23 drugs/patient and male = 6.18 ± 0.24 drugs/patient).

According to the ATC classification, the most commonly detected drugs were; the cardiovascular system (31.4%), nervous system (21.6%), gastrointestinal system (19.6%), blood and blood forming organs (11%), and genitourinary system and sex hormones (4.0%) (Figure 1). The most prescribed

Table 1. Demographic characteristics of patients.

Patients (n=228)		**Number of patients (%)**
Female/Male		139 (60.96%) / 89 (39.04%)
Age distribution	65-74	85 (37.28%)
	75-84	90 (39.47%)
	>85	53 (23.25%)
Number of patients with polypharmacy	1-4 drugs	82 (35.96%)
	≥5 drugs	146 (64.04%)
Number of drug-drug interactions per patient [Median (min-max)]: 3 (1 – 24)		
Number of chronic diseases per patient [Median (min-max)]: 3 (0 – 7)		
The 10 most common chronic diseases: Hypertension Diabetes mellitus Depression Coronary artery disease Dementia Hypothyroidism Congestive heart failure Urinary incontinence Benign prostatic hyperplasia Arrhythmia		 133 72 48 44 43 37 35 35 28 28
Renal function: eGFR (mL/min/1,73 m^2)	>60	127 (61.35%)
	30-59	68 (33.83%)
	15-29	10 (4.98%)
	<15	2 (0.99%)
Mean serum creatinine (mg/dL): 1.79 ± 0.52		

eGFR, Estimated glomerular filtration rate

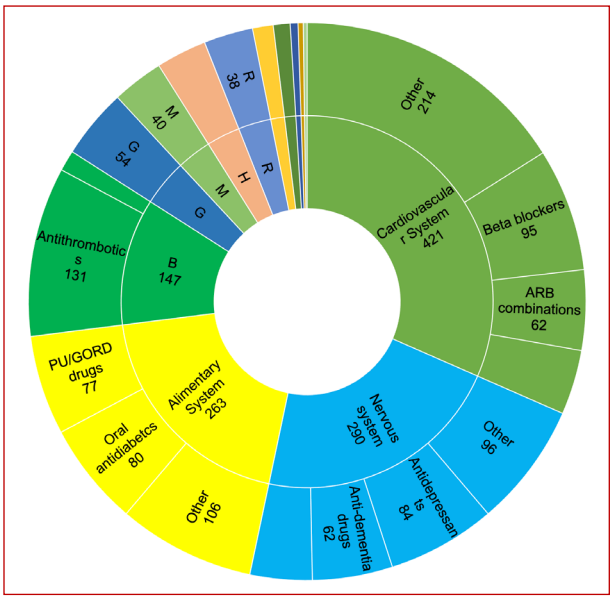

Figure 1. The most commonly prescribed drug types based on the ATC classification system.

ARB, angiotensin receptor blocker; B, blood and blood forming organs; G, genitourinary system and sex hormones; H, sstemic hormonal preparations, excluding sex hormones and insulins; M, musculo-skeletal system; PU/GORD, Peptic ulcer/ Gasroesophageal reflux disease; R, respiratory system

drug groups were antithrombotics (9.8%), beta-blockers (7.1%), antidepressants (6.3%), oral antidiabetics (6.0%), and drugs for peptic ulcer and gastro-esophageal reflux disease (5.7%) (Figure 1). The most prescribed drugs were acetylsalicylic acid, metoprolol, levothyroxine, sertraline, pantoprazole, metformin, clopidogrel, furosemide, atorvastatin, and amlodipine.

The majority (91.4%) of the drugs were administered orally. According to NFC classification oral ordinary or coated tablets, normal or retard capsules, and parenteral pre-filled pens were the most prescribed pharmaceutical forms (Table 2).

Polypharmacy and drug interactions

Polypharmacy was present in 146 (64%) patients. The frequency of polypharmacy was higher in male patients compared to females (p = .047; female = 59.0% and male = 71.9%).

Table 2. The most commonly prescribed drug formulations based on the New Form Codes (NFC) classification system

NFC category	Pharmaceutical form	N (%)
ABC	Oral solid ordinary film-coated tablets	449 (33.46%)
AAA	Oral solid ordinary tablets	364 (27.12%)
ABD	Oral solid ordinary enteric-coated tablets	129 (9.61%)
BBC	Oral solid retard film-coated tablets	64 (4.77%)
BAA	Oral solid retard tablets	56 (4.17%)
ACA	Oral solid normal capsules	51 (3.80%)
FRF	Parenteral ordinary pre-filled pens	29 (2.16%)
BCA	Oral solid retard capsules	20 (1.49%)
ABA	Oral solid ordinary coated tablets	20 (1.49%)
ACY	Oral solid ordinary other capsules	19 (1.42%)

Table 3. Distribution of drug interactions and examples of the most frequently encountered interactions

Interaction category	Drug Interaction n=889 (%)	Patient n=228 (%)
X Carvedilol – Rivastigmine Metoprolol - Rivastigmine Bisoprolol - Rivastigmine Rasagiline - Sertraline Lorazepam - Olanzapine Ketoconazole - Lercanidipine Diclofenac - (Codeine + Naproxen) Olanzapine - Tiotropium Doxazosin - Silodosin Quetiapine - (Umeclidinium + Vilanterol) Doxazosin - Tamsulosin Ketoprofen - Tenoxicam Escitalopram - Rasagiline Escitalopram - Citalopram Propiverine - Tiotropium (Ipratropium + Salbutamol) - Carvedilol Amiodarone - Quetiapine	18 (%2.02)	18 (%7.89)
D Esomeprazole - Clopidogrel Acetylsalicylic Acid - Ginkgo biloba Gliclazide - (Metformin + Vildagliptin) (Levodopa + Benserazide) - Olanzapine Acetylsalicylic Acid - Enoxaparin Gliclazide – Linagliptin Quetiapine – (Levodopa + Benserazide) Diclofenac – Sertraline Enoxaparin – Sertraline Escitalopram – Ginkgo biloba Morphine – Pregabaline (Paracetamol + Codeine) – Tramadol Iron – Levothyroxine Digoxin – Ranolazine Warfarin - Amiodarone	70 (%7.87)	49 (%21.49)
C Acetylsalicylic Acid – Sertraline Acetylsalicylic Acid – Clopidogrel Quetiapine – Sertraline Clopidogrel – Pantoprazole Amlodipine – Clopidogrel Insulin glargine – Metoprolol Gliclazide – Metformine	760 (%85.49)	120 (% 52.63)
A or **B**	41 (%4.61)	41 (%17.98)

There were no interactions between the drugs used by 41 patients (17.98%). In the remaining 187 patients, 848 pDDIs were identified. The median number of pDDIs per patient was 2 (min-max: 0-24). The majority of the pDDIs were category C interactions (n = 760, 85.5%) and occurred in 120 patients (52.6%). A further 70 possible category D interactions were found in 49 patients (21.5%), and 18 possible category X interactions were found in 18 patients (7.9%). A selection of the most frequently encountered pDDIs is shown in Table 3.

There was a strong positive correlation between the number of drugs used per patient and the number of pDDIs (Rs = .734; p < .001). According to the point-biserial correlation analysis, there was a strong correlation between the number of pDDIs and the presence of polypharmacy (r_{pb} = .702, p < .001). The number of pDDIs was significantly higher in patients with polypharmacy (p< .001; 5.49±0.37 and 1.61±0.16 for patients with and without polypharmacy, respectively).

Similar numbers of pDDIs were recorded in the female and male patients (4.47 ± 0.45 and 4.63 ± 0.40, respectively). However, there was a weak positive correlation between the number of pDDIs and the female gender (r_{pb} = .216, p <.001).

Clinician judgment of drug interaction significance

The geriatrician and the clinical pharmacist determined that 580 of the 848 pDDIs (68%) were clinically non-significant. Of the remaining pDDIs, 58 (7%) were considered important by the clinical pharmacist but not by the geriatrician, 49 (6%) were considered important by the geriatrician but not by the clinical pharmacist, 161 (19%) were considered clinically important by both of them (Figure 2). When individual assessments performed by the geriatrician and pharmacist were compared, the measure of agreement between the clinicians was more pronounced for the pDDIs in the more severe category. The clinicians had a perfect agreement on the significance of category X interactions (Cohen's κ = 1, p<.001) and substantial agreement on the significance of category D interactions (Cohen's κ = 0.714, p<.001). Their level of agreement was

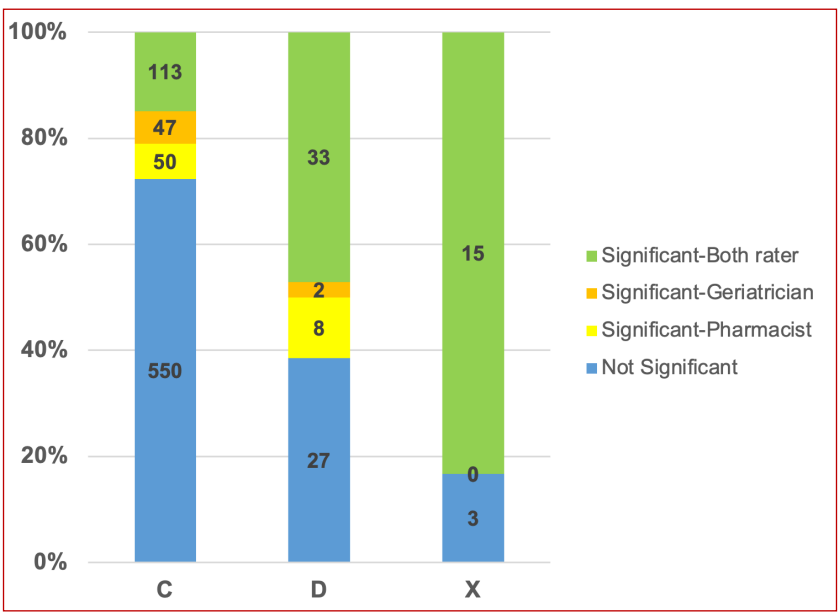

Figure 2. The clinical importance of the drug interactions according to the clinicians.

lower but still significant for category C interactions (Cohen's $\kappa = 0.619$, $p < .001$).

Possible interactions between quetiapine and sertraline, a proton pump inhibitor and clopidogrel, and acetylsalicylic acid and piracetam or Ginkgo biloba were most frequently rated as potentially significant by both clinicians.

DISCUSSION

Polypharmacy, which is commonly defined as the regular use of five or more drugs, is associated with increased PIM use, adverse events, and drug interactions (5,16–18). Polypharmacy is increasing worldwide at an alarming rate, and medicines optimization is complicated by the risks associated with drug interactions (9,19). As a result, patients are presenting to emergency departments with preventable drug-related adverse reactions or events (9).

In a study that involved ambulatory patients aged 50 years and older, it was found that an average of 5.9 drugs/patient had been prescribed, and polypharmacy was present in 69.9% of the patients (20). Similarly, in our study of 228 ambulatory elderly people presenting to the geriatric outpatient clinic of a tertiary hospital, it was found that a median of 6 drugs/patient had been prescribed, the polypharmacy rate was high (64%), and pDDIs were present in 82% of patients. The number of pDDIs was significantly higher in polypharmacy patients in our study. Consistent with findings reported in the literature, there was a weak positive correlation between patient age and the number of drugs used. In a prospective cohort study of 433 patients, adjusted odds ratios for drug interactions were found to increase from 0.91 to 4.40 in patients aged 65-69 years and 80 years or older (21). A repeated cross-sectional analysis of community-dispensed prescribing data performed in Scotland revealed that people aged ≥ 65 years were more likely to have at least one potentially serious DDI, and the proportion of elderly with any DDI increased with age (33.8%, 42.5%, and 46.0% in patients aged 60-69, 70-79, and 80+ years, respectively) (9). Therefore, it is crucial to review geriatric patients' prescriptions to prevent potential harm from pDDIs. Clinical pharmacists play a significant role in reviewing and determining the clinical relevance of pDDIs (5,22,23). Although clinical pharmacists are mainly involved in inpatient healthcare services in Turkey (5), the high pDDI rates detected in our study suggest that it might be useful to place pharmacists in geriatric outpatient clinics.

The results of previous studies are conflicting about the effect of gender on the prevalence of pDDIs. In a study, there were no significant differences between female and male patients (21). However, in another study by Neto et al., female gender was identified as a predictor for clinically important pDDIs (24). This discrepancy may be attributed to the fact that the former study was performed in public primary healthcare units where patients were attended by general practitioners. Although female patients used fewer drugs, the number of pDDIs was not significantly lower in female patients compared to male patients. As the female gender is a known factor for drug-related adverse events, geriatricians in our clinic might have paid more attention to this issue. The relationship between gender, polypharmacy, and drug interactions should be evaluated with further prospective studies.

The prevalence of severe DDIs and the related risk of adverse drug reactions are both very high in patients with PIM use (14); thus, special care must be taken when reviewing pDDIs in geriatric patients. In our study, the most commonly prescribed drugs were those that affect the cardiovascular system (31.4%) and nervous system (21.6%). The elderly group are more prone to experiencing drug-related adverse events associated with these two particular systems. In addition, high-risk and/or potentially inappropriate drugs such as antithrombotics,

antidepressants (especially selective serotonin reuptake inhibitors; SSRIs), and oral antidiabetics, were among the most prescribed drugs or drug groups (9.8%, 6.3%, and 6.0% of patients, respectively), which are referred to as potential PIMs in explicit criteria (12,13). However, the explicit criteria cannot replace the clinical opinion of a health professional. For example, four interactions between beta-blockers and rivastigmine were identified in our study. This is a category X interaction due to the potential for severe bradycardia, and this combination is also listed as a PIM according to the STOPP (Screening Tool of Older Persons' Prescriptions) criteria (Version 2). Yet, three of these four interactions were rated as clinically insignificant by both clinicians because the patients' heart rates were well above 60 beats per minute. In contrast, there were a number of duplication errors identified (e.g., two non-steroidal anti-inflammatory drugs, two SSRIs), all of which were rated as clinically significant by both clinicians.

When individual assessments performed by the geriatrician and clinical pharmacist were compared, the measure of agreement between the clinicians was found to be more pronounced for the pDDIs in the more severe categories. It has been reported that alerts generated by clinical decision support systems related to pDDIs are frequently overridden (56%-96%), with the most commonly stated reason being: "will monitor as recommended" (25). This is in line with our findings, as both the geriatrician and the clinical pharmacist rated 72% of the possible interactions in category C (monitor therapy) as not significant. Disregarding the recommendations of clinical decision support systems has been shown to increase the risk of adverse events (25). However, no decision support system has been developed that is 100% sensitive and specific in a real-world setting (25). Consequently, one of the ways to prevent the negative outcomes of pDDIs may be to implement internal reviews in geriatric assessment teams. With physicians and pharmacists in the geriatric assessment teams approaching patients and drug-related problems from different perspectives, the clinical consensus they reach on the importance of possible drug interactions may reduce the likelihood of harm due to drug interactions. Our previous finding of an 85% acceptance rate of pharmacist interventions in patients treated in a geriatric ward (5) may serve as a good indicator of the possible harmony that could be achieved between the two professions in geriatric assessment teams. In the present study, there was a perfect or substantial agreement between geriatricians and clinical pharmacists on the clinical significance of the high risk attributed to the interactions by the clinical decision support system.

Limitations

Because of the retrospective and cross-sectional design of this study, some patients' laboratory test values were not available at the data acquisition time point. When clinical data were missing, the geriatrician and clinical pharmacist relied on their expertise and professional judgment to define the clinical importance of the drug interactions.

CONCLUSION

When prescribing drugs for their elderly patients, clinicians should be aware of potential drug-drug interactions. The interaction risk could be particularly prominent in people with advancing age, greater number of concomitant drug use, or polypharmacy. Elderly people with polypharmacy often have complex treatment regimens that can lead to adverse events and drug interactions. In our study, the most important pDDIs were a result of the concomitant use of a beta-blocker and an acethylcholine esterase inhibitor, two serotonergic agents (selective serotonin re-uptake inhibitor and monoamine oxidase B inhibitor), two central nervous system depressants (a benzodiazepine and an antipsychotic), two drugs with prominent anticholinergic properties, two QTc prolonging

agents, two drugs that can increase bleeding risk (i.e. antiplatelet agents, P2Y12 antagonists, factor Xa inhibitors vitamin K inhibitor), and pharmacological duplications (non-steroidal anti-inflammatory drugs or alpha 1 receptor blockers). We found a substantial level of agreement between geriatricians and clinical pharmacists on the clinical significance of pDDIs. This presents an opportunity for clinical pharmacists and geriatricians to work together in outpatient clinics to prevent adverse events related to drug interactions. Although clinical pharmacists in Turkey generally work in inpatient settings, given the high risk of pDDIs in geriatric ambulatory patients, collaborative practices should be implemented to address this issue.

Conflict of Interest

There are no financial disclosures or sponsors to declare. The authors report no conflict of interest in this work.

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RESEARCH

EVALUATION OF PROGNOSIS AND RISK FACTORS OF DIFFERENTIATED THYROID CANCER IN A GERIATRIC POPULATION

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Abstract

Introduction: This retrospective study aimed to investigate the clinical and pathological features of differentiated thyroid cancer and to evaluate treatment outcomes in older adults.

Materials and Methods: Data from 1077 patients with differentiated thyroid cancer were noted. These patients were divided into two groups, aged < 65 years and aged ≥ 65 years, and the clinicopathological features of each were compared.

Results: Of the 1077 patients, 913 (85%) were under 65 years of age and the remaining 164 (15%) were aged ≥ 65 years. Of those aged < 65 years, 652 (71.4%) had papillary thyroid carcinoma and 261 (28.6%) had follicular thyroid carcinoma. Of the patients aged ≥ 65 years, 116 (70.7%) had papillary thyroid carcinoma and 48 (29.3%) had follicular thyroid carcinoma. The primary tumour size was significantly larger and the incidences of vascular invasion, lymph node metastasis, and distant metastasis were significantly higher in patients aged ≥ 65 years than in the younger patients ($p<0.001$, $p<0.001$, $p=0.001$, and $p=0.002$, respectively). There was no noteworthy difference between the two groups in terms of the number of tumours, tumour bilaterality, multifocality, and extravascular invasion ($p=0.860$, $p=0.590$, $p=0.404$, and $p=0.110$, respectively).

Conclusion: Primary tumour size was significantly larger and the incidences of vascular invasion, lymph node metastasis, and distant metastasis were significantly higher in patients aged ≥ 65 years. Older patients with differentiated thyroid cancer have worse pathologic features at the time of diagnosis therefore need more aggressive treatment such as more frequent and higher doses of radioiodine treatment.

Keywords: Thyroid Neoplasms; Thyroid Cancer, Papillary; Adenocarcinoma, Follicular; Neoplasm Metastasis; Geriatrics..

INTRODUCTION

Differentiated thyroid cancers (DTC) constitute 80–90% of all thyroid cancers (1). There are several factors associated with a favourable prognosis for differentiated thyroid cancer: age, tumor size, tumor stage, histologic subtype, absence of distant metastasis and response to radioiodine treatment (2). Age plays an important role in prognosis of DTC. Generally, younger patients (less than 45 years old) with DTC tend to have a better prognosis than older patients (over 45 years old).

Several studies have shown that younger patients with DTC have a lower risk of disease recurrence and mortality compared to older patients. This may be due to differences in tumor biology and the immune response to the tumor between age groups. In addition, younger patients may be more likely to receive aggressive treatment and have better overall health, which can also contribute to a better prognosis.

Age is an important factor for DTC. In the TNM classification for thyroid carcinoma, age was included as a prognostic factor, and the cut-off age was 45 years. Several publications compared survival between the two groups (i.e., patients younger and older than 45 years) (3–5). However, discussions regarding higher age limits are ongoing (6–8).

In particular, it is known that thyroid cancer incidence increases with age, with a peak incidence in the 6th and 7th decades of life. Despite this, there is limited research comparing the clinic and pathologic differences of DTC between young and old patients.

This study aims to investigate the clinic and pathologic characteristics of DTC in young and old patients, with a focus on identifying any differences in tumor characteristics and disease progression. By understanding the unique features of DTC in different age groups, clinicians can better tailor their management strategies and improve the overall care of patients with this disease.

MATERIALS AND METHODS

A total of 1077 patients with DTC registered in Başkent University Ankara Hospital outpatient clinic of Endocrinology from 2011 to 2021 were identified and retrospectively analysed.

Patients were divided into two groups based on ages, those aged < 65 years and those aged ≥ 65 years. The pathological and clinical features of the two groups were compared. Information about age, gender, body mass index (BMI), diabetes, hypertension, coronary artery disease (CAD), and cancer history were evaluated. These two groups were compared in terms of tumour size, tumour multifocality, bilaterality, tumour invasion (extracapsular and vascular invasion), lenf node (LN) metastasis, and distant metastasis. TNM staging was performed. Recurrence and mortality from any cause were also evaluated. Recurrence was defined as detection of a tumor in the thyroid bed, cervical lymph nodes or in distant organs.

Statistical analysis

All statistical analysis was performed using SPSS for Windows v16.0 (Statistical Package for Social Sciences) package program. Continuous data were presented as means ± standard deviation. Comparisons of various numeric parameters among groups were analyzed with the students t test. Comparisons of categorical parameters among groups were analyzed with pearson chi square test. Statistical significance was set at $p<0.05$.

RESULTS

Overall 1077 patients with differentiated thyroid cancer was analysed. Of these, 913 (85%) patients were aged < 65 years, and the remaining 164 (15%) patients were aged ≥ 65 years. The demographic and clinical characteristics of patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of patients diagnosed with DTC.

Variable	< 65 y (n=913)	≥ 65 y (n=164)	Pα,β value
Gender (female%)	701(76.8)	115(70.1)	0.067
Age, years*	44.7±11.6	71.8±6.0	<0.001
BMI, kg/m^2*	28.16±5.34	28.26±5.45	0.691
Comorbidities			
Diabetes (%)	151(16.5)	46(28)	<0.001
Arterial Hypertension (%)	152(16.6)	49(29.9)	<0.001
Dyslipidemia (%)	89(9.7)	21(12.8)	0.234
CAD(%)	71(7.8)	23(14)	0.009
History of cancer (%)	22(2.4)	25(15.2)	<0.001

*:Mean ± Standard Deviation, BMI: Body Mass Index, CAD: Coronary Artery Disease, α: p for Age and BMI: Difference between groups student's t test, β: p for comorbidities and gender: Difference between groups Chi-square test.

Of the patients aged < 65 years, 652 (71.4%) had PTC and 261 (28.6%) had follicular thyroid carcinoma. Of those aged > 65 years, 116 (70.7%) had PTC and 48 (29.3%) had follicular thyroid carcinoma. The primary tumour size was significantly larger (1.37±0.99 cm for the patients aged < 65 years and 1.86±1.59 cm for aged ≥65 years, p<0.001). The incidences of vascular invasion (22% vs 37.8%, p<0.001,) lymph node (16.9% vs 27.4%, p=0.001) metastasis, and distant metastasis (2.3% vs 6.7%, p=0.002) were significantly higher in patients aged >65 years than in younger patients.

The percentage of distant metastasis within patients having papillary thyroid carcinoma was 0.25% and within patients having Follicular thyroid carcinoma was 0.42%. The percentage of lymph node metastasis within patients having papillary thyroid carcinoma was 17% and within patients having Follicular thyroid carcinoma was 22%.

There was no significant difference between the two groups in terms of the number of tumours (1.97±1.18 in the group of patients aged <65 years and 1.93±1.28 for aged ≥65 years, (p=0.860)). In terms of multifocality, results do not indicate any remarkable difference (26.4% of patients aged <65 years and 24.4% of patients aged ≥65 years, p=0.590)). Similarly, there was no significant difference in percentage of patients within these two different age groups (21.2% and 18.3%, p=0.404) when bilaterality is considered. Extravascular invasion results indicated no remarkable difference (22.9% and 28.7%, p=0.110). All pathological features of the patients diagnosed with DTC are presented in Table 2.

When TNM Staging was performed, 42% of the patients in the geriatric patient group (65 years and older) were found to be in stage 4. The proportion of stage 4 patients under the age of 65 years was only 17%.

All of the patients had total thyroidectomy. The number of patients who underwent central lymph node dissection was significantly higher in those aged ≥ 65 years (p=0.039). The rate of lateral lymph node dissection was alike in both the groups (p=0.158).

The proportion of patients who underwent radioactive iodine treatment, and the dosing amount were significantly higher in patients aged ≥ 65 years

Table 2. Pathology results of patients diagnosed with DTC.

Variable	< 65 y (n=913)	≥ 65 y (n=164)	Pα,β value
Papillary thyroid carcinoma (%)	652(71.4)	116(70.7)	0.859
Follicular thyroid carcinoma (%)	261(28.6)	48(29.3)	0.859
Primary tumor size, cm*	1.37±0.99	1.86±1.59	<0.001
Number of tumors*	1.97±1.18	1.93±1.28	0.860
Multifocality (%)	241 (26.4)	40 (24.4)	0.590
Bilaterality (%)	193 (21.2)	30 (18.3)	0.404
Vascular invasion (%)	201 (22)	62 (37.8)	<0.001
Extracapsular invasion (%)	209 (22.9)	47(28.7)	0.110
LN metastasis (%)	154 (16.9)	45 (27.4)	0.001
Distant metastasis (%)	21(2.3)	11(6.7)	0.002

*: Mean ± Standard Deviation, LN: Lymph Node, α: p for primary tumor size and number of tumors: Difference between groups student's t test, β: p for papillary and follicular thyroid carcinoma, multifocality, bilaterality, vascular invasion, extracapsular invasion, LN and distant metastasis: Difference between groups Chi-square test.

(p<0.001 and p<0.001, respectively). The recurrence rates were similar in both groups (p=0.425). The all-cause mortality rate was significantly higher in patients than in those aged < 65 years (p<0.001).

There was no difference in terms of tumour size, vascular invasion, lymph node metastasis, and distant metastasis between patients aged 65–75 years and those aged 75 years and above. Extracapsular spread was more common in patients aged 75 years and above than in patients aged 65–75 years. The recurrence rate was similar in both groups; however, as expected, the rate of all-cause mortality was higher in patients aged 75 years and above.

DISCUSSION

Age has been recognized as an important prognostic factor in DTC. This may be due to the fact that younger patients tend to have less aggressive disease and better overall health, which may enable them to tolerate more aggressive treatments and have a better response to treatment. Our study demonstrated worse histopathological features as determinants of worse prognosis in elderly.

In this study we found larger tumor size and higher incidence of vascular invasion, lymph node metastasis and distant metastasis in patients aged ≥ 65 compared to younger patients. There was not any difference in terms of these conditions between ages 65-75 and above 75.

Tumor size is an important prognostic factor in patients with DTC and the size of the primary tumor in differentiated thyroid carcinoma may be a crucial factor in determining their likelihood of developing extrathyroidal extension, lymph node spread, and distant metastasis. Compared to patients aged < 65 years, geriatric patients had significantly higher incidences of vascular invasion, LN metastasis, and distant metastasis, which might be due to the late diagnosis of the patients (9). Some patients with PTC have poor outcomes depending on factors such as sex, tumour size, LN metastasis, presence

of extrathyroidal tissue infiltration, completeness of resection, and age at diagnosis (10). Certain studies have shown that DTCs in elderly tend to have a worse prognosis depending on larger tumor size, extrathyroidal extension and lymph node involvement at the time of diagnosis (11).

In one study, patients over 75 years of age had larger tumor size and higher tumor count than patients under 65 years of age and those aged 65-75 years. Advanced stage of tumor and metastasis (TNM) and probability of extracapsular invasion were higher compared to patients under 65 years of age and 65-75 years old (12). In our study, no difference was observed between patients aged 65–75 years and patients aged 75 years and above in terms of tumour size, vascular invasion, lymph node metastasis, and distant metastasis.) Extracapsular spread was more common in patients aged ≥ 75 years than in patients aged 65–75 years. In another study, older adults with papillary thyroid microcarcinoma were found to have more aggressive biological features and a higher recurrence rate, and it was reported that more aggressive treatment and strict follow-up could be considered in geriatric patients with a tumour diameter >5 mm (13). These more aggressive pathologic features connected to age may be related in diagnostic delay in elderly (14).

In our study there was no difference in frequency of variants of pathologic thyroid cancer. Some studies suggested relative increase in more histopathological subtypes of thyroid cancer in elder patients is related with worse prognosis (15).

Despite worse histopathologic features in our elder group, local recurrence rate was similar with young group. This is probably due to the fact that these patients treated more intense according to their worse pathologic characteristics. In our study all patients had total thyroidectomy, though central lymph node dissection was higher in older patients. We also found more frequent and more intense radioiodine treatment in elderly. The number of patients who underwent central lymph node dissection was significantly higher in those aged ≥ 65 years (p=0.039). The rate of lateral lymph node dissection was alike in both the groups (p=0.158). In addition, one study found no significant difference in central and lateral neck dissections performed in elderly and young patients (9). Another study indicated that patients in the elderly group were more likely to show central compartment lymph node metastasis (CLNM) (p<0.010), especially the ratio of CLNM >0.5 (p<0.010), more than patients <65 years of age (13), which was in line with our study.

There are some limitations of our study. First of all, retrospective design of our study is a major limitation. We did not investigate the side effects of more aggressive treatment in older patients. Further prospective studies are needed to decide most appropriate treatment approach in older population.

In conclusion, older patients with differentiated thyroid cancer have worse pathologic features at the time of diagnosis therefore need more aggressive treatment such as more frequent and higher doses of radioiodine treatment.

CONCLUSION

In conclusion, this study revealed that the primary tumour size was significantly larger and the incidences of vascular invasion, lymph node metastasis, and distant metastasis were significantly higher in patients aged ≥ 65 years. Older patients with differentiated thyroid cancer have worse pathologic features at the time of diagnosis therefore need more aggressive treatment such as more frequent and higher doses of radioiodine treatment.

Conflict of interest

The authors state that there is no conflict of interest.

Ethics approval

This was a retrospective study. This study has an approval from Başkent University Institutional Review Board (KA21/497, Project Number) and supported by Başkent University Research Fund.

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RESEARCH

POSTOPERATIVE ACUTE KIDNEY INJURY IN GERIATRIC GYNECOLOGIC ONCOLOGY PATIENTS AFTER MAJOR OPEN ABDOMINAL SURGERY: A RETROSPECTIVE COHORT STUDY

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Abstract

Introduction: This investigation's purpose was to determine the incidence of acute kidney injury, the associated risk factors, and the 90-day outcomes and kidney function of geriatric patients who underwent major open abdominal gynecologic oncologic surgery.

Materials and Method: This retrospective cohort study involved patients aged ≥ 65 years who underwent major open abdominal gynecologic oncologic surgery.

Results: The postoperative incidence of acute kidney injury in gynecologic oncologic surgical procedures was 22.1%, with a transient nature observed in 72% of patients. The in-hospital mortality rate was 4 %. Kidney function on the 90th day after acute kidney injury development revealed that estimated glomerular filtration rate regressed by over 25% in 6 patients (24%). Acute kidney injury development was associated with surgical time, intraoperative bleeding volume, bowel procedures, the presence of ascites, intraoperative hypotension, vasopressor use, postoperative diuretic use, postoperative hypoalbuminemia, prolonged post-anesthesia care unit, and hospital stay ($p < 0.05$). A logistic regression analysis of the risk factors for acute kidney injury revealed that surgery duration was a significant one ($p < 0.05$).

Conclusion: Postoperative acute kidney injury is an important postoperative complication associated with the development or progression of chronic kidney disease. This leads to a prolonged stay in the post-anesthesia care unit and in the hospital. Although acute kidney injury is frequently transient in geriatric patients following major open abdominal gynecologic oncologic surgery, developing preventive measures, encouraging team collaboration, and monitoring serum creatinine concentration in the early postoperative period are critical in complex surgical procedures.

Keywords: Postoperative Complications; Acute Kidney Injury; Geriatrics.

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INTRODUCTION

Acute kidney injury (AKI) is a condition characterized by a sudden loss of kidney function, resulting in urea and other nitrogenous waste products accumulating in the blood. Initially referred to as acute kidney failure in the 1950s, the term has evolved over time, and the condition has been called acute kidney damage since 2004. Since 2012, acute kidney injury has been defined as a sudden (in hours) reduction in kidney function encompassing both injury (structural damage) and impairment (loss of function) function (1,2).

When diagnosing postoperative AKI (PO-AKI), the Kidney Disease Improving Global Outcomes (KDIGO) guideline has established criteria for defining the condition as a kidney disease (1-3). PO-AKI is an independent risk factor for both in-hospital and long-term mortality. It also indicates an increased risk of chronic kidney disease (CKD) and progression to cardiovascular events (4-6). PO-AKI can occur in 6.7% to 39.3% of patients undergoing noncardiac surgery. AKI etiologies and mechanisms are multifactorial. This is a common postoperative complication, especially in geriatric patients, due to decreases in preoperative renal reserve, multiple comorbidities, and polypharmacy (5-10).

AKI occurring in the postoperative period can sometimes be transient (< 48 hours) and rapidly reversible. Alternatively, AKI may be persistent, with structural tubular damage and dysfunction. Recent studies have shown that even transient AKI is associated with increased hospital stay duration, morbidity, and mortality in hospitalized patients (9,11,12).

Few studies in the literature have investigated the incidence and risk factors of PO-AKI after major open abdominal gynecologic oncological surgery in geriatric patients. This study conducted a retrospective analysis of the incidence of AKI, risk factors associated with its occurrence, 90-day outcomes, and kidney function of geriatric patients who underwent major open abdominal gynecologic oncologic surgery.

MATERIALS AND METHODS

Study design and patients

In this retrospective, single-center cohort study, data were collected from 113 geriatric patients aged 65 years and older who underwent major open abdominal surgery in the gynecologic oncologic surgery clinic between January 2021 and March 2022. Their preoperative American Society of Anesthesiologists (ASA) scores from I–III were evaluated (Figure 1) after obtaining approval from our hospital's Ethics Committee for Clinical Research (E1-22-2381).

The study exclusion criteria were defined as geriatric patients who met any of the following criteria: surgical duration of ≤ 2 hours, AKI in the past 3 months, end-stage renal disease (i.e., an estimated glomerular filtration rate [eGFR] of ≤ 15 mL/min/1.73 m^2), a hospital stay of less than 4 days, less than 4 serum creatinine (sCr) measurements during hospitalization, and a missing or incomplete medical history.

Data collection and variables

For the study, patient information was obtained from anesthesia pre-intra-postoperative records, the hospital medical information system, the Republic of Turkey Ministry of Health e-nabiz application, and files and discharge records from the gynecologic oncologic surgery service. The following clinical data were collected:

1. Preoperative disease states, including hypertension, diabetes mellitus, ischemic heart disease (CHD), congestive heart failure, and other comorbidities, as well as patient demographic data.
2. Laboratory values, including hemoglobin, sCr, estimated eGFR, and serum

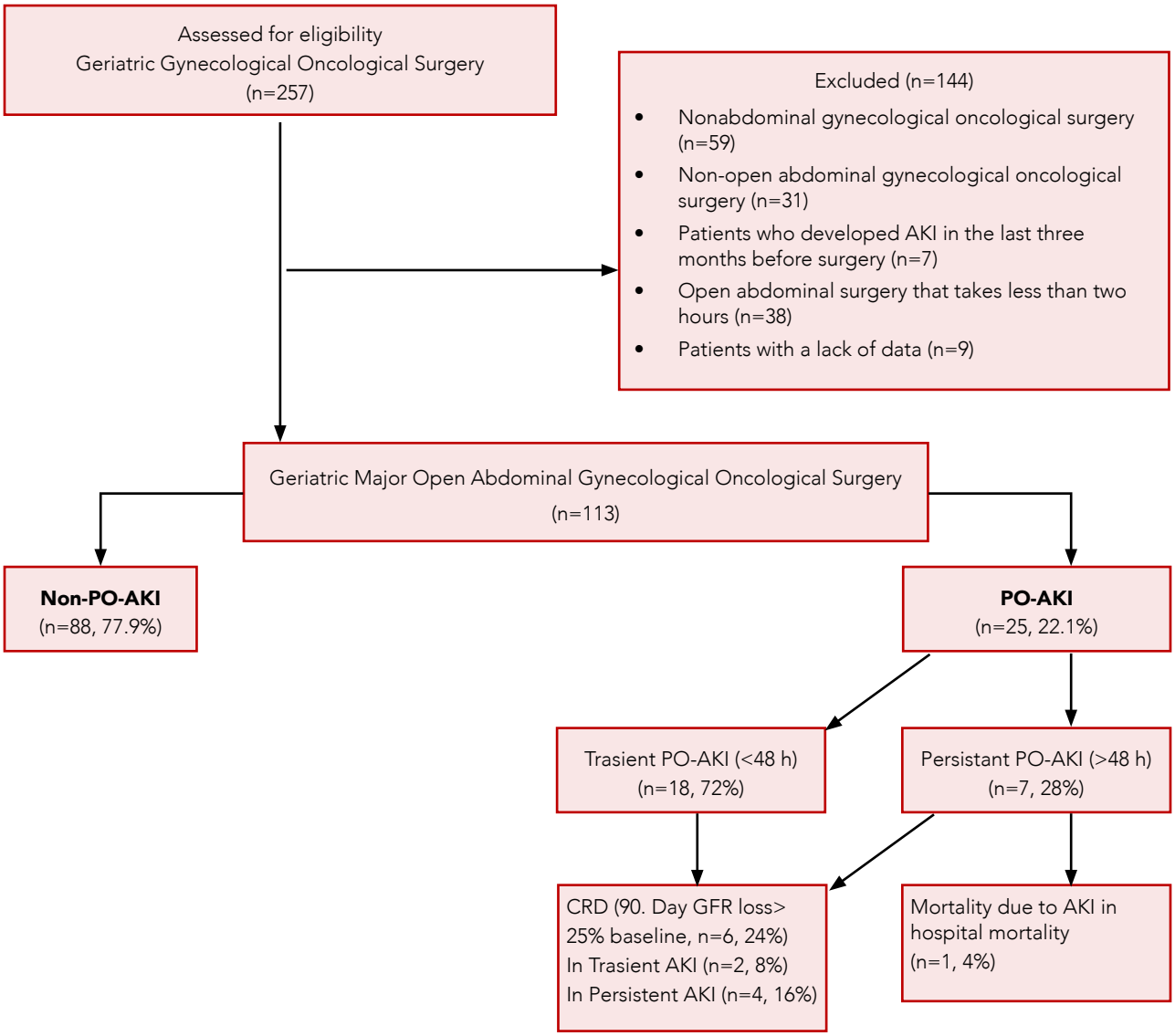

Figure 1. Patient selection and work flow chart.

albumin concentration, were measured preoperatively, postoperatively for the first three days, at discharge from the hospital, and 90 days after discharge.

3. Drugs were used preoperatively, intraoperatively, and postoperatively, including chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), vasoactive drugs, and furosemide.
4. The type and duration of surgery (in minutes), amount of ascitic discharge (in mL), blood loss (in mL), blood transfusion (in units), the total amount of crystalloid and colloid

infused (in mL), amount of fluid infused throughout the operation (in mL/h), bowel procedures, length of stay hospital and post-anesthesia care unit (PACU) duration (from the day of operation to discharge).

5. The ASA scores and General Surgery Acute Kidney Injury Risk Index were calculated and recorded (13).

Definition and calculation of kidney dysfunction

This study's primary aim was to determine the incidence and risk factors for PO-AKI considering sCr, according to KDIGO (2). The secondary outcome was to determine the risk factors associated with AKI, in-hospital mortality, hospital stay duration, and kidney function on the 90th day after hospital discharge.

Acute kidney injury staging

The study classified AKI in accordance with the established criteria set forth by the KDIGO guidelines. Specifically, AKI staging was based on sCr levels, as defined by KDIGO. According to the sCr levels defined by KDIGO, AKI is defined if either there is an increase in sCr by ≥ 0.3 mg/dL within 48 hours or an increase in sCr to ≥ 1.5 times the baseline. Therefore, AKI was classified into stages, considering that the baseline sCr was defined as the most recently measured sCr before surgery. The classification was as follows: stage 1a if there was (a) an increase in sCr 1.5–1.9 times baseline, stage 2 if there was (b) an increase in sCr 2.0–2.9 times baseline, and stage 3 if there was either (c) an increase in sCr ≥ 3 times or the initiation of RRT (1). Furthermore, transient AKI was defined when there is an increase in sCr meeting the sCr criteria of the highest stage maintained for ≤ 48 hours, and persistent AKI was defined when there is an increase in sCr satisfying the sCr criteria of AKI for > 48 hours (11,12). In this study, if sCr was not measured within the 90th day after discharge, the first sCr measured after day 90 was taken as a baseline for the post-discharge process.

Chronic kidney disease

Chronic kidney disease (CKD) is defined as a preoperative eGFR level of < 60 mL/min/1.73 m^2. CKD progression is defined as worsening of the eGFR category with a ≥25% reduction from baseline at 90 days in eGFR according to the 2012 Clinical Practice Guidelines for the Assessment and Management of Chronic Kidney Diseases: KDIGO (2).

Statistical analyses

The IBM SPSS 20 program for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Mean standard deviation, median, minimum, and maximum values were given in descriptive statistics for continuous data, and number and percentage values were given in discrete data. The Kolmogorov-Smirnov test was used to examine the conformity of the data to the normal distribution. The Mann-Whitney U test was used to compare continuous data between the non-AKI and AKI groups. Chi-square and Fisher's exact tests were used for group comparisons (cross tables) of nominal variables. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

In our study, the data of 113 out of 257 female patients aged 65 and over who had gynecological cancers surgery between January 2021 and March 2022 were analyzed, whereas 114 were excluded from the study (see Figure 1). The demographic characteristics of the patients, their medication status, and features specific to operations are seen in Table 1. Furthermore, PO-AKI was detected in 22.1% of the patients, as indicated in Table 2. Transient PO-AKI (PO-AKI time < 48 hours) was

Table 1. Preoperative medical status, baseline kidney functions, demographic and surgery characteristics of the patient with non-AKI and AKI.

	Non-AKI		AKI		p value
	Mean ± SD Median (Range)		Mean ± SD Median (Range)		
Age (year)	72.16±5.96 71 (65-89)		72.12±5.08 72 (65-83)		0.822 [a]
BMI kg/m^2	32.33±6.45 30 (17-50)		32.20±6.79 31 (22-45)		0.936 [a]
Duration of surgery (min)	258.98±79.16 247.5 (135-490)		308.00±84.53 315 (180-480)		**0.014** [a]
Preoperative AKI risk score	3.45±0.98 3 (0-5)		3.60±0.76 4 (2-5)		0.600 [a]
Baseline creatinine (mg/dL)	0.83±0.21 0.79 (0.51-1.42)		0.85±0.19 0.84 (0.55-1.39)		0.543 [a]
Baseline Hb (gr/dL)	12.24±1.64 12 (8.8-16.3)		11.80±1.74 11.6 (8.8-15.1)		0.278 [a]
Baseline GFR (mL/kg/ 1.73 m^2)	73.09±17.16 75 (37-106)		70.88±16.69 70 (36-96)		0.536 [a]
Type of Surgery	n	%	n	%	p value
Endometrial Cancer	48	54.5	11	44.0	0.326 [b]
Ovarian Cancer	32	36.4	13	52.0	
Cervical Cancer	8	9.1	1	4.0	
HT					
No	15	17.0	3	12.0	0.759 [b]
Yes	73	83.0	22	88.0	
DM					
No	49	55.7	18	72.0	0.143 [b]
Yes	39	44.3	7	28.0	
CAD					
No	59	67.0	20	80.0	0.213 [b]
Yes	29	33.0	5	20.0	
HF					
No	79	89.8	24	96.0	0.454 [b]
Yes	9	10.2	1	4.0	

Table 1 continued.

Table 1. Preoperative medical status, baseline kidney functions, demographic and surgery characteristics of the patient with non-AKI and AKI.

Preoperative use of nephrotoxic drugs					
No	79	89.8	21	84.0	
Yes	9	10.2	4	16.0	0.480 [b]
ACEIs/ARBs					
No	27	30.7	8	32.0	
Yes	61	69.3	17	68.0	0.900 [b]
Diuretics					
No	30	34.1	9	36.0	
Yes	58	65.9	16	64.0	0.859 [b]
Preop chemo. drug use					
No	76	86.4	19	76.0	
Yes	12	13.6	6	24.0	0.225 [b]
Acetyl salicylic acid					
No	66	75.0	18	72.0	
Yes	22	25.0	7	28.0	0.762 [b]
Beta blockers					
No	57	64.8	15	60.0	
Yes	31	35.2	10	40.0	0.661 [b]
Baseline GFR ml/min/1.73 m^2					
<60	22	25.0	8	32.0	
≥60	66	75.0	17	68.0	0.484 [b]

AKI: acute kidney injury, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HF: heart failure, ACEIs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers, a: $p > 0.05$ not significantly different with Mann Whitney U test, b: $p > 0.05$ not significantly different with Chi-Square test/Fisher's Exact test.

detected in 72% of geriatric patients with AKI. The KDIGO distribution of patients with AKI is shown in Table 2.

In-hospital mortality was detected due to AKI in one of 7 patients who developed postoperative persistent AKI (mortality n=1, 4%) (Figure 1). Mortality was not detected in any of the patients in the transient AKI group.

While testing 90-day kidney functionality, a more than 25% decline in GFR was detected in 24% (n=6) of the geriatric patients with PO-AKI, 8% (n=2) of patients with transient AKI, and 16% (n=4) of patients with persistent AKI (Figure 1). There was no significant difference between the groups of patients who developed and did not develop AKI with preoperative baseline eGFR < 60 mL/

Table 2. Comparison of intraoperative and postoperative data of patients with non-AKI and AKI.

	Non-AKI		AKI		p value
	Mean ± SD Median (Range)		Mean ± SD Median (Range)		
Bleeding during surgery (mL)	502.84±531.12 250 (50-3000)		742.00±689.60 600 (100-3500)		**0.016** [a]
Total use of crystalloids during surgery (mL)	3244.32±980.01 3400 (1000-5700)		3584.00±1184.07 3500 (1700-6000)		0.284 [a]
Total use of colloids during surgery (mL)	682.73±286.29 500 (100-1500)		682.35±327.74 500 (100-1500)		0.976 [a]
Total urine output during surgery (mL)	462.32±289.30 400 (90-1500)		499.60±338.43 400 (150-1400)		0.986 [a]
Total use of fluid during surgery (mL/h)	882.25±257.12 845 (400-1741)		817.12±232.42 825 (338-1299)		0.329 [a]
Length of stay in PACU (days)	1.50±0.85 1 (1-5)		2.88±2.61 2 (1-13)		**0.001** [a]
Length of stay in hospital (days)	7.06±3.28 6 (4-22)		11.08±6.17 9 (5-27)		**<0.001** [a]
	n	**%**	**n**	**%**	**p value**
Blood product					
No	64	72.7	15	60.0	0.221 [b]
Yes	24	27.3	10	40.0	
Bowel procedures					
No	79	89.8	18	72.0	**0.045** [b]
Yes	9	10.2	7	28.0	
Intraabdominal fluid (ascites)					
No	80	90.9	18	72.0	**0.022** [b]
Yes	8	9.1	7	28.0	
Blood product					
No	64	72.7	15	60.0	0.221 [b]
Yes	24	27.3	10	40.0	
Bowel procedures					
No	79	89.8	18	72.0	**0.045** [b]
Yes	9	10.2	7	28.0	

Table 2 continued.

Table 2. Comparison of intraoperative and postoperative data of patients with non-AKI and AKI.

Hypotension during surgery					
No	70	79.5	17	56.0	**0.017** [b]
Yes	18	20.5	11	44.0	
Use of norepinephrine during surgery					
No	86	97.7	21	84.0	**0.021** [b]
Yes	2	2.3	4	16.0	
Use of ephedrine during surgery					
No	70	79.5	14	56.0	**0.017** [b]
Yes	18	20.5	11	44.0	
AKI stage distribution	**n**	**%**			
KDIGO stage					
1	17	15			
2	6	5.3			
3	2	1.8			
PO-AKI					
No	88	77.9			
Yes	25	22.1			
PO-AKI duration time					
≤ 48 hour	18	72.0			
> 48 hour	7	28.0			

PO: postoperative, PACU: post-anesthesia care unit, a: $p > 0.05$ not significantly different with Mann Whitney U test, b: $p > 0.05$ not significantly different with Chi-Square test/Fisher's Exact test.

min/1.73 m^2 as visible in Table 1. In the group of patients who developed PO-AKI, the mean surgical time was longer, and the amount of intraoperative bleeding was significantly higher. In addition, PO-AKI was found to be significantly higher in patients who underwent a surgical bowel procedure, had abdominal ascites, developed intraoperative hypotension, and needed vasopressor support. AKI stage of the patients who developed PO-AKI see in Table 2. It is statistically significant that the length of hospital and PACU stay were longer, postoperative diuretic use was higher, and the decrease in postoperative serum albumin level was higher in patients who developed PO-AKI compared to patients who did not develop AKI (Table 2). As a result of the logistic regression analysis created with the effective risk factors for PO-AKI, it was determined that the duration of surgery was an effective risk factor for AKI and a 1-minute increase in the surgical time increased the incidence of PO-AKI 1.007 times [($p < 0.05$), Table 3]. The distribution graph of the serum creatinine values of the patients at the control, postoperative 1-3rd day, discharge, and 90th day after discharge is shown in Figure 2.

Table 3. Logistic regression analysis of risk factors for PO-AKI.

Variable	B	OR	95 % CI		p value
Duration of surgery (min)	0.007	1.007	1.001	1.014	0.031*
Bleeding during surgery (mL)	0.000	1.000	0.999	1.001	0.843
Bowel procedures	0.050	1.051	0.240	4.596	0.947
Intraabdominal fluid (ascites)	1.337	3.809	0.982	14.782	0.053
Hypotension during surgery	0.891	2.438	0.816	7.280	0.110

B: Regression coefficient, OR: Odds Ratio, CI: Confidence Interval, * $p < 0.05$ significantly different with logistic regression analysis.

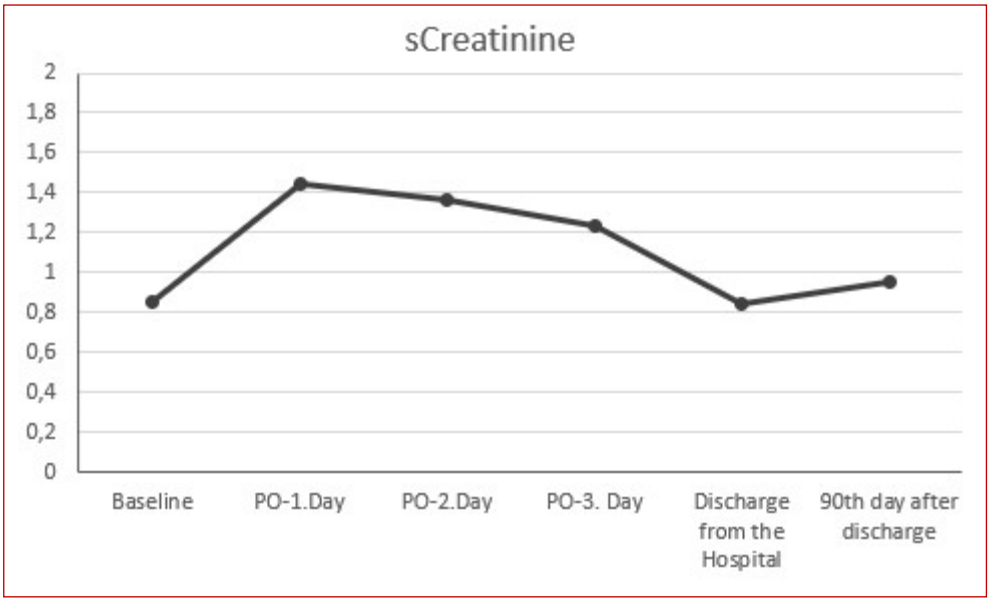

Figure 2. The curve of sCr levels of geriatric patients who participated in the study.

DISCUSSION

In our study, it was determined that the incidence of PO-AKI following gynecologic oncologic surgery among geriatric patients was 22.1%. PO-AKI was considered transient (< 48 hours) in 72% of the patients, whereas it was considered persistent (> 48 hours) in 28% of the patients. The development of PO-AKI was associated with surgical time, amount of intraoperative bleeding, patients undergoing bowel procedures, presence of intra-abdominal acid, intraoperative hypotension, vasopressor use, postoperative diuretic use, postoperative hypoalbuminemia, and prolonged PACU and hospital stay length.

Previous studies reported incidences of AKI as a common type of organ injury that occurs in patients who have undergone noncardiac surgery, with a frequency ranging from 3% to 39% (4,12,14,15). Studies demonstrated that the incidence of AKI is increasing in the geriatric patient population due

to the aging population and the corresponding increasing comorbidities, increasing prevalence of CKD and diabetes, polypharmacy, intravenous contrast agent use for imaging, and cardiovascular intervention procedures (6,7,9,10). AKI seen in 23–40% of elderly patients has a correlation between both CKD and mortality risk (6,9). The keys to recovering AKI prognosis are early diagnosis and early intervention.

Shen et al. analyzed AKI incidence at 5.76% for patients aged above 75 who had undergone major abdominal surgery in their retrospective cohort study, and it was demonstrated that the development of PO-AKI was higher in female patients (n = 22, 66.7%). Shen et al. found that the independent risk factors were older age, intraoperative hypertension, baseline GFR, serum albumin level, and the use of Hydroxyethyl starch (HES) + Non-steroidal anti-inflammatory drugs (NSAIDs) (6).

Privratsky et al. investigated PO-AKI incidence and risk factors according to age and gender in a multicenter retrospective study done in noncardiac, non-kidney/urologic surgery. In their study, it was determined that the incidence of PO-AKI was less prevalent in female patients aged below 50 (3.7%) than female (6.5%) and male (8.3%) patients aged above 50 and male patients below 50 (5.9%) (3). While the mean age of women over 50 was 66.7 years, emergency patients were included in this study. However, in our study, the mean age was 72.15, and only patients who underwent gynecological oncological surgery were included; therefore, this may explain the higher incidence of AKI in our study.

In a randomized controlled study with geriatric patients who underwent noncardiac surgery, Wu et al. evaluated the relation between PO-AKI and 3-year mortality and the incidence of PO-AKI was 15.5 %. In their study, the patients with AKI consisted of 85% with Stage 1, 10% with Stage 2, and 5% with Stage 3; however, it was not associated with 3-year mortality in elderly patients who underwent noncardiac surgery (16).

Li et al. conversely determined AKI incidence to be 39.0% in a retrospective study in which they analyzed patients aged 75 and over who developed AKI according to the KDIGO criteria and were hospitalized in the geriatric clinic. In those patients, the percentage of transient AKI was 41.4%, while the percentage of persistent AKI was 58.6% (11).

Vaught et al. analyzed the incidence of AKI in adult patients undergoing major gynecological surgery according to the Risk, Injury, and Failure; and Loss; and End stage kidney disease. (RIFLE) criteria at 13%. While the incidence of AKI was 5% in patients undergoing benign tumor surgery, it was 18% in patients with malignancy. In this retrospective cohort study, the average age of the patients who developed AKI was 60 years. Non-abdominal surgery patients were also included in the study, which had a younger patient population than our study (17).

There are various perioperative risk factors for the development of PO-AKI (18-21). Wu et al. found PO-AKI to be directly proportional to surgical time, total fluid infusion amount, cardiac complications, and length of hospital stay (16). Li et al. alternatively reported low hemoglobin levels; high blood urea, nitrogen, and uric acid levels; and patients who underwent mechanical ventilation as risk factors for the development of PO-AKI (11). Furthermore, in Shen et al.'s study, age, serum albumin level, baseline GFR, intraoperative hypotension, and use of HES+NSAIDs and HES+ furosemide were independent risk factors for the development of PO-AKI (6). Shaw et al. examined the association between intraoperative hypotension thresholds (MAP thresholds were ≤ 75, ≤65, and ≤ 55 mmHg) and the following two AKI subtypes (persistent and delayed) in a retrospective multicenter cohort study, and intraoperative hypotension was associated with persistent but not delayed AKI (22). Since our study was retrospective, we did not have the opportunity to determine the threshold value for MAP. The rates of both persistent and transient AKI in the patients

who developed and were treated for hypotension were significantly higher than in those who did not develop AKI.

Huepenbecker et al. reported that the percentage of AKI was higher after gynecologic surgery with enhanced recovery after surgery (ERAS) (13.1% versus 5.8%) in their study, in which they examined the incidence of PO-AKI after ERAS protocols in open gynecological surgery (23). In this study, bowel procedures, estimated blood loss, intraoperative PRBC transfusion, hypotension, vasopressor administration, surgical complexity of ovarian cancer, intraoperative administration, and higher mean intraoperative use of crystalloids and colloids were found in the patient group that developed PO-AKI as the factors that cause AKI. While the mean age of the patients who developed AKI in this study was 65, the mean age of the patients who developed PO-AKI was 72 in our study, and only patients with malignant and underwent open abdominal surgery were included in the study. The absence of reports of geriatric patients undergoing gynecologic oncologic major open abdominal surgery demonstrates that the incidence of PO-AKI is low in this patient population in our clinic.

Preoperative and/or postoperative hypoalbuminemia have been reported in studies of patients who developed AKI after major surgery (24,25). In our study, postoperative hypoalbuminemia developed at a higher rate in patients who developed AKI. In our study, the surgical complexity score was not considered; however, it can be interpreted that postoperative hypoalbuminemia may be associated with gynecologic oncologic surgical complexity.

Our study was a retrospective cohort study conducted at a single center covering the period from 2021 to 2022. While this allowed us to carefully examine the data from this specific center, we acknowledge that the narrow time range may limit the generalizability of our findings. Additionally, due to the restricted period, the sample size of the patients and the data collected may be relatively small. Nevertheless, we believe that our study provides valuable insights into this specific population and can serve as a foundation for further research in this area.

In conclusion, PO-AKI is a common but mostly temporary postoperative complication associated with chronic kidney disease, increased PACU and hospital stay in elderly patients after open abdominal gynecologic oncologic surgery. In order to ensure the prevention of the development of PO-AKI, it is imperative to ensure the continuity of oncological treatment in cancer patients and to prevent unwanted complications. It is important to reduce the incidence of AKI, especially in complex surgical procedures, by developing preventive strategies and team cooperation, ensuring the prevention of bleeding, avoiding unnecessary blood transfusion and nephrotoxic agents, ensuring hemodynamic stability, optimization of perioperative hydration, and close monitoring of sCr concentration in the early postoperative period.

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Disclosure Statement

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RESEARCH

COMPARISON OF BREAST CANCER PATIENTS OVER THE AGE OF 70 AND UNDER THE AGE OF 35

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Abstract

Introduction: Although breast cancer is a type of cancer that is mainly seen in advanced ages, its incidence is increasing in early ages in developing countries. While advanced age may create limitations in treatment due to the person's functional capacity and low life expectancy, treatments may be exaggerated at a young age due to the long-life expectancy and expectations from life. In this study, we aimed to examine possible differences in approach in two different age groups diagnosed with breast cancer.

Materials and Methods: The retrospective study included 123 patients over the age of 70 or under 35 who applied to our hospital's breast surgery outpatient clinic between 2016 and 2021 and were diagnosed with breast cancer. The patients' complaints at the outpatient clinic, the histopathological features of the tumor, and the treatments applied were compared.

Results: 64 (52%) of the patients included in the study were over 70 years old, and 59 (47%) were under 35 years old. Patients in both groups were applied to the outpatient clinic with a palpable mass. Histopathologically, invasive ductal cancer constituted the majority in both groups. While the elderly patients were lower grade and Estrogen receptor-positive, the younger patients were high grade, Estrogen receptor negative, and mostly triple negative.

Conclusions: Regardless of age, breast cancer is a cancer type that can have better results with early diagnosis. While making the treatment decision the decision should be made according to the characteristics of the tumor, comorbidity, and life expectancy, regardless of the patient's age.

Keywords: Breast Neoplasms; Aged; Age Distribution; Therapeutics.

INTRODUCTION

Breast cancer is a significant public health problem due to its high incidence; it is one of the most common types of cancer among women, with more than two million new cases diagnosed each year worldwide (1). Globocan, in its statistics for 2020, reported the number of new cases diagnosed with female breast cancer as 2.3 million (11.7%) (2). In addition , the incidence of breast cancer increases with age. For example, breast cancer is seen at a rate of 1/200 under the age of 40 and a rate of 1/14 in those over 70 (3). Breast cancer, which is seen more in advanced ages, starts to be seen at earlier ages. In the United States only %5 to %7 of all breast cancers are diagnosed in patients younger than 40 years (4). Age is one of the important prognostic features in breast cancer, and tumor characteristics and treatment options are other factors that play an important role in the prognosis. When young age and advanced age are compared regarding high mortality reasons, young people are diagnosed at a later stage and have more aggressive tumor characteristics(4). While advanced age is effective in prognosis due to numerous comorbidities and therefore limitations in treatment options, tumor subtypes with more aggressive features determine the prognosis in young people. While advanced age breast cancers sometimes remain under treatment due to comorbidities, younger patients may sometimes receive more treatment due to their expectations (marriage, childbirth, starting a business, long life expectancy). Apart from advanced age, female gender, early menarche, late menopause, late delivery, long-term use of hormones (birth control or hormone replacement), previous breast biopsy, genetic reasons (5-10%) are also among the risk factors of breast cancer(5). In the light of all this information, the diagnosis of breast cancer, which we know as a disease of advanced age, should not be overlooked in younger patients. Additionally, screening and treatment should not be missed also at advanced ages, benefit/harm calculation should be made when deciding on treatment, knowing that it can occur at an early age, and priorities for early age (pregnancy, long life desire and others) should be known. In this study, we aimed to emphasize the possibility of cancer as well as benign diseases in a very young patient who presents with a breast mass at a very young age, and that they should not be excluded from screening programs early due to the increase in life expectancy in older ages and that their treatment should be done as their comorbidities allow. For this purpose, patients under the age of 35 and over the age of 70 diagnosed with breast cancer who applied to the breast diseases outpatient clinic of our hospital were included in the study, and the patients' complaints, diagnosis stages, tumor location, clinical features of the tumor, pathological features and treatment options were compared. The advantages and disadvantages were evaluated by looking at the differences in the two age groups.

MATERIALS AND METHODS

Patients under the age of 35 and over 70 who applied to our hospital's breast diseases outpatient clinic between January 2016 and December 2021 and were diagnosed with breast cancer were retrospectively included in the study. Patients who were outside this age range, male gender, previously diagnosed with breast cancer, presenting with recurrence, and whose follow-up files could not be reached were excluded from the study. Information about the patients was obtained from the patient registry files and the hospital information system. The hospital ethics committee approved the study with the date of 08.08.2022 and approval number 241.

The patients were divided into two groups under 35 years old and over 70 years old. The complaint of admission to the outpatient clinic (mass, pain) and the location (right/left) of the mass were recorded. Tumor characteristics were classified according to the TNM system (primary

tumor size, axillary lymph node, and presence of distant metastases) according to the American Joint Committee on Cancer (AJCC) criteria. Tumor size was determined by ultrasonography (T1, T2, T3, and T4). Other radiological methods used for diagnosis (mammography, magnetic resonance), additional radiological methods (PET-CT), and the radiological status of the axilla were evaluated. According to the biopsy results, tumor histological type (in situ, invasive ductal, invasive lobular, and other), grade (I, II, or III), estrogen (ER), progesterone receptor (PR) status, and Her2 status were determined. All patients were discussed in the tumor council, and additional examinations and treatments were decided. Patients receiving neoadjuvant and/or adjuvant therapy were classified according to their treatment regimen. The type of surgery, breast-conserving surgery (BCS), simple mastectomy (SM), reconstructive procedures, sentinel lymph node sampling to the axilla (SLNB), and axillary dissection (AD) were classified in patients who received surgical treatment. Patients' hormone therapy and radiotherapy treatment status (whether they received it or not) were also categorized.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA). Variables are presented as mean±SD or median (range, interquartile range [IQR]) for continuous data and as a proportion for categorical data. Categorical parameters were analyzed with the Chi-square test. The conformity of continuous variable to normal distribution was assessed with the Kolmogorov-Smirnov test. The area under the curve (AUC), sensitivity and specificity values were calculated. Values of $p<0.05$ and $p<0.01$ were taken as significance levels. Two-sided p values <0.05 were considered statistically significant.

RESULTS

While 64 of the 123 patients included in the study were in an advanced age group, the rest 59 patients were in the younger age group. The characteristic features of the patients are given in Table 1. The mean age was 75 ± 4.5 in the advanced age group and 31 ± 3 in the younger age group. Considering the family histories, breast cancer was present in the first-degree relatives of 10 patients in the advanced age group and 9 patients in the younger age group. Genetic tests were performed only in the young patients, and it was determined that three patients had BRCA 1 and three patients had BRCA 2 mutations. Breast cancer was detected more in the left breast in both groups. It was observed that both groups applied to outpatient clinics more freuquently with a palpable mass. T2 (20-40 mm) was more common in the advanced age group (32 patients), and also T2 was more common in the younger age group (31 patients). In the axilla examination, the younger group came to the outpatient clinic with clinical and radiological positive results.

When the tumor histological types were examined, both groups had a high probability of invasive ductal cancer. It was found to be 78.1% above the age of 75 and 88.1% under the age of 35, respectively. When looking at other cancer types, mucinous cancers were also found in the advanced age group. When the molecular subtype was evaluated, ER positivity was mostly positive in the advanced age group (84.3%), while it was positive in 55.9% of the young age group, and this was observed to be statistically significant ($p<0.01$). Considering the progesterone receptor positivity, 71.8% was positive in the advanced age group, while this rate was 34.4% in the young age group, which was significantly different ($p<0.01$). Her2 receptor positivity was found to be lower in advanced age,and a statistical difference was observed ($p<0.01$). Triple negative was positive in 54 patients (84.3%) in the advanced-age breast cancer patients, it was positive

Table 1. The characteristic features of the patients

	Group I	Group II	p
n	64	59	
Age*	75 (± 4.5)	31(± 3)	
Family history	10	9	
BRCA I/II	0	6	
Pathological diagnosis n(%)			
Ductal carcinoma	50	52	
Lobular carcinoma	1	5	
Other	13	2	
T n(%)			0,615
T1	9	14	
T2	39	28	
T3	14	17	
T4	2	0	
Tumour grade n(%)			
G1	25	8	
G2	30	41	
G3	9	10	
ER positivity n(%)	54	33	p<0.01
PR positivity n(%)	46	21	p<0.01
Molecular subtype n(%)			
Luminal A	30	16	
Luminal B Her2 +	19	14	
Her2 -	8	16	
Her2 +	7	13	p<0.01
Triple -	54	33	p<0.01
Axillary metastatic lymph node n(%)	32	34	
Surgical procedure n(%)			
- breast coservative surgery	41	42	
- modified radical mastectomy	23	17	
SLNB			p<0.01
pozitif	12	15	
negative	29	23	
Neoadjuvant chemotherapy	13	31	p<0.01
Hormonotherapy	50	31	p<0.01

* MEAN±SD, SLNB: Sentinel lymph node biopsy, ER: Estrogen receptor, PR: Progesterone receptor

in 33 patients (67.7%) in the younger age group, and a statistical difference was again observed ($p<0.01$). While patients in the advanced age group were mostly Grade I (39%), it was observed that more Grade II (69.4 %) and III (16.9%) tumors were found in the younger age group.

While the neoadjuvant treatment was 52.5% in young people, this rate was 20.3% in the advanced age group. Also, hormone therapy was significantly higher in the advanced age group (78%), and it was determined to be 31(52.5%) patients in the younger age group. Considering the chemotherapy regimens, there was no difference in treatment in both groups. Cardiotoxic drugs were avoided only in elderly patients with insufficient cardiac function (usually by echo testing). On the other hand, especially in patients planning pregnancy, the gonadotropin-releasing hormone agonists(GnRHa) were given to 34.4% of the patients in the young age group.

Considering the surgical treatment options, breast-conserving surgery (71.1%) was preferred more in younger patients, while reconstructive procedures were added to 6 out of 17 patients who underwent a mastectomy. However, when the older patients were compared with the younger age group, mastectomy was more common (35.9% and 28.8%, respectively). While all patients treated with breast-conserving surgery received radiotherapy, only two elderly patients, due to comorbidity and two patients due to good tumor characteristics, did not receive radiotherapy. In the advanced age group, 27 patients continued their treatment with only hormone therapy after surgery (42.1%), while 21 patients continued their treatment with both hormone therapy and chemotherapy (32.8%).

DISCUSSION

We know that breast cancer, which we know as a disease of old age, is now more common in younger ages. However, with the prolongation of life expectancy, we should not exclude the elderly population from follow-up since the success is achieved with early and complete treatment in breast cancer. With this study, we aimed to emphasize that there are no significant differences in the examinations and treatments performed at the onset of the disease between the advanced age and the young age, and that we should not neglect the treatment of elderly patients due to possible comorbidities.

In preventing breast cancer, besides the risk factors that we can change, there are risk factors that we cannot change such as age and genetics risk factors. Although breast cancer was previously considered as a disease of advanced age, follow-up should be started early in cases with a genetic predisposition. Today, with the sensitivity of individuals and health personnel, early diagnosis has increased, and mortality rates have started to decrease with innovations in treatment. While mortality in young patients with breast cancer is due to cancer, it is due mainly to comorbidities in older patients. However, elderly patients should undergo surgical treatment just like younger patients, as with other cancers (6).

Considering the complaints of the patients who applied to the clinic, it was seen that both age groups applied with a higher rate of palpable mass. This situation shows that self-examination is essential in the diagnosis of breast cancer. However, there are also opposing views to this view. Breast examination may increase anxiety in individuals, or unnecessary biopsies may be performed by mistaking it for a false positive mass. Diagnosis is usually delayed since, in our country, routine mammography screenings are not performed under the age of 40, and also that the breasts become extremely dense in the 40s. The thought that palpable masses on physical examination may be more benign in patients under 35 years of age also leads to a late diagnosis. It is an advantage for older patients to be included in screening mammograms.

Thus, they are diagnosed at an early stage and receive less aggressive treatments. However, today's life expectancy has increased, and the removal of advanced-age patients from follow-up in the early period causes them to present with more advanced cancer stages later on (3). Although there are no studies on mammography screenings in advanced age group (over 75 years) patients, observational studies suggest that continuing screening is crucial in the early diagnosis of breast cancer. It has also been reported in these observational studies that it is beneficial to continue screening every two years in patients with an expected life expectancy of more than ten years (7). According to breast cancer screening programs in our country, patients between the ages of 40-69 are followed up with mammography once every two years (8). On the other hand, in international screening programs, screening starts at the age of 35-40 and is conducted once a year. Therefore, in the advanced age group, each patient should be evaluated individually, and the benefits and disadvantages of the screening should be determined. Furthermore, regardless of age group, self-examination should be taught (9,10).

Tumors were mostly detected in the left breast in both groups. In addition, in both groups, the upper outer quadrant was the most common tumor localization, and it is seen in the literature that the upper outer quadrant is the most common location (11).

While the axilla is positive with delayed diagnosis in elderly patients, we encounter axilla positivity in young patients due to the aggressive features of the tumor (3). In our patients, 50% of the advanced age group and 57.6% of the young age group were diagnosed as axilla positive at the time of application.

Considering the histological features of the tumor, the most common type of breast cancer in both groups was invasive ductal cancer, which was consistent with the literature. Lobular cancers are the second most common breast cancer, primarily seen in the younger age group. In the advanced age group, mucinous cancers, known to have a better prognosis, were the third most frequent after ductal and lobular cancers. When we look at the tumor's molecular characteristics, lower grade, ER/PR positive, and Her2 negative cases are more common in the advanced age group. In comparison, triple-negative or Her2-positive tumors and tumors with a higher grade are seen more commonly in younger patients (4). In our study, the grade was higher in young patients and lower in elderly patients, which was consistent with the literature. A study by Kroman et al. with 10,356 women from Denmark found that breast cancer patients younger than 35 years had a higher lymph node positivity rate (51%) (12). In a study, ER positivity increases with increasing age (83% between the ages of 55-64, while 91% over the age of 85) (3). Again, in a study by Zhang et al. in which elderly and young breast cancers were compared, ER positivity was found to be more prominent in the advanced age group(13).

Today, neoadjuvant chemotherapy is an inevitable option for the patient with the proper indication. It has significant benefits such as protecting the patient's breast, seeing the response to treatment, saving time for genetic tests, and, most importantly, reducing the possibility of axillary dissection. Neoadjuvant treatments come to the forefront of cancer treatment, as younger patients have more aggressive histopathological features and usually present with axilla positivity.

When deciding on treatment in young patients, the patient's expectations due to the patient's age, social status, marriage, or birth status are considered. Genetic counseling should be conducted in young patients with a family history, bilateral breast cancer and triple-negative cancers (14). Considering that there may be a pregnancy plan in early-stage young breast cancer patients, embryo, mature/immature oocyte, and ovarian tissue preservation

can be provided. Each method has its advantages and disadvantages. GnRHa, is still an experimental treatment, is an noninvasive, easily applicable method that does not require a donor (sperm) and does not cause chemotherapy delay either (15). As it was still an early stage, ovarian preservation with GnRHa was achieved to 21 of our patients who were planning pregnancy.

Comorbidities, and life expectancy, regardless of age, should be considered when planning treatment in elderly patients. Anesthesia risks should be determined, and the treatment decision should be made accordingly. In elderly patients, when the treatment decision is made based on age alone, the patient may receive inadequate treatment. In patients at risk of receiving chemotherapy due to the possible toxic effects of chemotherapy (cardiac, hepatic, etc.), In one analysis of women >70 years receiving chemotherapy, the rate of febrile neutropenia was 19% and the treatment discontinuation rate was 23% . Adjuvant trastuzumab is associated with cardiac toxicity(16)

Treatment can also be started with hormone therapy in appropriate indications. Older women are more likely to have ER-positive disease, which is associated with improved prognosis and is treatable with adjuvant endocrine therapy. (16) However, in a review comparing surgery and hormone therapy (tamoxifen) in which seven randomized controlled studies were summarized, there was no difference in overall survival. However, there was a significant difference in progression-free survival (10).

Regarding surgical treatment options, breast-conserving surgery (BCS) is more prominent in young patients. At the same time, mastectomy comes to the forefront in elderly patients to reduce the possibility of lactation and radiotherapy. When breast-conserving surgery is performed in the early stage and estrogen receptor-positive patients in the advanced age group, locoregional recurrence is not high. Adding hormone therapy and/or radiotherapy to the treatment further reduces the possibility of recurrence. In our patients, BCS was chosen in 71.7% of young patients, while mastectomy was chosen in 35.9% of elderly patients. Since local recurrences are more common after BCS than mastectomy in young patients with aggressive tumor characteristics, radiotherapy should be inevitable in this age group, especially during treatment (17). Again, since there may be aesthetic concerns in this age group, the patient should be informed about the surgical and reconstructive procedures (repair with implant, expander, flap). In our patients, reconstruction was performed with implants in 2 patients and flaps in 4 patients in the young age group.

Axillary approach is essential in the treatment and prognosis. Today, axilla interventions are very minimal. Regardless of age, sentinel lymph node sampling (SLNB) can be performed by controlling the response to treatment in patients with positive axilla before neoadjuvant therapy (18). Axillary dissection with severe comorbidities such as lymphedema is avoided. While lymphedema is seen in 21.4% of axillary dissection, it is seen in 0-7% with SLNB (19,20). Considering the recent studies in patients with advanced age and comorbidities, if the axilla is thought to be clinically and radiologically negative, it is shown that treatment can be continued without any intervention for the axilla in patients with early-stage and estrogen receptor-positive, and it does not have a negative effect on survival (21). Since the elderly patient group is a heterogeneous group, treatment planning should be done by considering the center and the facilities of that center while planning the treatment.

Radiotherapy is inevitable after BCS and can be added according to the patient's stage in patients who have undergone mastectomy (22). There are studies in which advanced-age patients were ignored because of complications such as cardiac morbidity, secondary malignancies, rib fracture, and tissue necrosis. In the CALGB 9343 study, when BCS patients who received only tamoxifen without radiotherapy and BCS patients who received both

radiotherapy and tamoxifen were compared, local recurrence was found to be more common in the group that did not receive radiotherapy. However, both groups had no difference in overall survival and distant metastasis (23). Another study stated that only endocrine treatment could be given in patients over 65 years, with tumors smaller than 3 cm, node-negative, and hormone receptor-positive (24).

Many studies have shown that, except for rare cases, breast cancer has a good prognosis in older patients, while it has a worse prognosis in younger patients. Although the duration of local recurrence could not be evaluated in our study due to the short follow-up period, recurrence is seen in the literature at a higher rate in patients under 45 years of age. Again, it was shown that the probability of locoregional recurrence increases by 7% with each decrease in age under 40 years (25).

Our study showed that screening programs should be started at an earlier age in our country in order to diagnose at an earlier stage. Individuals who cannot enter screening programs at a young age should be taught the importance of self-examination, competent health personnel should be taught about the importance of examination, and it is necessary to prevent elderly patients from leaving screening programs in the early period due to the prolongation of their life span. Due to the increase in life expectancy today, treatment should not be planned incompletely by looking only at age, even in elderly patients who do not have comorbidities. In patients with comorbidities, less invasive surgeries (breast conserving surgery or sentinel lymph node sampling) or medical treatments that may have fewer side effects (such as hormone therapy) can be applied. Perhaps, it may be a mandatory health policy to control whether mammography is performed in patients who come for their routine follow-ups (such as blood pressure or blood sugar measurements). We hope that future studies and developing technological methods will provide an earlier diagnosis.

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RESEARCH

ASSOCIATION OF DUAL ANTIPLATELET THERAPY WITH ADVERSE OUTCOMES IN OCTOGENARIAN PATIENTS WITHOUT ATRIAL FIBRILLATION WHO UNDERWENT PERCUTANEOUS CORONARY INTERVENTION

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Abstract

Introduction: Dual antiplatelet therapy is routinely recommended to prevent stent restenosis and reduce ischemic complications after percutaneous coronary intervention. Octogenarians have a higher ischemic burden than younger patients on moreover they have a higher risk of bleeding. Therefore, we intended to analyze and compare the efficacy and safety of clopidogrel and the potent P2Y12 inhibitor ticagrelor in octogenarians undergoing percutaneous coronary intervention without atrial fibrillation.

Materials and Methods: This retrospective cohort study analyzed records from three local research hospitals. In our study, 226 patients aged 80 years or older undergoing had coronary intervention for both acute coronary syndrome and stable coronary artery disease were included after the exclusion criteria had been applied between January 2019 and April 2021.

Results: The median dual antiplatelet therapy duration was similar between two groups. 84.3% of patients in the clopidogrel group and 56.7% of patients in the ticagrelor group had no bleeding at one year follow-up, which was statistically significant ($p<0.001$). The minor bleeding rate was significantly higher among patients receiving ticagrelor (21.7%) compared to those receiving clopidogrel (7.2%; $p=0.02$). Also, the rate of major bleeding was significantly higher in patients receiving ticagrelor (20.0%) than in patients receiving clopidogrel (7.8%; $p<0.010$). Rates of all-cause death and ischemic endpoints were similar in both treatment groups at one year follow-up.

Conclusions: Clopidogrel and ticagrelor were similar in terms of all-cause mortality and ischemic events with increased rates of all types of bleeding in patients treated with ticagrelor.

Keywords: Octogenarians; Ticagrelor; Clopidogrel; Hemorrhage; Dual Anti-Platelet Therapy; Aged.

INTRODUCTION

Coronary artery disease (CAD) is the most common manifestation of atherosclerotic vascular disease. Despite pharmacological and interventional advances, CAD remains the primary cause of death worldwide (1). As the incidence of CAD increases with age and longevity continues to improve, we see more elderly people in cardiology clinical practice. The incidence of elderly patients with CAD is increasing as the prevalence of CAD increases with age, and longevity continues to increase (2). Percutaneous coronary intervention (PCI) relieves symptoms in patients with CAD and is a life-saving intervention for ACS, and is being performed extensively all over the world. Advanced age is an exclusion criteria in most of the clinical trials (3,4). Octogenarians have higher ischemic burden, more ischemic risk factors and increased risk of bleeding, than their younger counterparts (5). This increase in risk is also due to the increasing burden of comorbidities such as hypertension, chronic kidney disease, diabetes mellitus, which increases with age. Since atherosclerosis is a progressive disease by its nature, an increase in thrombotic events is observed with the increase of atherosclerotic plaques in elderly patients. Also, coagulation disorders and susceptibility to bleeding increase in elderly patients and care should be taken in the use of antithrombotic drugs in these patients.

Dual antiplatelet therapy (DAPT), which is acetylsalicylic acid in combination with a P2Y12 inhibitor, should be used to prevent stent restenosis, reoccurring ischemic events and stent thrombosis in patients after PCI. Guidelines recommend using potent P2Y12 inhibitors in CAD patients with acute coronary syndrome (ACS) and clopidogrel in stable coronary artery disease (SCAD) (3). Of the P2Y12 inhibitors, ticagrelor and clopidogrel can be used in patients over 75 years of age. Challenges remain in determining the best DAPT and duration due to drug compliance problems with increasing age, high ischemic burden, and increased risk of bleeding. Also new stent technologies allow us to use shorter-duration DAPT so we should also consider the type of stent before deciding the duration of DAPT. In this study, we compared the safety and efficacy of clopidogrel and the more potent P2Y12 inhibitor ticagrelor in patients 80 years and older, undergoing PCI.

MATERIALS AND METHODS

This study is a retrospective cohort study that analyzed the records of three local research hospitals. A total of 620 octogenarian patients who underwent PCI between January 2019 and April 2021 were screened, and 226 patients aged ≥ 80 years were recruited to the study after the exclusion criteria had been applied. The follow-up period was one year. The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Hospital Research Ethics Committee.

Patients aged 80 years and older who applied to the hospital with ACS or SCAD and underwent coronary stenting were included in the study. Patients with atrial fibrillation (AF) and those who started AF in their 1-year follow-up were excluded from the study; furthermore, patients with other indications that require anticoagulant therapy were not included. Intercalarily, in this study, exclusion criteria included patients having a history of severe intolerance or allergy to one of the study drugs (acetylsalicylic acid, clopidogrel, or ticagrelor), known intracranial aneurysm, cerebral arteriovenous malformation or intracranial mass, active bleeding at treatment initiation, thrombolytic therapy, an initial platelet count < 100,000 per microliter of blood, an Hb level < 10 g/dl, receiving oral anticoagulation, severe kidney failure requiring dialysis, severe liver dysfunction, mechanical complications due to ACS, and use of the following drugs in combination: antifungal agents, antiepileptic agents and specific antivirals.

The comorbidity status of the patients was calculated using the Charlson comorbidity index (6). The primary endpoint of our study was bleeding, as defined by the Bleeding Academic Research Consortium (BARC) (7). Secondary endpoints included minor and major bleeding, target vessel revascularization (TVR), non-fatal stroke, and all-cause mortality within 1 year of follow-up. Minor bleedings include ecchymosis of the skin, bleeding gums, and nosebleeds. Major bleeding is defined as life-threatening severe bleeding and this includes intracranial and gastrointestinal bleeding, hemoglobin decrease > 3 g/dL, significant bleeding requiring blood transfusion, and fatal bleeding (7). Trauma-related hemorrhages were excluded from the analysis.

All the statistical analyses in this study were conducted using STATA software (version 17.0; Stata Corp., College Station, TX). Continuous data are presented as mean ± standard deviation, and quantitative variables are presented as numbers and percentages. Student's t-test if continuous variables are parametric, Mann-Whitney test was used to detect statistical differences. In addition, chi-square test and Fisher's exact test were used to compare categorical data. All tests were two-sided, and p-values <0.05 were considered statistically significant. Predictors of major bleeding were determined using univariate and multivariate regression analyses. Variables that are significant in the literature and clinically were selected and analyzed.

RESULTS

Our study included a total of 226 patients, of which 166 patients were in the clopidogrel group and 60 patients were in the ticagrelor group. The mean patient age was 84.6 ± 3.4 and 54.4% of the patients were male. Diabetes mellitus, hypertension, stroke, heart failure rates and Charlson comorbidity index were similar between the two groups. Significantly there were more active smokers in the ticagrelor group than the clopidogrel group ($p < 0.001$). Approximately half of the patients in the clopidogrel and ticagrelor groups had non-ST-elevation myocardial infarctions (59.6% and 53.2%), respectively.

The median DAPT duration was 276 days in the clopidogrel group and 271 days in the ticagrelor group and was similar. The blood parameters of the two groups were similar. Table 1 shows the basic demographic and clinical characteristics of the patients.

No bleeding (BARC 0) was seen significantly more often in the clopidogrel (85.5%) group compared with the ticagrelor group (56.7%; $p<0.001$). Bleeding that did not require medical intervention (BARC 1) was observed in 4.8% of patients using clopidogrel and in 21.7% of those using ticagrelor. Bleeding that required medical intervention (BARC 2) was observed in 3.6% of patients using clopidogrel and in 8.3% of those using ticagrelor. Overt bleeding with hemoglobin drops of 3–5 g/dL and bleeding requiring transfusion (BARC 3a) were observed in 5.4% of patients receiving clopidogrel and 11.7% of those receiving ticagrelor. A drop in hemoglobin < 5 g/dL and overt bleeding requiring surgical intervention for control (BARC 3b) was observed in one patient in the clopidogrel group, and intracranial hemorrhage (BARC 3c) was observed in one patient in the clopidogrel group. Fatal bleeding (BARC 5a) was seen in only one patient in the ticagrelor group. Minor bleeding was significantly more prevalent in the ticagrelor group (25%) than in the clopidogrel group (7.2%; $p=0.01$). Major bleeding was also significantly more prevalent in the ticagrelor group (18.3%) than in the clopidogrel group (7.2%; $p=0.017$). The rates of stroke, TVR, and all-cause death during the 1-year follow-up period were similar between the treatment groups. All crude outcomes, including BARC bleeding, minor and major bleeding, stroke, TVR, and all-cause mortality, are shown in Table 2.

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	All (n=226)	**Clopidogrel Group (n=166)**	**Ticagrelor Group (n=60)**	**p value**
Age, mean (SD)	84.6 (3.4)	84.9 (3.7)	83.7 (2.4)	0.012
Sex, n (%)				
Male	123 (54.4)	83 (50.0)	40 (66.7)	0.026
Female	103 (45.6)	83 (50.0)	20 (33.3)	
Diabetes Mellitus, n (%)	76 (33.6)	52 (31.3)	24 (40.0)	0.22
Hypertension, n (%)	183 (81.0)	131 (78.9)	52 (86.7)	0.19
Current smoker, n (%)	42 (18.6)	22 (13.3)	20 (33.3)	**<0.001**
Heart Failure, n (%)	9 (4.0)	6 (3.6%)	3 (5.0)	0.64
Left Ventricular Ejection Fraction, n (%)	51.5 (9.5)	51.2 (9.4)	52.2 (9.7)	0.51
Stroke, n (%)	33 (14.6)	27 (16.3)	6 (10.0)	0.24
Previous PCI, n (%)	41 (18.1)	37 (22.3)	4 (6.7)	**0.007**
Previous CABG, n (%)	20 (8.8)	18 (10.8)	2 (3.3)	0.079
Presentation Type, n (%)				
STEMI	84 (37.2)	58 (34.9)	26 (43.3)	0.46
Non-STEMI	131 (58.0)	99 (59.6)	32 (53.3)	
Stabile Angina	11 (4.9)	9 (5.4)	2 (3.3)	
Access Side, n (%)				
Femoral	214 (94.7)	156 (94.0)	58 (96.7)	0.43
Radial	12 (5.3)	10 (6.0)	2 (3.3)	
PRECISE DAPT Score, mean (SD)	29.8 (8.8)	30.3 (9.0)	28.5 (8.2)	0.19
DAPT duration (Days), mean (SD)	275.2 (124.4)	276.6 (123.6)	271.4 (127.8)	0.78
Charlson Comorbidity Index, mean (SD)	7.5 (1.8)	7.6 (1.8)	7.3 (1.8)	0.19
DAPT switch (%), n (%)	**30 (13.3)**	**1 (0.6)**	**29 (48.3)**	**<0.001**
DAPT Dyspnea, n (%)	8 (3.5)	1 (0.6)	7 (11.7)	**<0.001**
Systolic Blood Pressure, mean (SD)	125.8 (21.6)	124.2 (20.7)	130.4 (23.5)	0.055
White Blood Cell Count, mean (SD)	9.7 (3.6)	9.8 (3.8)	9.4 (2.9)	0.48
Hemoglobin, mean (SD)	12.7 (1.6)	12.6 (1.5)	12.8 (1.8)	0.32
Platelet Count, mean (SD)	230.9 (68.0)	231.8 (66.9)	228.6 (71.5)	0.75
Creatinine, mean (SD)	1.07 (0.3)	1.05 (0.3)	1.1 (0.2)	0.31
Total Cholesterol, mean (SD)	172.8 (43.8)	174.5 (46.1)	167.9 (36.5)	0.34
LDL Cholesterol, mean (SD)	108.1 (39.9)	110.1 (41.6)	102.3 (34.4)	0.21

CABG: coronary artery bypass graft, DAPT: dual antiplatelet therapy, LDL: low-density lipoprotein, PCI: Percutaneous coronary intervention

Table 2. Crude Outcomes of the Study Population

	All (n=226)	Clopidogrel Group (n=166)	Ticagrelor Group (n=60)	p value
BARC, n(%)				
0	176 (77.9)	142 (85.5)	34 (56.7)	
1	21 (9.3)	8 (4.8)	13 (21.7)	
2	11 (4.9)	6 (3.6)	5 (8.3)	
3a	16 (7.1)	9 (5.4)	7 (11.7)	**<0.001**
3b	1 (0.4)	1 (0.6)	0 (0.0)	
3c	1 (0.4)	1 (0.6)	0 (0.0)	
5a	1 (0.4)	0 (0.0)	1 (1.7)	
Minor Bleeding, n (%)	27 (11.9)	12 (7.2)	15 (25.0)	**0.001**
Major Bleeding, n (%)	23 (10.2)	12 (7.2)	11 (18.3)	**0.017**
Stroke, n (%)	21 (9.3)	17 (10.2)	4 (6.7)	0.41
Target Vessel Revascularization, n (%)	12 (5.2)	9 (5.3)	3 (5)	0.61
All-cause Mortality, n (%)	31 (13.7)	23 (13.9)	8 (13.3)	0.92

Table 3. Results of Multivariate logistic regression analyses of major bleeding

	Odds Ratio	[95% Conf. Interval]		p value
		Lower	Upper	
Age	1.114	0.968	1.282	0.132
Ticagrelor	6.257	2.225	17.592	**0.001**
Stroke	2.576	0.783	8.477	0.119
Systolic Blood Pressure	0.977	0.954	1.000	0.046
Heart rate	1.007	0.971	1.044	0.705
Left Ventricular Ejection Fraction	1.012	0.957	1.071	0.670
White Blood Cell	1.000	1.000	1.000	0.905
Hemoglobin	0.681	0.509	0.911	**0.010**
Platelet	1.000	0.993	1.007	0.995
Creatinine	0.901	0.263	3.082	0.868

In the multivariate analysis, independent predictors of major bleeding included ticagrelor use (OR = 6.2; 95% CI: 2.2–17.5), systolic blood pressure (OR = 0.9; 95% CI: 0.9–1.0), and hemoglobin (OR = 0.7; 95% CI: 0.5–0.9). Age, stroke history, heart rate, left ventricular ejection fraction, white blood cell count, platelet count, and creatinine were not associated with major bleeding (Table 3). The results of the univariate and multivariate logistic regression analyses of major bleeding are shown in Figure 1.

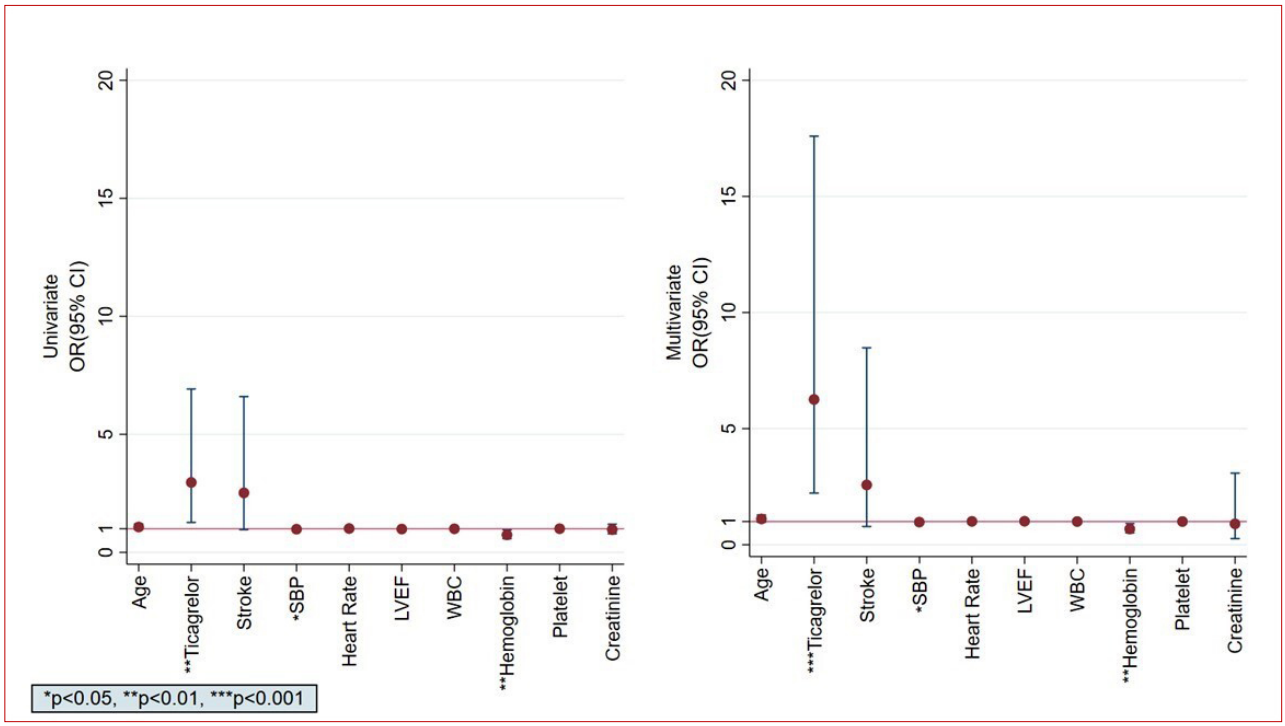

Figure 1. Univariate and Multivariate Logistic regression results for major bleeding.
SBP: Systolic blood pressure; LVEF: Left ventricular ejection fraction; WBC: White blood cell

DISCUSSION

Octogenarians are a fragile group and are often omitted from clinical trials. In this study, we intended to find out the effect of DAPT in octogenarians. We enrolled patients aged 80 years or older and were given DAPT following PCI and divided them into two groups according to their use of clopidogrel and ticagrelor. The most important exclusion criteria in this study were patients with AF and those requiring additional anticoagulant therapy. We did not find any significant difference between the clopidogrel and ticagrelor groups in terms of all-cause death, stroke, and TVR rates in our study. However, the ticagrelor group had higher minor and major bleeding rates. In this study, ticagrelor use was the most significant independent risk factor for major bleeding in octogenarians. In addition, patients in the ticagrelor group developed a higher rate of dyspnea rate than the patients in clopidogrel group which was the main reason for switching from ticagrelor to clopidogrel. The switching rate was 48,3% in ticagrelor group. Nuisance and minor bleeding were also more prevalent in the ticagrelor group.

Octogenarians have both tendency to thrombosis and bleeding at the same time. Vascular wall flexibility, coagulation, hemostatic system, and endothelial functions deteriorate with age. In addition, changes in endothelial functions, changes in metabolism and increase of the atherosclerotic burden also pose a risk in the elderly. For this reason, in elderly patients, medical treatments should be arranged with a profit-loss logic, considering the balance between bleeding and thrombosis. This can be explained with a yin-yang philosophy; if the potency of the antiplatelet drug increases, the risk of thrombosis decreases while the risk of bleeding increases, on the other hand

if the potency of the antiplatelet drug decreases, the risk of thrombosis increases while the risk of bleeding decreases. Increasing PCI rates in elderly patients have increased the need for DAPT, which has put clinicians in a difficult choice process. While considering the DAPT choice in elderly patients, the safety rather than the potency of the drug can be used as a criterion.

Previous studies have shown that clopidogrel and aspirin reduce the risk of myocardial infarction (MI), stroke, and death (8). Therefore, DAPT including clopidogrel is widely used to reduce cardiovascular events. The efficacy of aspirin and clopidogrel in patients with ischemic events has been proven and its safety has been demonstrated in this study. It is expected that the efficiency will increase and the reliability will decrease when the two are used together. Newer P2Y12 inhibitors, including ticagrelor and prasugrel, have stronger antiplatelet inhibitory effects than clopidogrel, which may increase bleeding while reducing thrombotic events (8-10). However, in elderly patients (>75 years old) prasugrel has not shown any net clinical benefit and is not recommended; only clopidogrel and ticagrelor should be used in this group (11). Since our study included patients aged 80 and over, clopidogrel or ticagrelor added to aspirin constituted the DAPT regimen.

A study of 18,624 patients with a median age of 62 found that ticagrelor was more effective than clopidogrel in reducing the rates of vascular death, stroke, and MI in patients with ACS (9). Similarly, in another study that included patients with a median age of 65 and previously implanted coronary stent, ticagrelor reduced vascular events compared to clopidogrel but increased the risk of major bleeding (12). Data on DAPT with ticagrelor for octogenarians remain insufficient, as this population is not included in randomized clinical trials, as mentioned above.

A prospective randomized study (POPular AGE trial) which included elderly patients (aged > 70 years), compared the efficacy and safety of clopidogrel versus ticagrelor or prasugrel in patients with non-ST-elevation ACS (13). 95% of patients in ticagrelor or prasugrel group received ticagrelor as a treatment so this study was more like a clopidogrel versus ticagrelor study. There was no difference between clopidogrel and ticagrelor in terms of mortality, stroke, or MI risk in elderly patients. Major bleeding and fatal bleeding were significantly less prevalent in the clopidogrel group than in the ticagrelor group. The median patient age in that study was 77 years, and only 36% were octogenarians. Our study is consistent with the POPular AGE trial as there was no difference between clopidogrel and ticagrelor group in terms of mortality, stroke, and TVR rates; however, major and minor bleeding were significantly less prevalent in the clopidogrel group than in the ticagrelor group. In the POPular AGE trial, only 53% of patients completed ticagrelor treatment (13). Due to significant bleeding and dyspnea, ticagrelor treatment compliance was low, especially in elderly patients. In our study, the rate of switching from ticagrelor to clopidogrel was high among octogenarians (48.3%), similar to the POPular AGE trial.

In a recently randomized trial; SCAD patients who underwent PCI, ticagrelor and clopidogrel had similar efficacy. Considering the 30-day bleeding rates, ticagrelor significantly increased minor bleeding but there was no significant effect on major bleeding (14). Patients with SCAD correspond to nearly 5%, therefore, subgroup analysis of patients with SCAD could not be performed in our study. However, since it was evaluated for all patient groups, ticagrelor increased minor bleeding as well as major bleeding in our study.

In contrast to trials mentioned above, a multinational registry study comparing ticagrelor and clopidogrel in 1,717 patients aged > 80 years found that bleeding risk was not a contraindication for choosing a more potent antiplatelet after ACS. According to this registry, ticagrelor reduced

the incidence of all-cause death compared to clopidogrel, without a statistically significant increase in major bleeding (15). Ticagrelor's hazard ratio for bleeding was 1.49, although this was not statistically significant due to the low number of events.

There are several scoring systems to predict the bleeding risk of patients on dual antiplatelet and/or anticoagulant therapy. Current guidelines recommend using the PRECISE-DAPT score to estimate bleeding risk and duration of DAPT, which is a composite of patients' age, creatinine clearance, hemoglobin level, white blood cell count and previous spontaneous bleeding. A score of ≥ 25 is accepted as a high risk for bleeding events and in this case, it is recommended to shorten the duration of DAPT. (16). In our study the mean PRECISE-DAPT score was 29.8; and was similar in both the clopidogrel and ticagrelor groups (30.3 vs 28.5; p=0,43). As can be seen, although the PRECISE-DAPT score was lower, there was more major bleeding in the ticagrelor group. We can interpret that scoring systems which are widely used are not sufficient to evaluate bleeding risk in elderly population. Since age is a variable for almost all of them, advanced age directly increases the score. In the future a subgroup scoring system could be developed for this population for a more accurate risk prediction.

The strength of this study lies in the fact that it was conducted on a frail group of patients, who are typically excluded from medical research, thus making a valuable contribution to our understanding of the healthcare needs of this vulnerable population. This study has several limitations, mainly its retrospective and has a non-randomized design. Since the study was retrospective, DAPT treatment duration was not standardized, but rather left to the attending physician's choice. Moreover, this study was based on hospital registries, so there is a chance patients may not have reported all of their minor bleedings. Due to the limited patient population, patients with SCAD unresponsive to medical treatment were also included in this study in addition to patients admitted with ACS. However, current guidelines only recommend ticagrelor over clopidogrel as part of DAPT in ACS. In addition, the frailty and cognitive status of the patients were not compared in our study. Frailty and cognitive status are an important parameter that will affect the outcomes.

CONCLUSIONS

In octogenarians, clopidogrel and ticagrelor have similar all-cause death, stroke, and TVR rates. However, major, and minor bleeding were significantly higher in the ticagrelor group than the clopidogrel group. Furthermore, due to the side effects, such as bleeding and dyspnea, many patients receiving ticagrelor switched to clopidogrel. According to our study DAPT is safer with clopidogrel than with ticagrelor in octogenarians. However larger, randomized trials are needed to evaluate the efficacy and safety of ticagrelor and clopidogrel in octogenarians.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Ethical approval

This study was conducted following the Declaration of Helsinki and was approved by the Second Ethical Committee of the Ankara City Hospital with number E2-21-929.

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RESEARCH

ASSOCIATES OF COGNITIVE FUNCTIONS IN AGED TURKISH ADULTS: INSIGHTS FROM A PSYCHIATRY OUTPATIENT CLINIC

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Abstract

Introduction: The aim of this study was to determine the cognitive function and its influential factors in elderly adults in Turkey.

Materials and Methods: 127 patients aged over 65 years referred to a psychiatry outpatient clinic for the first time were included to cross-sectional and descriptive study. Patients were assessed by Carlson Comorbidity index, Montreal Cognitive Assessment Test, Geriatric Depression Scale, Beck Anxiety Inventory, Nottingham Health Profile and Lawton Instrumental Activities of Daily Living Scale.

Results: The mean age of the patients was 69.7±4.2 years and 55.1% (n=70) of the participants were female. The primary diagnosis was Generalized Anxiety Disorder in 48.8% and Major depressive disorder in 51.2% of the patients. In multivariate analysis, age (OR:0.759, 95% CI:0.630-0.914, p=0.004), income <3800 TL (OR:14.72, 95% CI:1.78-121.51, p=0.013), medication usage (OR:0.171, 95% CI:0.035-0.845, p=0.030) and Geriatric Depression Scale score (OR:0.876, 95% CI:0.785-0.977, p=0.017) remained as independent predictors of Montreal Cognitive Assessment Test score.

Conclusion: In Turkish adults with Generalized Anxiety Disorder or Major depressive disorder who admit to a psychiatry outpatient clinic for the first time, various parameters including age, education, income, leisure activity, medication usage, depression, Lawton Instrumental Activities of Daily Living Scale score and Nottingham Health Profile score are linked with cognitive impairment. However, only age, income, medication usage and depression independently associate with cognitive impairment in this highly specific patient population.

Keywords: Cognitive Dysfunction; Geriatric Psychiatry; Depression; Quality of Life.

INTRODUCTION

As the elderly population has substantially increased not only in Turkey but worldwide, aging is considered a global phenomenon. It is predicted that in 2050, approximately one in six people will be 65 years or older (1). Daily activities such as walking, climbing stairs, and getting up without assistance are important tasks for aging individuals. However, cognitive impairment (CoI) and alterations in musculoskeletal and neuromuscular functioning that occur due to the aging process negatively impact such activities and reduce quality of life (QoL) (2).

CoI is characterized by the deterioration of executive functions, memory, attention, orientation, and speech. Elderly adults with CoI are more dependent and have more comorbidities and poorer QoL (2). CoI prevalence in the elderly varies from 5% to 36% (1-3). Studies indicate that CoI is significantly linked with advanced age, the female gender, low education level, low income, daily living, lifestyle, social support, nutritional status, and chronic diseases (2, 3). Mental disorders, such as depression and anxiety, also adversely impact cognitive functions and QoL in older adults. Generalized anxiety disorder (GAD) and late-life depression (LLD) are major public health problems leading to functional decline, physical disability, and overuse of health services in the elderly population (4, 5). Both conditions can induce significant impairments in cognitive functions and independent living skills and thus reduce QoL (4, 6).

Among the various factors that negatively affect cognitive functions in the elderly, age and education level have been investigated more frequently, and their impacts are comparatively greater (6, 7). However, other factors have been understudied, especially in the Turkish population. The present study sought to examine the relationships among cognitive status, daily living activities, and QoL in older Turkish adults who had applied to a psychiatry outpatient clinic for the first time and were diagnosed with major depressive disorder (MDD) or GAD.

METHODS

Study Design and Participants

The study used a cross-sectional and descriptive design and was conducted between October 2021 and October 2022 in a psychiatry outpatient clinic of an university hospital in Turkey. Consecutive patients aged 65 and over who had applied to the clinic for the first time and were diagnosed with MDD or GAD according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders were included in the study. Clinical evaluation and routine blood tests were performed on all participants to exclude other causes of somatic and psychiatric disorders. Demographic and clinical characteristics, comorbidities, medications, and neuropsychometric test results were gathered prospectively. Patients with neurological diseases (e.g., Parkinson's disease), obstructive sleep apnea syndrome, heart failure, renal failure, hepatic disease, or a history of alcohol or other psychoactive substance use were excluded from the study. Patients who couldn't speak and write Turkish were also excluded.

The eligible patients underwent neuropsychometric evaluations performed by a psychiatrist. A sociodemographic data form and the Charlson Comorbidity Index (CCI) were also completed for each patient. Afterwards, cognitive status was assessed using the Montreal Cognitive Assessment (MoCA), and depression and anxiety were measured using the Geriatric Depression Scale (GDS) and Beck Anxiety Inventory (BAI), respectively. QoL and disturbances in everyday activities were assessed using the Nottingham Health Profile (NHP) and Lawton Instrumental Activities of Daily Living Scale (IADL), respectively.

The study protocol was approved by the local ethics committee of the hospital, and all

procedures were performed in accordance with the principles defined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Outcome Measures

The sociodemographic data form, which was prepared by the investigators, included participant age, gender, education, area of residence, marital and living status, occupation, income per month, comorbidities, medications, and leisure activities. The CCI is a questionnaire developed by Charlson et al. to control for comorbid diseases and monitor patient prognosis (8). Scores range from 0 (no conditions) to 6. Higher scores indicate a more severe burden of comorbidity.

The MoCA is a brief cognitive screening tool that was developed to detect mild CoI. The scale covers a wide range of cognitive functions, including spatial/executive ability, naming, language fluency, attention, memory, abstract thinking, and orientation. It is a one-page 30-point test that can be completed in approximately 15 minutes (9). In the Turkish version of the MoCA, a score above 20 is evidence of CoI (10).

The GDS is a 30-item questionnaire developed to screen for depressive symptoms in the elderly. The Turkish validity and reliability study was performed by Sağduyu et al., and the cut-off score was determined to be 13/14 (11). The BAI is a self-report questionnaire that was developed by Beck et al. and consists of 21 items that inquire about the common somatic and cognitive symptoms of anxiety. Higher BAI scores indicate more severe symptoms. The validity and reliability study of the Turkish version of the BAI was published by Ulusoy et al (12).

The NHP is a two-part questionnaire developed to evaluate patients' subjective health status. The first part, which includes 38 dichotomized (yes/no) items, focuses on six dimensions of subjective health: pain, vital energy, sleep disorders, physical mobility, emotional reaction, and social isolation. The second part focuses on the affected areas, and only the first part was used in our study. Higher NHP scores indicate more severe health status. The Turkish validity and reliability study of the NHP was published by Küçükdeveci et al (13).

The IADL evaluates an individual's independence in routine daily activities (e.g., phone use, transportation, shopping, food preparation, housekeeping, laundry, medication use, and money management). The Turkish validity and reliability study was performed by Işık et al (14).

Statistical Analysis

All statistical tests were performed using SPSS for Windows v22.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to evaluate the distribution of numerical variables. According to the results of this test, an independent samples t-test or analysis of variance (ANOVA) was applied to the normally distributed numerical data, which conformed to the normal distribution, and the results were presented as mean±standard deviation. On the other hand, the Mann–Whitney U test was used for the abnormally distributed variables, and the results were presented as the median with interquartile ranges (percentiles 25th and 75th). Categorical variables were presented as counts with percentages and compared using the chi-squared test or Fisher's exact test. Independent predictors of MoCA scores were determined by logistic regression analysis. Variables that could be associated with the MoCA score and/or reached statistical significance in comparative analyses, such as age, education, income<3800 TL per month, leisure activity, medications, GDS score, IADL total score, and NHP total score, were included in univariate analysis. Afterwards, the variables that were determined to have a p-value <0.1 in univariate analysis were included in multivariate analysis. A two-sided p-value of less than 0.05 was considered statistically significant for all tests.

RESULTS

Baseline characteristics of the patients and their comparisons according to the MoCA scores are presented in Table 1. The entire study population consisted of 127 patients for statistical tests after the application of the exclusion criteria. The mean age of the patients was 69.7±4.2 years and 55.1% (n=70) of the participants were female. The primary

Table 1. Basal characteristics of the study participants

Variables	All patients (n=127)	MoCA score ≤21 (Cognitive impairment) (n= 66)	MoCA score >21 (Normal cognition) (n= 61)	p value
Age (years)	69.7±4.2	71.4±4.6	67.8±2.6	<.001
Gender (female)	70 (55.1%)	39 (59.1%)	31 (50.8%)	.349
Education				
Primary school	85 (66.9%)	55 (83.3%)	30 (49.2%)	<.001
Secondary school	22 (17.3%)	8 (12.1%)	14 (23%)	
High school and above	20 (15.7%)	3 (4.5%)	17 (27.8%)	
Area of residence				
Rural	62 (48.8%)	32 (48.5%)	30 (49.2%)	.427
Urban	65 (51.2%)	34 (51.5%)	31 (50.8%)	
Occupation				
Unoccupied	66 (52%)	37 (56.1%)	29 (47.5%)	.030
Retired	61 (48%)	29 (43.9%)	32 (52.5%)	
Marital status				
Single	29 (22.8%)	19 (28.8%)	10 (16.4%)	.196
Married	98 (77.2%)	47 (71.2%)	51 (83.6%)	
Living status				
Alone	13 (10.2%)	11 (16.7%)	2 (3.3%)	.042
Spouse	91 (71.7%)	43 (65.2%)	48 (78.7%)	
Family	23 (18.1%)	12 (18.2%)	11 (18%)	
Income (per months)				
<2800 TL	73 (57.5%)	45 (68.2%)	28 (45.9%)	<.001
2800-3800 TL	32 (25.2%)	17 (25.8%)	15 (24.6%)	
>3800 TL	22 (17.3%)	4 (6.1%)	18 (29.5%)	
Number of comorbidities				
0	19 (15.0%)	6 (9.1%)	13 (21.3%)	.104
1	57 (44.9%)	34 (51.5%)	23 (37.7%)	
>1	51 (40.2%)	26 (39.4%)	25 (41.0%)	
Medication	109 (85.8%)	61 (92.4%)	48 (78.7%)	.027
Leisure activity	70 (55.1%)	30 (45.5%)	40 (65.6%)	.023
Primary diagnosis				
Generalized Anxiety Disorder	62 (48.8%)	28 (42.4%)	34 (55.7%)	.134
Major Depressive Disorder	65 (51.2%)	38 (57.6%)	27 (44.3%)	

Abbreviations: TL= Turkish lira

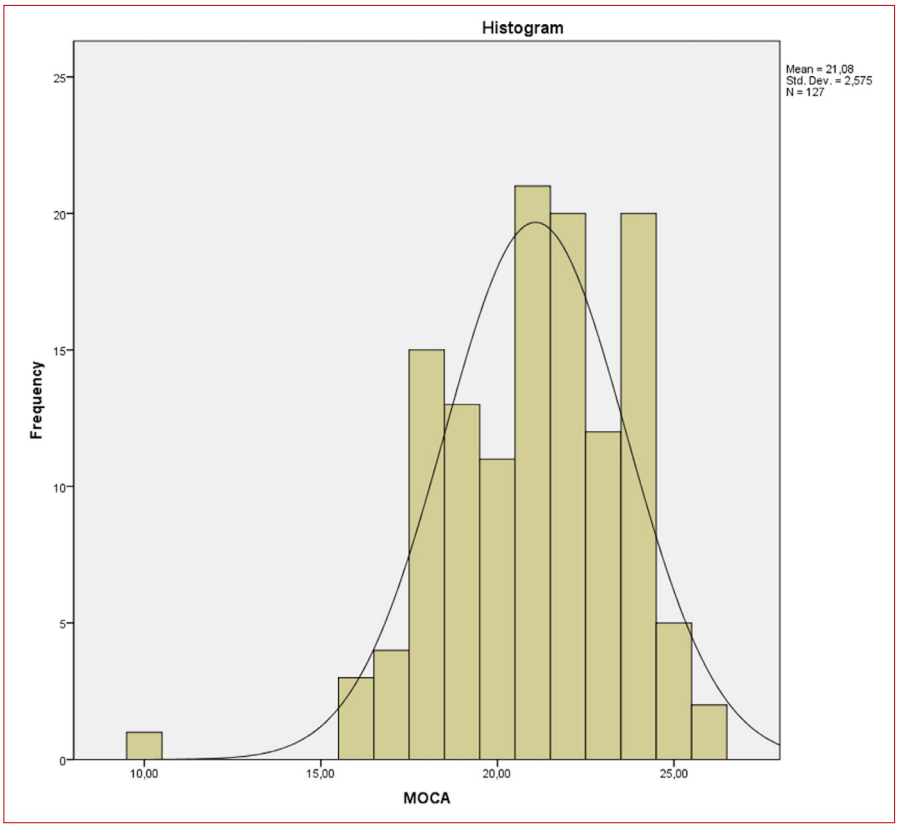

Figure 1. Distribution of Montreal Cognitive Assessment (MoCA) test score among the study population

diagnosis was GAD in 48.8% (n=62) of the patients and MDD in 51.2% (n=65). The mean MoCA score of the study population was 21.07±0.22 as demonstrated in Figure 1. The patients were categorized into two groups according to their MoCA test score and classified as CoI and normal cognition: MoCA score ≤21 (CoI) (n=66) and MoCA score >21 (normal cognition) (n=61). Patients with CoI were older, less educated, and had lower income compared to patients with normal cognition ($p<0.001$ for all). Occupation and living status significantly differed between groups, whereas gender, area of residence, marital status, number of comorbidities, and primary diagnosis were comparable among the groups. The percentage of patients using a medication was significantly higher ($p=0.027$), and percantage of patients that allowed time for leisure activity was significantly lower ($p=0.023$) in patients with CoI compared to patients with normal cognition.

A comparison of the neuropsychometric test results of the study participants according to their MoCA scores is given in Table 2. The GDS scores of patients with CoI were significantly higher ($p=0.009$), whereas BAI and CCI scores were comparable between groups. NHP total score and subscale scores were significantly lower in CoI patients compared to patients with normal cognition ($p<0.001$ for all). Moreover, the IADL total score and subscale scores, except the IADL handling medications score, were significantly lower in the CoI group than in the normal cognition group.

Table 2. Neuropsychometric tests of the study participants

Variables	MoCA score ≤21 (Cognitive impairment) (n= 66)	MoCA score >21 (Normal cognition) (n= 61)	p value
GDS	16.4±4.4	13.9±6.1	.009
BAI	14.8±8.2	14.6±6.2	.891
CCI	3.8±1.3	3.4±1.1	.062
NHP total score	250.7±103.4	156.7±72.7	<.001
NHP energy level	38.3±32.8	9.9±20.5	<.001
NHP pain	36.7±26.5	19.9±19.7	<.001
NHP emotional reaction	57.4±25.0	42.3±27.8	<.001
NHP social isolation	37.8±25.6	17.2±25.1	<.001
NHP sleeping	47.4±33.4	50.1±30.1	.644
NHP physical activity	32.9±25.5	17.1±17.6	<.001
IADL total score	15.2±4.1	18.4±2.8	<.001
IADL using telephone	2.2±0.7	2.6±0.5	<.001
IADL shopping	2.1±0.6	2.4±0.5	<.001
IADL preparing food	1.9±0.6	2.3±0.5	<.001
IADL house keeping	1.1±0.7	1.5±0.5	<.001
IADL transportation	2.6±0.8	3.1±0.6	.001
IADL handling medications	2 (1–2)	2 (2–2)	.081
IADL handling finances	0.88±0.73	1.35±0.60	<.001

Abbreviations: BAI= Beck Anxiety Inventory, CCI= Charlson Comorbidity Index, GDS= Geriatric Depression Scale, IADL= Lawton Instrumental Activities of Daily Living Scale, NHP= Nottingham Health Profile

Predictors of the MoCA score assessed by logistic regression analysis are presented in Table 3. All parameters included in the regression model were significantly associated with the MoCA score in univariate analysis. In multivariate analysis, age (OR:0.759, 95% CI:0.630–0.914, p=0.004), income <3800 TL (OR:14.72, 95% CI:1.78-121.51, p=0.013), medication usage (OR:0.171, 95% CI:0.035–0.845, p=0.030), and GDS score (OR:0.876, 95% CI:0.785–0.977, p=0.017) remained as significant and independent predictors of MoCA test scores. Education, leisure activity, IADL total score, and NHP total score did not reach statistical significance in the multivariate analysis.

DISCUSSION

Our study results indicate that age, income, medication usage, and high depression scores are independent predictors of CoI in older adults

Table 3. Predictors of MoCA test score by logistic regression analysis

	Univariate		Multivariate	
	Odds Ratio (95%CI)	**P value**	**Odds Ratio (95%CI)**	**P value**
Age	.753 (.663-.856)	<.001	.759 (.630-.914)	.004
Education	1.39 (1.17-1.64)	<.001	1.11 (.914-1.37)	.274
Income <3800 TL	30 (5.89-152-62)	<.001	14.72 (1.78-121.51)	.013
Leisure activity	2.28 (1.11-4.68)	.024	1.86 (.670-5.20)	.232
Medication	.303 (.101-.908)	.033	.171 (.035-.845)	.030
GDS score	.913 (.852-.979)	.011	.876 (.785-.977)	.017
IADL total score	1.25 (1.14-1.45)	<.001	1.01 (.855-1.21)	.848
NHP total score	.988(.983-.993)	<.001	.994 (.987-1.001)	.103

Abbreviations: CI=Confidence interval, GDS= Geriatric Depression Scale, IADL= Lawton Instrumental Activities of Daily Living Scale, MoCA= Montreal Cognitive Assessment, NHP= Nottingham Health Profile, TL= Turkish lira

suffering from GAD or MDD. Education, leisure activity, IADL total score, and NHP total score were also associated with the MoCA test score but mediated by other contributing factors. Also, anxiety had no association with CoI. To our knowledge, this is the first study investigating predictors of CoI in Turkish adults of older age who suffer from GAD or MDD.

Among the many disorders affecting the elderly, CoI, depression, and anxiety deserve special attention, as they have a high prevalence and adverse effects on independent living activities and health-related QoL (HR-QoL) (3, 4). Some older individuals protect most of their cognitive abilities throughout their lives, while others suffer from neurodegenerative diseases or even severe dementia (15). The scope of our work was to investigate cognitive function status and its influential factors in patients aged 65 years and older who applied to the psychiatry outpatient clinic and were diagnosed with GAD or MDD. It is already known that cognitive functions, such as working memory, executive function, and attention, tend to decrease with increasing age, even in healthy aging individuals (15). In a similar manner, we found that the risk of CoI increased with age in older patients with GAD or MDD.

Impaired cognitive function negatively affects the daily lives of elderly people. It is known that instrumental daily living activities that include complex activities, such as shopping or administering drugs, require a high level of cognitive function. The relationship between cognitive function and daily living activities is largely dependent on IADL, according to previous studies (16, 17). In our study, like the literature, patients with impaired cognitive functions had significantly lower IADL, including managing finances, making communication, shopping and meal preparation, house cleaning and home maintenance, and managing transportation. Our univariate comparison of patients with and without CoI showed a significant difference for the IADL total score, but this association did not reach statistical significance in multivariate analysis. Recent studies showed that lower education levels, lower income, and depression seem to have negative effects on IADL in elderly (18). IADL might have been affected by these contributing factors,

which could be the reason why the IADL total score failed to associate with MoCA test scores in an independent manner.

Late-life depression (LLD) is a remarkable public health concern, as it is quite common in the aging population. It also leads to physical disability and functional decline and negatively impacts QoL. The prevalence of clinically considerable depressive symptoms varies between 11% and 53% in elderly patients, according to diverse studies (4, 5). These high rates can be explained by multifaceted factors, such as aging, physical disability, and CoI (4). LLD is related to the risk of cognitive decline, mild CoI, and dementia (5, 19). Patients with LLD suffer from cognitive complaints, and it is estimated that 20-50% of elderly with LLD have cognitively impaired abilities (4). In our study, consistent with the literature, the depression scores of the CoI group were significantly higher and independently associated with the MoCA test scores. The relationship between depression and cognitive functions is bidirectional (4, 5, 19). Depressive symptoms often lead to cognitive complaints, and perceived CoI may lead to anxiety and probable fear of dementia accompanying depression (4, 19). Some research suggests a concurrent incidence between depressive symptoms and MCI, while others indicate that poor cognitive function may lead to depression. Another possible explanation is that these two conditions occur concurrently due to the presence of hippocampal atrophy in both CoI and depression. Another common finding is that depression is a significant risk factor for subsequent CoI (4). It has also been suggested that cognitively affected depressive older adults continue to be cognitively impaired even if depression has been cured (4, 20). Briefly, we can suggest that depressive symptoms may lead to and worsen CoI. However, from a clinical point of view, LLD is often underrecognized, underreported, and undertreated. Depression alone and worsening IADL scores can negatively affect cognition (18).

Anxiety is frequently observed in CoI, prodromal stages of dementia, and physiological aging (5). Anxiety prevalence in the elderly population ranges between 3.7-43%. Anxiety symptoms have been studied less than depression, and their relationship with cognition is controversial (5). Some researchers have suggested that anxiety symptoms are adversly related to cognition, while others have demonstrated that comorbid depressive symptoms account for this relationship (5). Several reports state anxiety symptoms as a risk marker for cognitive decline, but there are many inconsistencies among studies. On the other hand, some researchers have reported a lack of an association akin to our study. Eventually, anxiety appears to be important in predicting the progression from MCI to dementia rather than predicting CoI (5).

CoI in older people leads to a gradual decline in many physical abilities, functional independence, and social relationships, subsequently resulting in worsening QoL (19). Also, memory complaints are linked to low satisfaction with social support and higher depressive symptoms (19). In our study, HR-QoL was measured using NHP. HR-QoL shows perception of how a health condition affects physical, mental, emotional, and social well-being and the functional ability to perform everyday activities (20, 21). Examining the HR-QoL of elderly people with CoI is important for accurate future health interventions. However, whether QoL is already disturbed in the early stages of CoI is controversial. Also, the relationship between QoL and cognition is not well understood (21). Some research has suggested that QoL is altered in CoI, while others have not. Also, the association between CoI and QoL is affected by negative aging stereotyping and depression (20, 21). In our study, there was no independent association between the total NHP score and CoI, which made us consider that the association between QoL and CoI is mediated by other contributing factors. Moreover, in our study, patients with CoI showed more detoriated HR-QoL

in all areas except the sleep subscale than patients with normal cognitive function. The findings of our study are consistent with previous studies, which suggest that lower QoL is associated with higher CoI in elderly people (20). Our results are of clinical importance because there are limited data about HR-QoL in patients with MCI and in the preclinical/prodromal phase of Alzheimer's disease.

There are scientific facts that older adults may alter the risk of CoI by keeping their brains active. Prior observational studies have shown that higher leisure activity engagement has been linked to better cognition and a lower risk of dementia (6, 22). A recent study also suggested that depressive symptoms negatively affect cognitive functions by decreasing continued activities that help promote cognitive reserve. Also, a negative association between leisure activities and CoI might indicate that either a higher level of engagement provides protection against dementia and/or decreased level of engagement is an early marker of cognitive impairment. Being engaged in more reading and hobby activities is associated with a lower risk of CoI (6, 22). Consistent with the literature, there is a significant association between leisure activities and cognition in univariate analysis but not in multivariate analysis.

To our knowledge, most people with CoI live in low-medium income countries (2, 23). Higher levels of income have been associated with better cognitive functions in a cohort study, and another recent research study suggested a positive relationship between healthy cognition and a stable economic state (3, 23). Similarly, elderly adults with higher monthly incomes had significantly better cognition in our study. Additionally, medication usage had a remarkable effect on cognition in our study. Studies have shown that using many drugs at the same time can aggravate CoI. Medication-related CoI is relatively common in the elderly and is underrecognized. Individuals at higher risk are elderly with baseline cognitive impairment. Medications should be considered a potential cause when a patient presents with cognitive alterations. A recent study suggested that polypharmacy was especially associated with CoI in older adults. Various drugs including anticholinergic drugs, H2 receptor antagonists, cardiac drugs, statins, and antibiotics can cause CoI. Interactions between drugs and the accumulation of the same side effects should also be considered in CoI (24).

There are significant limitations in our study that need to be acknowledged. The MoCA test was used to evaluate the cognitive functions of the study participants. The MoCA test has been shown to be sensitive in detecting people with mild cognitive impairment (9). However, it would have been more valuable if we had performed multiple cognition tests. Also, the study was performed in a single center with a relatively limited number of patients from the Turkish population. The lack of an age-and gender-matched community dwelling control group without a psychiatric condition is another limitation of the study. Also, the cross-sectional nature of the study limits the generalization of the results.

In conclusion, in Turkish adults with GAD or MDD who are admitted to a psychiatry outpatient clinic for the first time, various parameters, including age, education, income, leisure activity, medication usage, depression, IADL, and HR-QoL, are linked with CoI. However, only age, income, medication usage, and depression were independently associated with CoI in this highly specific patient population.

Authors' Notes

All authors have made substantial contributions to conception and design, or acquisition of data, analysis, and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards.

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Informed consent was obtained from all individual participants included in the study.

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Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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RESEARCH

MIDTERM OUTCOMES OF ELECTIVE ENDOVASCULAR AORTIC REPAIR IN OCTOGENARIANS: WHEN IS IT TOO OLD?

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Abstract

Introduction: Endovascular aortic repair outcomes in octogenarians remain unclear. We aim to investigate whether the results for octogenarians differ from those of the younger population in elective endovascular aortic repair.

Materials and Methods: From January 2013 to January 2022, 313 patients were treated with elective endovascular aortic repairs. Patient demographics and perioperative and postoperative features were obtained from the hospital database. The primary goals were to explore the early mortality rates of patients aged 80 years and older and compare them with those under 80. The secondary goal was to analyze the comorbid factors.

Results: A total of 245 patients were under 80 years old, and 68 patients were 80 years and older. The early mortality rate was 2.94% in the octogenarians and 0.81% in the rest, and there was no significant difference between the two (p = 0.24). However, being 80 years and older led to a significantly lower survival probability at the five-year follow-ups. The American Society of Anesthesiologists' score was found to help predict late mortality risk and patient selection for elective endovascular aortic repair.

Conclusion: As octogenarians are fragile and sensitive to complications, patient selection, careful consideration of life expectancy, and clinical assessment are key to repair. Furthermore, age should not be an independent exclusion criterion in the endovascular aortic repair treatment decision.

Keywords: Aortic Aneurysm, Abdominal; Endovascular Procedure; Octogenarians.

INTRODUCTION

Improvements in the medical management of the progressive nature of atherosclerosis, population screening with ultrasonography, computed tomography (CT), and the aging of the world population have led to a considerable number of octogenarians emerging as candidates for elective abdominal aortic aneurysm (AAA) repair. As age-related diseases are expected to increase, the incidence and prevalence of cardiovascular diseases in the elderly are becoming more common day by day for healthcare professionals (1).

Being 80 years and older has been indicated as the cut-off point for age-based risk estimation in elective endovascular aortic aneurysm repair (EVAR) procedures (2). Alberga et al. studied 12,054 EVAR and 3,815 open surgical repair patients divided into octogenarian and non-octogenarian groups and found a 1.9% operative mortality rate for EVAR and an 11.8% mortality rate for open surgical repair in octogenarians (3). Although EVAR has provided a better solution for AAA, EVAR treatment in octogenarians for elective AAA is still subject to controversy due to the lower life expectancy (4). Even though the technical process may be similar, it is undeniable that elderly patients are fragile and more sensitive to complications. The current European Society for Vascular Surgeon (ESVS) guidelines point out that it is reasonable to consider elective AAA repair for octogenarians with reasonable life expectancy and quality of life after informing them of the pros and cons of different treatment strategies, including conservative options (5). However, there is no consensus on the comprehensive midterm and long-term results for EVAR in patients 80 years and older.

Our paper aimed to compare the early and midterm outcomes of elderly patients undergoing EVAR with those of younger patients. Furthermore, the groups were compared according to complications, endoleaks, and reinterventions. We also aimed to emphasize the factors affecting postoperative mortality and assess the hazard ratio.

METHODS

Data Source and Patient Selection:

From January 2013 to January 2022, 313 patients underwent elective EVAR by the same cardiovascular surgeon team in our clinic. A total of 245 patients were under 80 years old, and 68 patients were 80 years or older. In this study, elderly patients were defined as those who had turned 80 years old or older in the procedural year. The endovascular team assessed all patients in terms of their suitability for EVAR treatment. According to our clinical preferences, EVAR has been the first-choice treatment modality for abdominal aortic aneurysms if suitable to the instruction for use. The patients' preferences have correlated with surgeons', and the selections have been made under consensus. Conventional surgery has been performed in inadequate neck anatomies, unhealthy landing zones, or contraindications to EVAR as a necessity, not selection. Contrastly, EVAR has been performed in patients with unacceptable high risk to conventional surgery as a last chance to prevent aneurysm-related death even if unsuitable for use. Data were retrospectively obtained from the hospital database and records. The study protocols followed the Declaration of Helsinki, and the design was reviewed and approved by the Institutional Review Board (E1-19-161).

Early mortality, or in-hospital mortality, occurs in the first month after procedures, and mortality after the first month is called late mortality. Evaluating early and late mortality in elderly patients was the primary goal. The secondary goal was to assess the hazard ratio of being 80 years or older and other comorbidities and secondary reinterventions.

The same endovascular team performed all procedures in a hybrid operating room. Five types of brands (Ankura AAA (Lifetech), AFX (Endologix), Endurant-II (Medtronic), the Gore Excluder (Gore),

and the E-vita Abdominal XT (Jotec)) were used in these procedures. The unibody Endologix endograft was used in 70 patients (23.3%); the rest received bifurcated modular endografts. General anesthesia was performed on 254 patients (81.1%); the remainder was subject to loco-regional anesthesia. Endoleaks were assessed with completion angiography and then treated. Angiography was obtained with contrast or carbon dioxide (CO_2). For 16 patients (5.1%) who had severe chronic kidney disease (CKD) or a high risk of kidney failure, we performed contrast-free angiography with a procedure using CO_2.

Postoperative Follow-Up:

Clinical and radiological assessments were performed in the first month, the 6th month, the 12th month, and annually after the procedures. All patients had colored Doppler ultrasonography (CDUS), and case-by-case CDUS or contrast-enhanced CT angiography was performed according to the patients' individual characteristics, as previously described (6). Secondary interventions, as if needed, were performed by the same team, and complete angiography was then carried out. Mortalities, morbidities, and reinterventions were investigated and documented.

Statistical Analysis:

The variables were explored using visual (e.g., histograms and probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests) to determine the normality of their distribution. Normally distributed continuous variables were expressed as means ± standard deviations (SD) or median values with ranges, if not normally distributed. Categorical variables were expressed as numbers and percentages. Demographic parameters, operating variables, and follow-up data were compared using the Mann–Whitney U test, Student's t-test, and chi-square test. A Student's t-test was conducted to analyze the preoperative and follow-up diameters of the aneurysm sacs. A Kaplan–Meier analysis was conducted to demonstrate the probability of survival and event freedom. A log-rank analysis was performed to compare the groups in the Kaplan–Meier curves. In the Kaplan–Meier survival curves with confidence limits, the upper and lower confidence limits were computed in SPSS following the generated Kaplan–Maier estimate. The hazard ratio (HR) and 95% confidence intervals (CI) were estimated with different Cox proportional hazard models to estimate the independent predictors of survival, with adjustment for the predefined possible risk factors. A p-value of < 0.05 was statistically significant, and all statistical analyses were performed using the SPSS for Windows version 20.0 statistical software program (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 313 patients underwent the EVAR procedure in 9 years. Patients treated with EVAR were divided into two groups according to whether they were 80 years of age, which was the cut-off point. Group 1 included 245 younger patients under 80 years old, while Group 2 included 68 patients who were 80 years old and older. Group 2 also included 10 patients aged 90 years and older. The baseline characteristics of all patients are presented in Table 1. The groups were compared according to these characteristics, and the homogeneity of the groups was assessed. The number of elderly patients with CKD (baseline creatinine levels of 1.8 mg/dl and above) was significantly higher than that of the other group ($p = 0.011$). The octogenarians had higher American Society of Anesthesiologists (ASA) scores at the preoperative assessments by an ordinal increase ($p = 0.045$). Smoking was significantly higher in Group 2 (p=0,025). There were no statistically significant differences between the two groups when comparing other baseline characteristics (Table 1). Furthermore, there was no

Table 1. Demographics and comorbid factors within the groups.

Baseline characteristics of the patients			
Parameter	**N (%) or mean (range) (N=222)**		**p**
	Group 1 n = 245 Aged under 80 years	**Group 2 n = 68 Aged 80 years and over**	
Age[years]	67.27 ± 6.21 (42–79)	83,91 ± 3.93 (80–97)	
Male gender	230 (93.8%)	55 (80.8%)	*0.002
ASA grade:			
2	30 (12.2%)	7 (10.2%)	*0.045
3	95 (38.7%)	17 (25%)	
4	87 (35.5%)	30 (44.1%)	
5	33 (13.4%)	14 (20.5%)	
Hypertension (HT)	181 (73.8%)	51 (75%)	0.87
Diabetes mellitus (DM)	63 (25.7%)	17 (25%)	0.905
Hyperlipidemia (HL)	75 (30.6%)	24 (35.2%)	0.465
Coronary artery disease (CAD)	104 (42.4%)	33 (48.5%)	0.371
Peripheral artery disease (PAD)	20 (8.2%)	6 (8.8%)	0.86
Chronic obstructive pulmonary disease (COPD)	69 (28.1%)	25 (36.7%)	0.171
Chronic kidney disease (CKD)	28 (11.4%)	16 (23.5%)	*0.011
EF < 30	6 (2.4%)	2 (2.9%)	0.686
Smoking	135 (55.1%)	27 (39.7%)	*0.025
Malignancy	14 (5.7%)	5 (7.3%)	0.907
TIA/CVE	9 (3.6%)	6 (8.8%)	0.104
AAA diameter [mm]	62.15 ± 13.47 (52–116)	65.33 ± 16.2 (55–118)	0.101
≥ 6.0 cm	130 (53%)	39 (57.3%)	0.96

EF: Ejection fraction, TIA/CVE: Transient ischemic attack/cerebrovascular event, AAA: Abdominal aortic aneurysm.

significant difference in perioperative procedural features. The most used type of endograft was the modular type, and the average lengths of the intensive care unit stay and hospital stay were the same.

Cumulative Kaplan–Meier survival analyses were generated for the probability of survival, event freedom, and secondary intervention. In the first postoperative month, two patients died in both groups, and the mortality rates were 2.94% in elderly patients and 0.81% in younger patients. There was no statistical difference between the groups according to the early mortality rate (p = 0.24; Table 2). In 5 years of follow-up, overall late mortality after elective EVAR was 54 patients (17.2%), with 39 in Group 1 (15.9%) and 15 in Group 2 (22%). Being 80 years and older led to a significantly worse survival probability (p = 0.013) and event freedom rate (p = 0.035) in the Kaplan–Meier analysis (Figure 1). Secondary reinterventions were performed on 20 patients (6.3%), including 15 patients in Group 1 and 5 in Group 2. The log-rank analysis indicated that both groups had similar curves for secondary intervention rates (p = 0.81). Octogenarians had

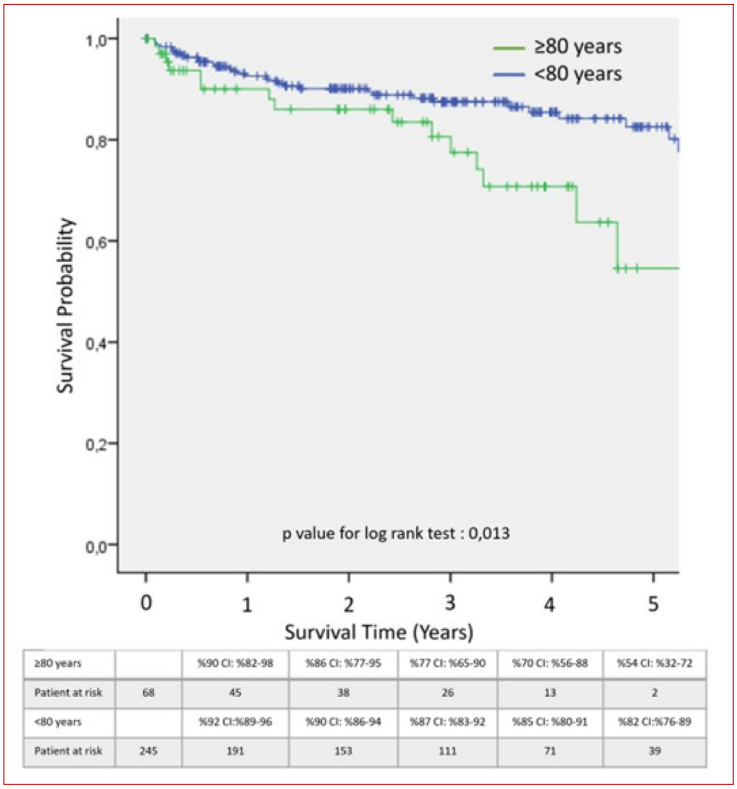

Figure 1. Kaplan–Meier analysis of survival for groups. Survival curves are demonstrated by the green line for individuals ≥ 80 years old and the blue line for those < 80 years old. The probability of the groups is shown, respectively, with 95% confidence intervals (CI) for group 1 at 82% (76–89%) and group 2 at 54% (32–72%; p = 0.013).

Table 2. Perioperative features and procedural details in the groups. Causes of in-hospital mortality by groups were documented

Perioperative procedural features			
Feature	**N (%) or median (range) (N = 313)**		**p**
	Group 1 n = 245 Aged under 80 years	**Group 2 n = 68 Aged 80 years and over**	
General anesthesia	202 (82.4%)	52 (76.4 %)	0.58
Local/regional anesthesia	43 (17.5%)	16 (23.5 %)	
Duration of the procedure [minutes]	120 (80–370)	125 (95–365)	0.89
Fluoroscopy time [minutes]	14 (4–78)	14 (5–80)	0.91
Amount of contrast agent [ml]	60 (0–160)	50 (7–120)	0.96
Length of intensive care unit stay [hours]	4 (1–240)	4 (2–120)	0.76
Length of hospital stay [days]	2 (1–30)	2.5 (0–21)	0.56
Early-stage mortality	2 (0.8%)	2 (2.9%)	0.24
Causes of death by groups	One patient died in postoperative 1st day due to cardiac reasons One patient died in postoperative 2nd day due to Acut Miyocard Infaction	One patient died in postoperative 1st day due to Acut Kidney Failure One patient died in postoperative 8th day due to Acut Kidney Failure	

Table 3. Outcomes after EVAR in groups and reinterventions for endoleaks.Causes of late mortality were documented by groups

Follow-up data			
Data	**Group 1 (n)**	**Group 2 (n)**	**Reinterventions**
Endoleaks:			
Type Ia	4	2	4 proximal extensions 2 ballooning procedure
Type Ib	4	1	5 distal extensions
Type II	18	8	26 untreated (follow-up)
Type III	4	2	2 open conversions 4 endovascular relining 2 untreated (patient preference)
Type V	0	1	1 follow-up
Limb occlusion	1	2	1 femoral-femoral artery bypass 1 endovascular intervention 1 untreated (asymptomatic)
Late conversion to open surgery	2	0	
Secondary intervention	15	5	
Late mortality	39	15	
**Causes of Late Mortality*	6 aneursym-realted 17 cardiac reasons 7 cancer 3 pnomonia 3 chronic renal insufiency 3 unknown	3 aneursym-realted 7 cardiac reasons 2 cancer 1 pnomonia 2 unknown	

lower late survival rates, with a similar secondary reintervention rate after elective EVAR. Moreover, there were 10 patients aged 90 years and older, and no early mortality was observed.

Clinical data were obtained from routine follow-ups, the data of which are shown in Table 3. In our patient cohort, there were 44 (14%) endoleaks, of which 26 were type 2 (59%). The rates of type 1 and type 3 endoleaks necessitating secondary interventions were 3.5% and 2.2%, respectively. There were 20 secondary interventions in total. Open conversions after EVAR were performed on two patients after failed endovascular attempts. Limb occlusion after EVAR occurred in three patients. One was treated with a cross-over femoral-femoral artery bypass, another with endovascular intervention, and the last was untreated because of being asymptomatic. Additionally, type 5 endoleaks were present in one patient (Table 3).

Univariant and multivariant Cox regression models revealed independent risk predictors for late mortality. After we determined the primary risk factors for late mortality with an unadjusted analysis, we performed a multivariate analysis. Having CKD (basal creatinine levels ≥ 1 .8mg/dl; unadjusted HR: 2.37; 95% CI: 1.212–4.664; p = 0.012), an ASA-

Table 4. Multivariate and univariate Cox regression analysis for factors.

Parameter	Unadjusted analysis			Adjusted analysis		
	P-value	HR	95% CI	*P-value*	HR	95% CI
Age ≥ 80	*0.015	2.149	1.158–3.988	*0.014	2.302	1.18–4.48
Gender (male)	0.145	23.381	0.33–1624.7			
CAD	0.89	1.609	0.931-2.782			
PAD	0.356	1.492	0.638-3.493			
ASA grade 5	*0.002	2.6	1.23–4.93	*0.022	2.186	1.12–4.26
Diabetes mellitus	0.18	0.609	0.296–1.256	0.36	0.705	0.33–1.49
COPD	*0.022	1.94	1.101–3.42	*0.015	2.073	1.15–3.72
Malignancy	*0.001	5.094	2.62–9.904	*0.001	4.47	2.12–9.42
Renal diseases	*0.012	2.37	1.212–4.664	0.9	1.04	0.485–2.26
EF<30%	*0.015	4.324	1.332–14.05	*0.044	3.99	1.03–15.37
Symptomatic aneurysm	*0.019	1.976	1.12–3.48			
AAA diameter ≥ 6.0 cm	0.22	1.44	0.803–2.582	*0.031	1.88	1.036–3.42

CAD: Coronary Artery Disease, PAD: Pepheral Arterial Diseases, ASA: American Society of Anesthesiologist classifications, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, AAA: Abdominal aortic aneurysm.

5 score (unadjusted HR: 2.6; 95% CI: 1.23–4.93; p = 0.002), chronic obstructive pulmonary disease (COPD; unadjusted HR: 1.94; 95% CI: 1.101–3.42; p = 0.022), or being symptomatic significantly increased the late mortality rate. Patients with diabetes mellitus (DM) were likely to have lower late mortality rates, but this difference was not significant. Being 80 years and older (unadjusted HR: 2.149, 95% CI: 1.58–3.98; p = 0.015) and having a malignancy (unadjusted HR: 5.04, 95% CI: 2.62–9.904; p = 0.001) were independent hazard factors for late mortality. These two factors also increased the late mortality rates in the multivariant analysis (respectively, adjusted HR: 2.302, 95% CI: 1.18–4.48; p = 0.014; adjusted HR: 4.47, 95% CI: 2.12–9.42; p = 0.001). Among these covariates, having low EF was found to decrease survival in both the univariate and multivariate analyses (respectively, unadjusted HR: 4.324, 95% CI: 1.332–14.05; p = 0.015; adjusted HR: 3.99, 95% CI: 1.03–15.37; p = 0.044; Table 4).

DISCUSSION

Age is a well-known independent risk factor for procedural-related death (2), and EVAR treatment is a preferred solution in elderly patients for elective AAA (3, 4). Scallen et al. compared the long-term results of open surgical repair (OSR) and EVAR in octogenarians and demonstrated significantly lower early mortality for EVAR over OSR, with a survival benefit of one year. However, there was no survival advantage during the 5-year follow-up period. Long-term outcomes have also been found to be similar, except for an 18% late reintervention rate in the EVAR group (7). In our nine years of experience, we treated 68 octogenarians and nonagenarians

with EVAR. We found that the early and midterm outcomes of endovascular procedures for patients 80 years and older had acceptable results, despite the patients being 80 years and older having twice the HR in late survival. According to early mortality, the groups had similar mortality rates. The early mortality rate was 2.94% in the elderly patients and 0.81% in the younger participants. Although the re-interventional rates in both groups were similar, elderly patients may be less able to recover from the complications than younger participants. Interestingly, there was no mortality in the nonagenarians. Therefore, discussing the patient's life expectancy and clinical assessment should be key for deciding on the operation, not how old they were.

Even though this study was constructed retrospectively, the comorbid factors were similar within both groups, except for gender, smoking, and having CKD. In fact, gender may not alter the outcomes after EVAR treatment, as previously described (8). In the present study, the male population was higher for both groups, and younger participants had a significantly higher male population. CKD was associated with increased morbidity and death in EVAR treatment (9). The fact that there was a higher incidence of CKD in the elderly patients could have a negative effect on outcomes. Other comorbidities were similar for both groups in the present study.

Endoleaks remain the most common complication after EVAR. Type 1 and 3 high-flow endoleaks especially require reintervention (10). Due to the same rate of early complications and reinterventions, there may be the same early mortality rates for octogenarians and others.

The multivariate analysis indicated that being 80 years and older led to a two-fold increase in the HR for survival. As previously described, octogenarians treated with EVAR had higher mortality rates than their younger counterparts (11). However, Budtz-Lilly et al. reported outcomes such as a 1.8% mortality rate for octogenarians after EVAR as for younger participants (12). In a previous study, concomitant malignancy was associated with higher mortality after TEVAR (13). In our research, having a malignancy led to a four-fold increase in mortality. Assessing life expectancy might therefore be wise for a cancer patient before EVAR. Furthermore, in our study, we found that patients with COPD who underwent EVAR had higher mortality rates, and CKD had no effect on late mortality. This could be attributed to the performance of contrast-free angiography and the use of CO_2 in CKD cases. Another result indicated that the ASA score was correlated with the mortality rate. Not every elderly patient has a higher ASA score, and not every elderly patient has a similar risk. ASA scores may therefore be helpful in identifying the appropriate candidates for elective EVAR. Specifically, EVAR may be considered a good and safe treatment for octogenarians, as long as they have a score under ASA-5 (14). Although not reported in the results, two patients did not accept the EVAR treatment due to high ASA scores and operational risks and were treated medically. In this respect, discussions with patients having high ASA scores are also practical to improve outcomes.

We found similar cumulative reintervention rates for both groups. Because elderly patients are fragile and sensitive to complications, the results may be even worse in the octogenarian. Rueda-Ochoa reported that EVAR in octogenarians has a long-term beneficial impact on their life expectancy. However, perioperative complications and reinterventions nearly doubled the long-term mortality rate in octogenarians (15).

According to the EVAR-2 trial, EVAR versus only medical treatment could not improve the outcomes in 60 years and older patients who were physically ineligible for open repair (16). Based on this study, no-intervention for abdominal aortic aneurysm might be a suitable option in octogenarian unless the physical status had been considered. Our study indicated that performing an EVAR on a patient over 80 years of age and performing an intervention

on a patient under 80 years of age with COPD has almost the same risk. Although age is a comorbid factor, it cannot be a definitive contraindication. AAA repair aims to prevent rupture and, to prolong the life. Since medical treatment alone will not eliminate the risk of rupture, we consider it appropriate to perform EVAR to increase survival in suitable patients. Another important inference is that the survival curves of the groups differ after 2 years following the procedure. Therefore , a balance between the risk of intervention and the benefits of prolonging and maintaining the quality of life is thus needed. In this context, the inclusion of all patient groups, regardless of suitability for open surgery, strengthens our study. Finally, it should be added that there are some limitations to this research due to it being a single-center, retrospective-designed study. Long term follow-ups and more data are needed for further evalution.

CONCLUSION

Being an octogenarian implies a two-fold increase in the HR for overall mortality. Not every octogenarian has the same operational risk, and not all EVAR indications are vital and beneficial to perform. Therefore, clinical assessment and understanding of the risk-benefit ratio are the keys to effective EVAR treatment in elderly patients. Despite shorter life expectancy and comorbidities, EVAR's early and midterm outcomes are acceptable in octogenarians, and age should not be an exclusion criterion. Our single-center experience shows that EVAR can be performed safely in the geriatric patient group.

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RESEARCH

RELATIONSHIP BETWEEN DIFFERENT NUTRITIONAL SCORES IN ELDERLY PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE IN THE CORONARY INTENSIVE CARE UNIT

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Abstract

Introduction: The relationship between heart failure and malnutrition is significant. The most commonly used nutritional indices are theprognostic nutritional index, controlling nutritional status, and albumin–bilirubin grade. We aimed to investigate the clinical impact of nutritional status in elderly acute decompensated heart failure patients and the relationship between the prognostic nutritional index, controlling nutritional status, and albumin–bilirubin grade nutritional indices to detect 12-month and 3-month rehospitalization rates, mortality, and length of stay in the Coronary Intensive Care Unit. Our study is the first to evaluate the controlling nutritional status and albumin–bilirubin grade in our study cohort in Turkey.

Materials and Methods: The medical records of 1162 patients hospitalized in the Coronary Intensive Care Unit were evaluated retrospectively. A total of 123 patients were included.

Results: We found a statistically significant difference between the prognostic nutritional index, albumin–bilirubin grade and controlling nutritional status scores and mortality. However, the most statistically significant relationship was found in the prognostic nutritional index score. We found that as the nutritional scores worsened, the length of hospital stay was prolonged. The albumin–bilirubin grade score in the short term and controlling nutritional status score in the long term were not statistically significant to show rehospitalization.

Conclusion: Prognostic nutritional index is an independent predictor of mortality, short- and long-term rehospitalizations, and length of stay in elderly patients with acute decompensated heartfailure. Its predictive power was better than the albumin–bilirubin grade and controlling nutritional status scores evaluated in our study.

Keywords: Heart Failure; Malnutrition; Aged; Coronary Care Unit; Nutritional Status.

INTRODUCTION

Malnutrition is becoming a growing health problem in elderly patients and is associated with increased mortality and morbidity in several clinical conditions (1–3). According to a recent scientific statement from the American Heart Association, the prevalence of malnutrition in patients admitted to the CICU can be as high as 78% in critically ill patients (4).

There is a complex relationship between heart failure (HF) and malnutrition. Malnutrition may worsen functional capacity and renal function and may increase susceptibility to infections. On the other hand, worsening HF may cause malnutrition and even cachexia (5).

The prevalence of malnutrition was 46% in a recent meta-analysis of HF patients. Moreover, it showed that the all-cause mortality of patients with malnutrition was almost twice that of non-malnutrition patients with HF (6). In another study that evaluated the nutritional status of intensive care patients, the prevalence of malnutrition was found to be as high as 47.6% upon admission (7).

The most commonly used nutritional indices are the prognostic nutritional index (PNI), controlling nutritional status (CONUT), and albumin–bilirubin grade (ALBI). Previous studies have shown that these nutritional indices are associated with prolonged hospital stay, readmission, and all-cause mortality in patients with cardiac and non-cardiac conditions (8–11).

The PNI is especially designed to assess perioperative surgical risk in patients with cancer. Previous studies showed an increased mortality risk in HF patients with a decreased PNI. However, the prognostic impact of PNI remains uncertain in elderly patients with acute HF in cardiac intensive care units (CICU) (8,12,13).

The CONUT score is derived from the values of serum albumin concentration, peripheral blood total lymphocyte counts, and total cholesterol levels. Higher CONUT scores show worse nutritional status and are associated with worse clinical outcomes (14–16).

The relationship between serum albumin levels and nutritional status is well known, and ALBI seems to be a new indicator of mortality and prognosis for heart failure patients in limited studies (17–19).

Although there is growing interest in the assessment and treatment of malnutrition, specific standardized assessments and treatment protocols are still lacking for CICU patients. Different nutritional indices are evaluated in different patient populations (12,20–22).

Therefore, we aimed to investigate the clinical impact of nutritional status in elderly acute decompensated HF patients and the relationship between the PNI, CONUT, and ALBI nutritional indices to detect 12-month (RH12M-long term) and 3-month (RH3M-short term) rehospitalization rates, mortality, and length of CICU stay.

MATERIALS AND METHODS

Study population

This was a single-center retrospective study. The medical records of 1,162 patients admitted to our CICU between January 2019 and January 2021 were evaluated retrospectively. Patients older than 65 years old and hospitalized with acute decompensated heart failure were included in the study.

Patients with acute coronary syndrome, severe liver cirrhosis (Child–Pugh score B or C), sepsis, malignancy, or elective hospitalizations, such as electrical cardioversion, pacemaker replacement, or implantation and heart transplantation recipients, were excluded.

Patients with missing laboratory data, insufficient medical records, or loss during follow-up were also excluded.

A total of 123 patients were included in the study.

The baseline characteristics, co-morbidities, and laboratory and echocardiographic parameters were noted.

The research protocol was approved by the Başkent University Institutional Review Board (Project no:KA21/44)

Assessment of Nutritional Status:

Nutritional indices were calculated from the first 24 hours' blood sample results.

The PNI value was calculated according to the following formula– 10x serum albumin (g/dL) + 0.005 × total lymphocyte count (mm3).

The CONUT score was calculated using the following equation:

Serum albumin [g/dL] + total lymphocyte count [mm3] + total cholesterol [mg/dL].

The ALBI grade was calculated using the following formula:

ALBI = (log10 bilirubin (μmol/L) × 0.66) + (albumin (g/L) × −0.085).

Assessment of end points

The rehospitalization rates, mortality, and length of CICU stay were evaluated using our hospital's medical record database. All the patients were also contacted via telephoning to exclude possible hospitalizationsin other hospitals.

Statistical analysis

The data were analyzed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) software. The data were expressed as mean ± standard deviation and median (range) for continuous variables and percentage for categorical variables. The CONUT, PNI and ALBI scores were the continuous variables. When we evaluated the continuous variables, CONUT and PNI showed skewed distribution, while ALBI showed normal distribution. The normally distributed data were analyzed by a t-test and the variables that did not show normal distribution were compared using Spearman's rank correlation and Mann–Whitney U tests. A p value of <0.05 was considered statistically significant.

RESULTS

We assessed nutritional status at admission using three indices to estimate the clinical impact on elderly patients in the CICU.A total of 123 patients were included in the study.

The mean age was 76.3 years. The demographic and clinical properties of the study population are shown in Table 1.

The median PNI, CONUT, and ALBI scores were 116±81.5, 3.4±2.1, and -2.32±0.37, respectively.

We defined all-cause mortality in 17.1% (21) of the patients during a median follow-up duration of 12±9 months.

The median length of CICU stay (LOS) was 6 days. We showed a statistically significant correlation between LOS and all nutritional scores. Longer LOS was correlated with worse nutritional status (Table 2).

Relationship between the length of stay of the patients and the PNI, ALBI, and CONUT scores

The PNI score was inversely correlated with LOS(p=0.02). A positive and low-level significant correlation was found between the LOS and ALBI scores (p=0.014). A positive and significant correlation was found between the LOS and CONUT score measurements (p=0.003). The length of the CICU stay decreased as patients' PNI scores increased (negative correlation), and the LOS increased as CONUT / ALBI scores increased (positive correlation) (Table 2).

Relationship between mortality and the PNI, ALBI, and CONUT scores

We showed a statistically significant difference between the PNI, ALBI, and CONUT scores and

Table 1. Demographic and clinical properties of the study population

Variables	Total (n=123)
Age (years, mean ±SD)	78.2± 9
Men, n (%)	66 (55.9)
Hypertension, n (%)	69 (58.5)
Diabetes Mellitus, n (%)	46 (39)
Coronary artery disease, n (%)	69 (58.5)
Stroke /TIA, n (%)	13 (11)
AF /PAF, n (%)	64 (54.2)
Hemoglobin, mg/dL	12±2
Plateletcount, 10^9/L	218.6±80
White blood cell count, 10^9/L	10.7 ±24.5
Creatinine, mg/dL	1.3±0.5
AST (U/L)	25.8±15.3
ALT (U/L)	22.4±17.8
Albumin, g/dL	3.64±0.4
HDL cholesterol, mg/dL	43.5±13
LDL cholesterol, mg/dL	86.2±30
Triglyceride, mg/dL	101.8±49
LVEF, %	38.5±14
TAPSE	16.1±4
SPAB, mmHg	49.5±17
ASA, n (%)	53 (43.1%)
β-Blocker, n (%)	86 (69.9%)
Clopidogrel, n (%)	20 (16.3%)
RAS inhibitors, n (%)	65 (52.8%)
Diuretics, n (%)	121 (98.4%)
Inotrops, n (%)	13 (10.6%)

SD (Standard deviation), TIA: transient ischemic attack, AF: atrial fibrillation, PAF: paroxysmal atrial fibrillation, AST: aspartate transaminase, ALT: alanine transaminase, HDL: high-density lipoprotein, LDL low-density lipoprotein , LVEF: left ventricular ejection fraction, TAPSE: transannular systolic excursion, SPAB: systolic pulmonary artery pressure calculated by echocardiography, ASA: acetylsalicylic acid, RAS: renin–angiotensin system (RAS inhibitors include angiotensin-converting enzyme inhibitor or angiotensin receptor blockade)

Table 2. The relationship between the length of stay and the PNI, ALBI and CONUT scores.

		PNI score	ALBI score	CONUT score
LOS (day)	r	-,215	,246	,291
	p	,020*	,014*	,003**
	N	118	99	103

p<0.05*, p<0.01**, LOS: the length of CICU stay

Table 3. Relationship between mortality and PNI, ALBI and CONUT scores.

	Mortality -/+	N	mean	SD	p
PNI	-	21	82,36	22,68	,001**
	+	97	121,17	88,36	
ALBI	-	17	-2,15	0,42	,019*
	+	82	-2,37	0,34	
CONUT	-	18	5,11	2,56	,002**
	+	85	3,11	1,94	

p<0.05*, p<0.01**, SD: standard deviation, PNI: the prognostic nutritional index, CONUT: the Controlling Nutritional status, ALBI:the albumin–bilirubin grade, -: ex, +: survive

mortality. As shown in Table 3, the CONUT and PNI scores were better in the patients who survived.

Relationship between the PNI, ALBI, and CONUT scores according to the rehospitalization in first 3 months (RH3M)

A significant difference was found between the PNI and CONUT scores according to the rehospitalization in the first 3 months. The difference between the PNI and CONUT scores of patients with and without rehospitalization in the first 3 months was statistically significant (Table 4). However, there was no significant difference between the ALBI scores according to the rehospitalization in the first 3 months (p>0.05).

Table 4. The relationship between PNI, ALBI and CONUT score according to the RH3M.

	RH3M +/-	N	mean	SD	p
PNI	+	12	78,36	22,96	,002**
	-	106	118,33	85,24	
ALBI	+	12	-2,35	0,33	,903
	-	87	-2,33	0,37	
CONUT	+	12	4,75	2,30	,033*
	-	91	3,29	2,13	

p<0.05*, p<0.01**, SD: standard deviation, PNI: the prognostic nutritional index, CONUT: the Controlling Nutritional status, ALBI:the albumin–bilirubin grade, RH3M: the rehospitalization in first 3 months, -: none, +: rehospitalized

Table 5. The relationship between PNI, ALBI and CONUT score according to the RH12M.

	RH12M +/-	N	mean	SD	p
PNI	+	22	88,25	23,07	,013*
	-	96	120,23	89,23	
ALBI	+	20	-2,49	0,36	,039*
	-	79	-2,30	0,36	
CONUT	+	20	3,95	2,50	,442
	-	83	3,34	2,10	

p<0.05*, p<0.01**, SD: standard deviation, PNI: the prognostic nutritional index, CONUT: the Controlling Nutritional status, ALBI:the albumin–bilirubin grade, RH12M: the rehospitalization in first 12 months, -: none, +: rehospitalized

Relationship between the PNI, ALBI, and CONUT scores according to the rehospitalization in the first 12 months (RH12M)

A significant difference was found between the PNI and ALBI scores according to the rehospitalization after the first 12-month follow-up duration (p<0.05). The difference between the PNI and ALBI scores of patients with and without rehospitalization in the first 12 months was statistically significant (Table 5). However, no significant difference was found between the CONUT scores according to the rehospitalization in the first 12 months (p>0.05).

DISCUSSION

The malnutrition can impediment the healing of diseases. The assessment of only one index of malnutrition may not provide adequate information because the nutrition is not a static condition. Our study is a retrospective analysis to evaluate the nutritional status and the relationship between

different nutritional scores in elderly patients hospitalized with acute decompensated HF.

The main results from the study were as follows: First, PNI was an independent predictor of mortality, short-and long-term rehospitalizations, and LOS in elderly patients hospitalized with acute decompensated HF. Second, its predictive power was better than the other nutritional scores of ALBI and CONUT evaluated in our study. Third, our study is the first to evaluate the role of CONUT and ALBI scores in elderly acute decompensated HF patients in Turkey. Previous studies have shown that the PNI score is associated with mortality and prognosis. Consistent with the literature, our results showed that the PNI score strongly impacted rehospitalization rates and mortality rates.

The difference between The CONUT and PNI scores is the total cholesterol. Albumin decreases as a negative acute-phase reactant and the leukocyte count increases as a marker of inflammation. Therefore, we can say that these scores were in balance and that they represent malabsorption and chronic inflammation in heart failure. We also know that, the underlying mechanism is not only the bad nutritional status but also the acute decompensation of heart failure. Liver dysfunction and congestion are common and contribute to mortality, especially in heart failure. Although studies have been conducted to assess the utility of the ALBI score in HF patients, they have mostly evaluated the effect of liver dysfunction on heart failure (18,19). In our study, the relationship between ALBI scores and length of hospitalization, mortality, and long-term rehospitalization was found to be statistically significant.

Keskin et al. reported that PNI was an independent predictor of mortality and poor prognosis in STEMI patients in a younger population (23,24). Our patient cohort consisted of elderly patients with complex comorbidities. However, similar results were obtained in our study. In a recent study in Turkey, the CONUT score was found to be better than the PNI score in predicting mortality in cardiac TX candidate patients. However, patients with acute decompensated HF were excluded, and the population was younger than in our study (25). Additionally, previous studies have generally evaluated single nutritional scores and compared the roles of low and high scores (8,9,20).

The ALBI scores in the short term (RH3M) and the CONUT scores in the long term (RH12M) were not statistically significant in showing rehospitalization. However, the PNI score was found to be the most statistically significant score in showing both. As expected, all were found to be significantly associated with mortality. Furthermore, the most statistically significant relationship was found in the PNI score. These findings highlight the importance of nutritional scores as a rapid assessment tool to determine the nutritional status of elderly patients with acute decompensated HF.

The aim of our study was to compare the superiority of the scores to each other, but we were unable to perform such a subgroup analysis due to the small number of the study population. We believe that our results may help future meta-analyses or clinical studies.

CONCLUSION

Malnutrition and HF have become public health problems due to advanced age and poor prognoses in developed countries. Mortality indicators for elderly patients are constantly being investigated in the aging population. In our study, we showed the importance of the CONUT, PNI, and ALBI scores in predicting mortality, rehospitalization, and LOS in elderly patients with acute decompensated HF. Nutritional status is important to reflect their immune competence and physical condition, which are the components of their general condition. Nevertheless, malnutrition causes some complications in patients with HF, so the assessment of malnutrition is essential in the CICU. We believe

that large randomized studies are needed on this subject.

Limitations

Our study's main limitations were its retrospective design and a single-center study. The size of the study was relatively small and needs to be confirmed in larger multi-center studies. Due to the retrospective design, how nutritional status could be improved or what the impact of the solutions for this is on the mortality and rehospitalization of patients could not be evaluated. Finally, we did not investigate changes in nutritional status after 1 year.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of this manuscript.

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RESEARCH

EFFECT OF BALLOON KYPHOPLASTY TREATMENT FOR OSTEOPOROTIC VERTEBRAL FRACTURE ON SPINAL BALANCE

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Abstract

Introduction: Osteoporotic vertebral fractures and spinal degeneration are common consequences of aging, and co-occurrence of these two pathologies can impair spinal balance leading to development of further deformities. The most common treatment measure for osteoporotic vertebral fractures is percutaneous balloon kyphoplasty which can potentially improve spinal balance along the sagittal and coronal planes. However, there is limited evidence in support of this issue to date.

Materials and Methods: This study included 49 patients (27 males, 22 females) who were diagnosed with osteoporotic vertebral fracture. The patients were evaluated preoperatively and one year postoperatively using three-dimensional thoracolumbar computed tomography scans. The lumbar lordosis and sacral slope angle were used to assess the sagittal plane, while coronal plane assessment was carried out using Cobb's angle. The angle values before and after treatment were compared statistically.

Results: The mean age of the study participants was 72.16 years (range: 61–94 years), and 28.6% and 71.4% of the patients exhibited thoracic and lumbar vertebral fractures, respectively. Moreover, 19 patients exhibited spontaneous or minor traumatic vertebral fractures, and 16 patients diagnosed with degenerative scoliosis exhibited a significant improvement in Cobb's angle after treatment. The comparison of pre-and postoperative mean sacral slope and lumbar lordosis angles showed an increase in both values and these differences, although not statistically significant, in agreement with previous literature.

Conclusion: Percutaneous balloon kyphoplasty has become an increasingly popular treatment measure for osteoporotic vertebral fracture due to its ability to effectively correct spinal imbalance in patients.

Keywords: Kyphoplasty; Osteoporosis; Spinal Fractures; Postural Balance.

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INTRODUCTION

Spinal degeneration, an inevitable consequence of aging, typically affects the intervertebral discs, facets, vertebral endplates, and ligaments and can eventually lead to spinal deformity (1). Severe vertebral degeneration is often associated with impaired spinal balance, resulting in deformities such as degenerative scoliosis, spondylolisthesis, and/or kyphosis. Previous studies have shown that spinal degeneration and its accompanying deformities are relatively common in elderly individuals, affecting their quality of life considerably (2).

Osteoporosis, another inevitable consequence of aging, is also relatively common and can be attributed to chronic vitamin D deficiency, hormonal withdrawal syndromes, malnutrition, immobility, and steroid use, particularly in socio-culturally underdeveloped societies. It is characterized by decreases in the anatomical strength of the bone structure and bone matrix density, leaving the lower thoracic and lumbar vertebrae particularly susceptible, as they bear the majority of the body weight. An initial microtrauma to the bones can, over time, lead to vertebral deformities and severe collapse fractures that affect the patient's spinal balance, resulting in symptoms of varying severity (3).

Minimally invasive methods have become increasingly popular in spinal surgery, such as percutaneous balloon kyphoplasty (PBK), used for the treatment of pathologies affecting multiple vertebrae (e.g., osteoporosis), has been shown to be associated with significantly lower morbidity and mortality rates than other treatment methods (4). PBK typically involves percutaneous insertion of a Jamshidi biopsy needle into the collapsed vertebral corpus, followed by inflation of a balloon that facilitates reshaping of the deformed vertebrae. The balloon is then removed and materials such as poly methyl acrylate (PMMA) that harden in the corpus and restore the strength of the vertebrae are placed in the cavity created to allow three-dimensional remodeling (5). Previous studies have shown that elderly patients with severe preexisting spinal degeneration exhibit a marked improvement following PBK treatment for osteoporotic vertebral fractures (OPVFs), and it has been suggested that this can likely be attributed to partial recovery of spinal balance. A limited number of studies to date have evaluated improvements in spinal balance along the coronal and sagittal planes following PBK treatment for OPVF (6). A limited number of studies to date have evaluated improvements in spinal balance along the coronal and sagittal planes following PBK treatment of OPVF, potentially due to the rarity of co-occurrence of deformities along both of these planes (7,8). Therefore, the current study aimed to evaluate the effects of PBK treatment for OPVF on coronal and sagittal balance in elderly patients.

MATERIALS AND METHODS

Patient population

This retrospective study examined 112 patients who underwent PBK treatment between 2016 and 2022 at a neurosurgery clinic of a university hospital. Of these, 49 patients (27 males, 22 females) who were over 60 years of age, diagnosed with OPVF, and had completed the first year of postoperative follow-up were included in the final study sample. Local ethics committee approval was obtained (13-06, 30/11/2022). Patients with a previous history of spinal surgery, spinal tumors, congenital malformations, or exposure to major trauma were not included. The study was carried out in accordance with the Declaration of Helsinki, and data on the patient's age, gender, fracture level, presence of trauma, and quantity of PMMA injected during treatment were recorded. The Cobb's angle, sacral slope (SS) angle, and lumbar lordosis (LL) angles were measured pre- and postoperatively, and the changes in these measures after treatment and the amount of PMMA used were also assessed.

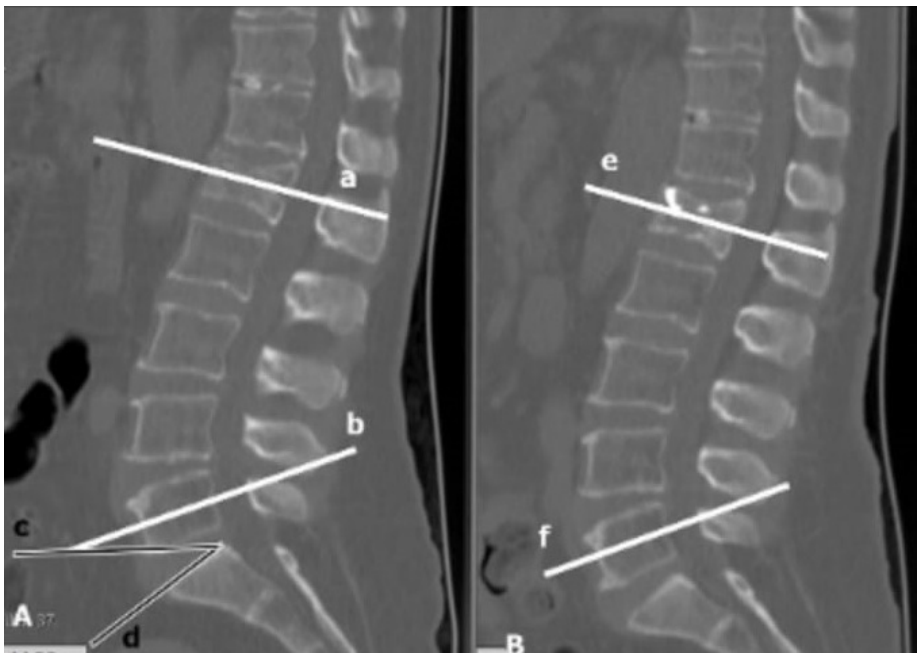


Figure 1. LL angle (between lines a and b) on a sagittal CT image. (A) Preoperative SS angle (between lines c and d), and (B) no significant change in LL angle (between lines e and f) seen postoperatively.

Radiological analyses

The patients included in the study sample were placed in a neutral supine position and thoracolumbar computed tomography (CT) scanning was carried out using the Aquilion Lightning™ system, a 16-row 32-section helical CT manufactured by Canon Medical. The resultant images were transferred to a computer using the DICOM PACS program, and the LL, SS, and Cobb's angles were measured using the Clear Canvas program. During thoracolumbar CT scanning, CT was checked that it was obtained from the T1 vertebral upper-end plate to the femoral head of pelvis. The SS angle was defined as the angle formed by a line parallel to the S1 endplate and a reference horizontal line, while the LL angle was defined as the angle between the horizontal midpoints of L1 and L5 (Figure 1). In 16 patients with lumbar degenerative scoliosis, the Cobb's angle was defined as the angle between two planes drawn along the upper and lower ends of the affected region (Figure 2).

Statistical analysis

All statistical analyses were performed using SPSS, version 23.0. Descriptive analyses included calculation of the mean, standard deviation, and minimum and maximum values for numerical variables and frequencies and percentages for categorical variables. Following confirmation of a normal distribution, an independent t test was used to examine the association between the pre- and postoperative (after one year of follow-up) Cobb's, SS, and LL angles. The Mann-Whitney U test was used to examine the association between the amount of PMMA used and postoperative changes in the Cobb's angle as the data were not normally distributed. The level of statistical significance was set at p-value of <0.05.

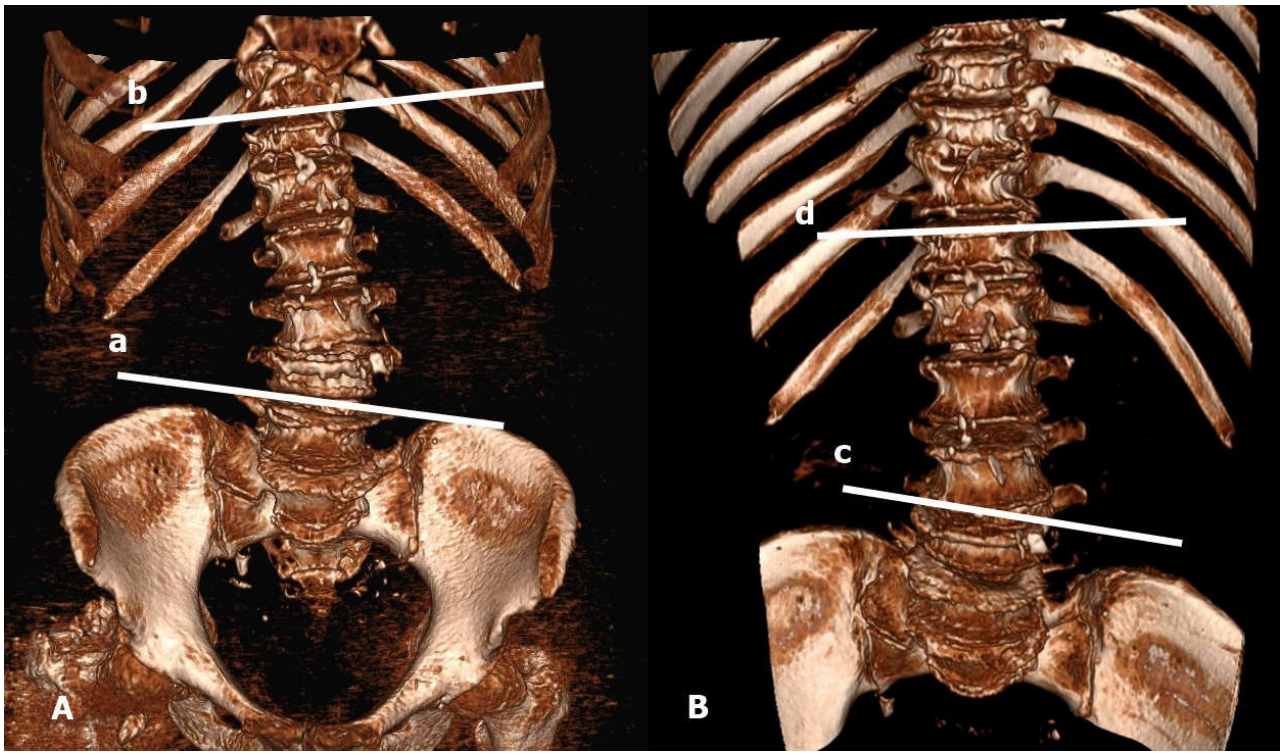


Figure 2. Three-dimensional reformat CT image showing collapse of the L3 vertebral corpus. (A) Preoperative Cobb angle (between lines a and b) of 18˚, and (B) postoperative Cobb angle (between lines c and d) of 14˚.

RESULTS

The mean age of the study participants was 72.16 years (range: 61–94 years), and 28.6% and 71.4% of the patients were diagnosed with thoracic and lumbar vertebral fractures, respectively. Additionally, 19 patients exhibited spontaneous or minor traumatic vertebral fractures. Table 1 includes a heatmap showing the correlation between the pre- and postoperative SS, LL, and Cobb's angles.

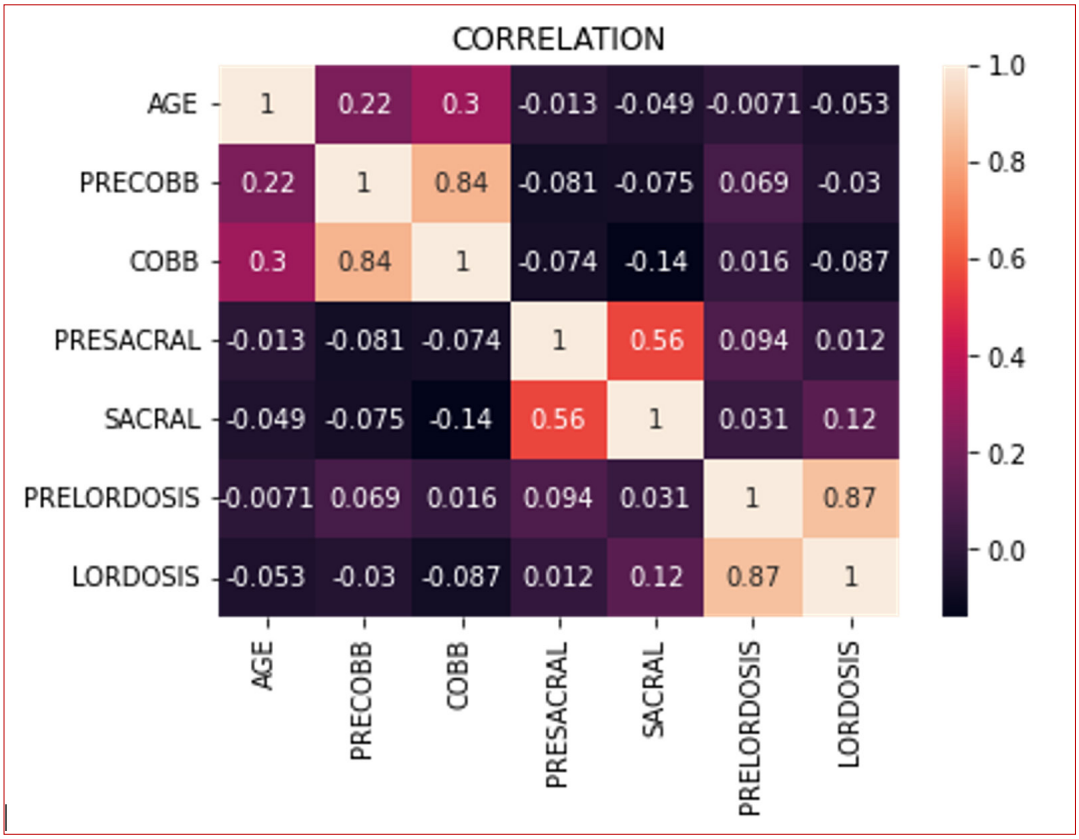
The mean postoperative Cobb angle was significantly lower than the mean preoperative Cobb angle in 16 patients diagnosed with degenerative scoliosis ($p = 0.050$, Graph 1). Moreover, comparison of pre-and postoperative mean SS and LL angles showed an increase in both values and these differences, although not statistically significant, were in agreement with previous literature (Graph 2).

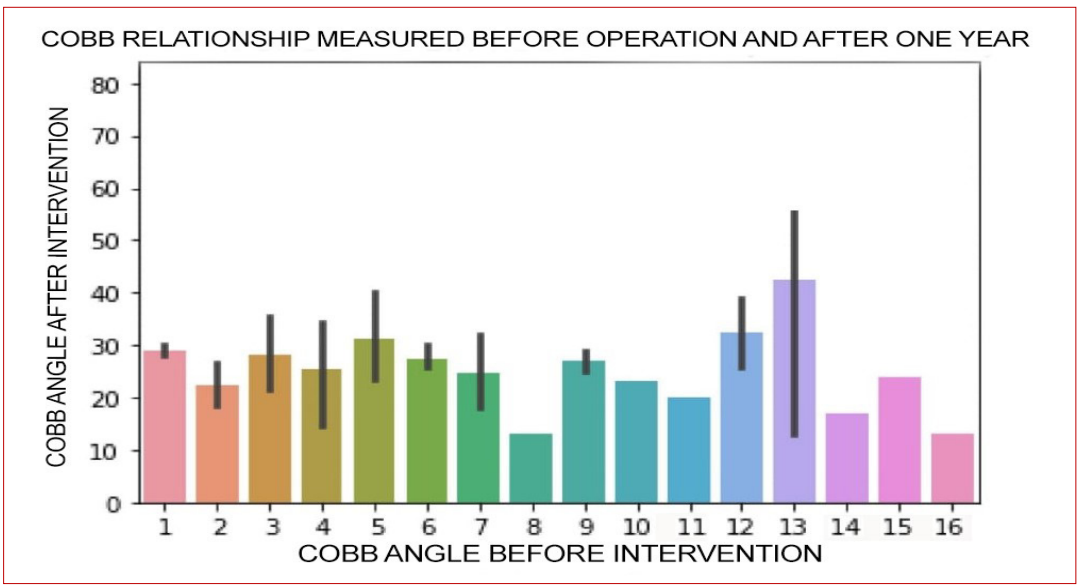
Examination of the relationship between the amount of PMMA used and the change in Cobb's angle after treatment showed that patients who exhibited no change and those who exhibited a decrease one year postoperatively received 3.37 cc and 3.57 cc of PMMA, respectively. A larger mean amount of PMMA was used in patients exhibiting decreases in their Cobb's angles one year postoperatively, although this difference was not statistically significant.

DISCUSSION

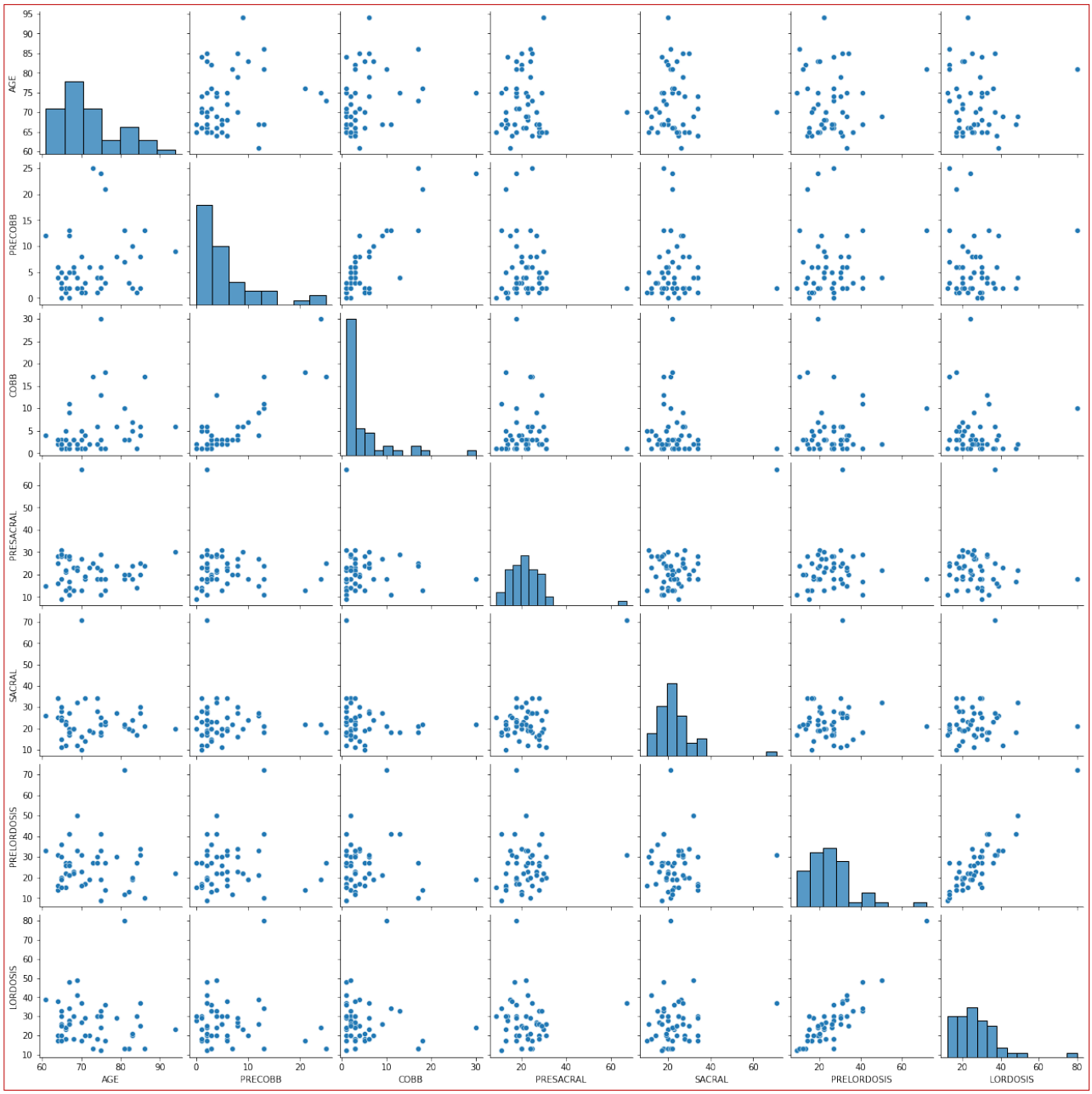
Impaired spinal balance, commonly caused by spinal degeneration and OPVF, has a relatively

Table 1. Heatmap showing correlation between pre- and postoperative SS, LL, and Cobb's angles.





Graph 1. Bar-plot showing pre- and postoperative Cobb's angle values.



Graph 2. Pair-plot graph showing association between variables.

high incidence rate among elderly individuals and this can be attributed to spinal aging caused by a combination of various environmental and genetic factors (9,10). The quality of life of patients diagnosed with OPVF and prominent three-dimensional irregular vertebral collapses may be affected considerably by the fracture itself as well as the development of postural dysfunction secondary

to spinal imbalance (5,9). Previous studies have concluded that partial restoration of spinal balance through PBK treatment of OPVF in elderly patients can improve their quality of life considerably (7,8,11).

Fechtenbaum et al., observed poorer sagittal balance in elderly patients diagnosed with OPVF than in age-matched healthy controls with no spinal complaints (12), while Ishikawa et al., reported that patients with OPVF exhibited higher rates of spinal curvature and compromised postural balance (13). The majority of evidence on improvements in spinal balance in the sagittal and coronal planes following PBK treatment for OPVF has been obtained from reviews of the current literature, with very few clinical studies examining this due to the rarity of both deformities occurring simultaneously (8,14,15). Cao et al. suggested that patients with OPVFs affecting the thoracolumbar junction were more susceptible to spinal imbalances, and PBK treatment resulted in significant improvements in spino-pelvic alignment and overall sagittal balance (7). In the current study, Cobb's angle was used to measure changes in coronal balance, and comparison of the pre- and postoperative values showed a statistically significant improvement after treatment.

While impaired sagittal balance is typically compensated for by the thoracic, lumbar, sacral, and hip joints, compensation of coronal imbalance is more difficult in the elderly population and usually relies on positional stance (16, 17). Therefore, the most common symptom of three-dimensional spinal deformity is impaired coronal balance, and treatment measures tend to result in marked improvements (18). In the current study, OPVF patients with degenerative scoliosis exhibited a significant improvement in the Cobb's angle after PBK treatment and, as this angle is minimally affected by compensatory mechanisms for spinal balance, this change can likely be attributed to the treatment itself. However, further prospective studies using larger sample sizes are necessary to confirm this.

OPVF most commonly affects the lumbar vertebrae as this region bears the main load of the trunk, is frequently traumatized, and is more mobile than the other vertebral levels (4). In the current study, lumbar vertebral fractures were observed in 71% of patients. At the same time, the LL angle was higher than that of thoracic kyphosis in healthy individuals. Pathologies affecting the lumbar vertebrae often lead to severe spinal imbalance along the sagittal plane (19). The current study assessed sagittal balance using the SS and LL angles, and comparison of the pre- and postoperative values showed a larger change in the latter compared to the former, although this difference was not statistically significant (as shown in the heatmap in Figure 1).

OPVF can occur spontaneously or after a minor trauma. In their large cohort study including 4349 patients with osteoporosis, Melton et al. found that the majority of new bone fractures observed in 896 patients during the follow-up period occurred spontaneously or could be attributed to minor trauma. Moreover, vertebral fractures without any clinical symptoms were more common in these patients than in the normal population (20). Similarly, in the current study, 19 patients were diagnosed with OPVFs that developed either spontaneously or after minor trauma.

Important considerations of PBK treatment include differences in outcomes between bilateral/unilateral injections and by the amount of PMMA injected, with previous studies suggesting that injection of PMMA at an optimal angle from the side with an intact pedicle can reduce the risk of complications (21,22). Therefore, unilateral PMMA injections were performed in the current study. With regards to the amount of PMMA required, the general consensus leans toward quantities that can safely fill the cavity (22). The current study observed no association between the amount of PMMA injected and the extent of improvement in coronal balance, as patients exhibiting a significant

improvement in the Cobb's angle have received only a very slight excess of PMMA. In the future, larger studies should aim to examine these outcomes on the vertebral side where coronal balance is deviated.

The advancement of science and informatics have made the severity of disease, treatment outcomes, and risk of complications more predictable. Rath et al., proposed the multiple linear regression model that examined the coexistence of metabolic and infectious diseases taking various demographic and medical parameters into consideration, and suggested that it could be used to predict the patient's clinical progression (23). Similar studies could be used for OPVF treatment, and the rate of deformity improvement after PBK can be predicted at a higher rate.

The current study included patients who underwent a standard PBK surgical procedure under fluoroscopy. PMMA was injected from the most suitable side of the pedicle and to the most reliable localization of the vertebra. Although the extent of correction of the spinal imbalance can potentially be improved through administration of the injection on the side/location with the greatest collapse using advanced technologies such as intraoperative CT and/or robotic surgical equipment, these methods are limited by their ethical considerations (increased X-ray exposure, infection rate, surgery time and anaesthesia medication) and poor cost-effectiveness (24,25).

CONCLUSIONS

Elderly patients diagnosed with OPVFs exhibit a significant improvement in symptoms after PBK treatment, potentially due to its ability to effectively correct sagittal and coronal imbalances.

Conflict of Interest

The authors declare that there is no conflict of interest between them

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RESEARCH

A SINGLE-CENTER, CROSS-SECTIONAL PREVALENCE STUDY OF CERVICAL DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS

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Abstract

Introduction: In this study, we aimed to investigate the prevalence and characteristics of cervical diffuse idiopathic skeletal hyperostosis using computed tomography scans of the cervical vertebra.

Materials and Methods: This study was performed using the Picture Archiving and Communication System of our hospital. Computed tomography images of 1744 patients were included in this study. The patients were divided into age groups by decade. The characteristics of the cervical osteophytes and intervertebral bridging were recorded. Cervical diffuse idiopathic skeletal hyperostosis was diagnosed based on the criteria described by Resnick and Niwayama.

Results: The mean age of the study group was 48 years. The prevalence rate of cervical diffuse idiopathic skeletal hyperostosis was 6.3% (6.4% in males and 6.2% in females). The difference between genders was not statistically significant (p=0.908). The prevalence rates significantly increased as age increased. The prevalence rate of cervical osteophytes was 36.5% (33.9% in males and 40.6% in females). The most frequently affected level was C5-6 (16.9%), and the vertebra was C6 (30.6%). Osteophytes were localised in the midline with a rate of 75.5% and was most frequently found in the 70–79 age group (81.2%).

Conclusion: In our study, we detected the prevalence rates of cervical diffuse idiopathic skeletal hyperostosis and cervical osteophytes, which were 6.3% and 36.5%, respectively. In comparison, the most frequently affected vertebra and intervertebral levels were, respectively, C6 (30.6%) and C5-6 (16.9%), and cervical osteophytes was most often formed in the midline (75.5%).

Keywords: Geriatrics; Hyperostosis, Diffuse Idiopathic Skeletal; Prevalence; Cervical Vertebrae; Osteophyte.

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INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH), or Forestier's disease, is a chronic and non-inflammatory disease characterised by diffuse osteophyte formations in the vertebra due to ossification of the anterior longitudinal ligament, which connects the ventral aspects of the vertebrae and surrounding tissues (1, 2). Its diagnosis is based on those criteria described by Resnick and Niwayama, the presence of calcification and ossification along the ventrolateral aspects of at least four adjacent vertebral bodies (3 intervertebral levels); the preservation of disc levels; and the absence of apophyseal joint degeneration or sacroiliac inflammatory changes (3).

DISH's pathophysiology has not yet been clearly described; however, a strong relationships with metabolic diseases, such as obesity and type 2 diabetes mellitus, has been identified in the literature (4). It has been reported that its prevalence ranges between 2.6% and 30.8% in the general population. DISH also increases with age, and it is more commonly seen in males and in developed populations. The male-female ratio was approximately 2:1 (5). Thoracic vertebrae are the most frequently involved region followed by cervical and lumbar vertebrae. The clinical signs of the disease vary depending on the involvement site. The most commonly found symptoms are pain and limited motion in the affected vertebral site (4, 6).

The prevalence of DISH of the cervical vertebrae (C-DISH), or cervical Forestier's disease, was reported as between 0 and 7.9% in various studies (7, 8). C-DISH is usually asymptomatic. However, though rarely, various symptoms and signs may be related with the localisation of pathological ossification and its impact on the neighbouring pharynx, oesophagus and trachea. C-DISH symptoms also include cervical pain, limited motion, dysphagia, dysphonia, snoring, obstructive sleep apnoea, stridor, vocal cord paralysis, coughing, spinal cord compression, pharynx/hypopharynx injury due to post-traumatic osteophyte fracture, dyspnoea, aspiration pneumonia, weight loss, thoracic exit syndrome, Horner's syndrome, spinal fracture, stroke and myelopathy. These symptoms may be accompanied by difficulties in intubation-extubation and airway management. Cardiopulmonary arrest has been also reported, though rarely. The symptomatic patients are mostly male, and dysphagia is the most frequently seen symptom (75%) (6, 9-13).

There are no disease-specific standard laboratory findings. The diagnosis of DISH is established radiologically. The disease is most commonly identified coincidentally in standard radiographies. Computed tomography (CT) is the most important imaging technique in its diagnosis, and it displays the relationship of DISH with neighbouring organs as well as its shape and size (Figure 1A, 1B). The larynx, hypopharynx, trachea and oesophagus can be examined comprehensively using magnetic resonance imaging (MRI), barium oesophagography, video laryngoscopy (Figure 1C), gastroscopy and bronchoscopy (4, 12).

Differential diagnosis of DISH, includes diseases that cause excessive ossification in the axial skeleton, such as ankylosing spondylitis, degenerative spondylosis, seronegative spondyloarthropathy, acromegaly, parathyroid disorders, fluorosis and ochronosis (4).

Symptomatic therapy is primarily applied for its treatment. In the case of failed conservative treatment, surgical therapy can be planned if conditions such as myelopathy and fracture develop (9, 14).

In recent years, some epidemiological research has been carried out among some ethnic groups, particularly in Europe and Far East regions. Most of research on DISH are case reports or case series. There are not yet any adequate comprehensive prevalence studies for all ethnic populations (10). Due to the rapid aging of the world's population, clinicians are increasingly diagnosing C-DISH in

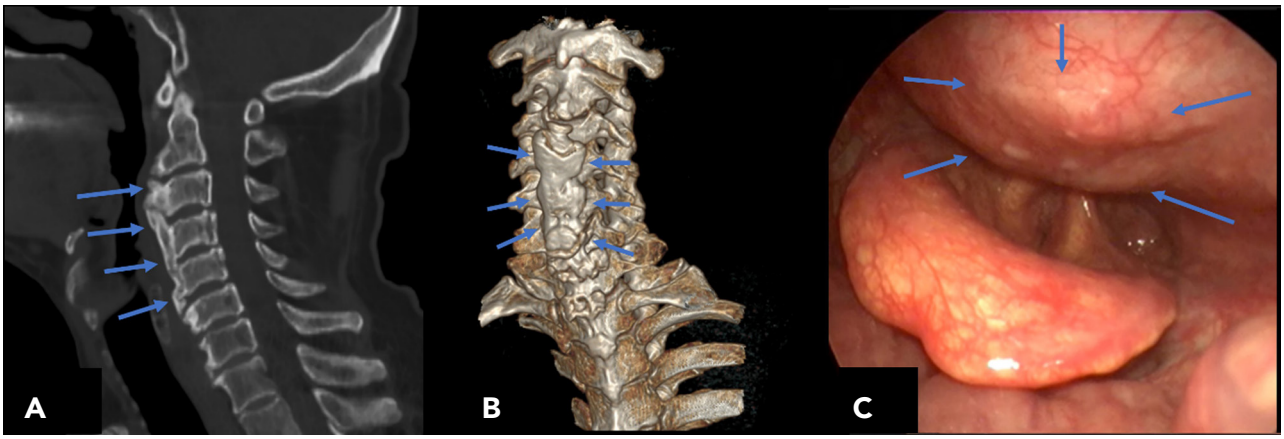

Figure 1. The images of a patient diagnosed with C-DISH

A. Sagittal CV-CT image of a 65-year-old male patient with C-DISH. B. 3D reconstruction of CV-CT image of the same patient. C. Videolaryngoscopic image of the same patient (blue arrows indicate C-DISH).

patients who have cervical complaints. However, sufficient prevalence studies from Türkiye on C-DISH could not be found in the literature. This study aimed to investigate the prevalence and characteristics of C-DISH using computed tomography scans of the cervical vertebra (CV-CT).

MATERIALS AND METHODS

This cross-sectional study was carried out in accordance with the Helsinki Declaration upon receiving approval from the Non-Invasive Clinical Research Ethics Committee of Amasya University (19.01.2022-53136). The study used our hospital's PACS system between February 1, 2022 and May 31, 2022. The study included the images of 2192 patients who underwent CV-CT for any reason between January 1, 2020 and December 31, 2021. First, CT images of 373 patients under the age of 20 were excluded from the study. Then, when CV-CT images were examined, 34 patients with previous cervical surgery findings, 18 patients with severe traumatic cervical injury findings, and 23 patients with cervical disc herniations and severe disc deformities that cause changes in the intervertebral distances findings were excluded from the study. Finally, after the CV-CT images of 448 patients were excluded from the study, the study continued with those of 1744 patients. The patients were divided into the following age groups: 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and 80 and over. No research was performed addressing aetiology, accompanying comorbid disease and patient complaints.

Radiological Examination

All CV-CT images were obtained with 1.25-mm-thick slices on the axial plane using GE Revolution CT 128-Slice (GE Healthcare, USA), and then sagittal reconstructions were created. CV-CT images were examined based on bone dose using the picture archiving and communication systems (PACS). Cervical vertebrae (C1, C2, C3, C4, C5, C6, C7) and intervertebral distances (C1-2, C2-3, C3-4, C4-5, C5-6, C6-7) were evaluated. The following were then recorded separately: the presence and number of the cervical osteophytes (C-O) in vertebral bodies, the localisation of C-Os in the vertebral body (right, left, medial, right&medial together, left&medial together, right&left&medial together), and the presence and number of intervertebral bridging.

The predominant localisation of osteophytes was taken into consideration for the patients believed to have osteophytes in multiple vertebrae. The relationship between the 7th cervical vertebra and 1st thoracic vertebra was not evaluated. The diagnosis of C-DISH was based on the criteria described by Resnick and Niwayama (3).

All CV-CT images were evaluated by two senior Ear, Nose and Throat specialists. Prior to the study, the researchers twice evaluated the CT images of 50 patients with an interval of 20 days based on the interobserver agreement.

Statistical Analysis

All data were analysed using the Statistical Package for the Social Sciences (SPSS) (IBM) Version 25 software. Student t test, χ^2 tests and Wald Z test were used according to their applicability. A type 1 error level below 5% ($p< 0.05$) was accepted as statistically significant.

RESULTS

The kappa coefficient of the interobserver agreement was 0.89 and 0.94, respectively.

Of the 1744 patients included in the study, 1069 (61.3%) were male and 675 (38.7%) were female. The mean age of the study group was 48±19.7 (20-96) years (males: 45.7±19 [20-95], females: 51.7±20.2 [20-96]). The higher mean age of females in the study group was statistically significant (p=0.001). C-DISH was diagnosed (C-DISH+) in 110 (68 males [61.8%] and 42 females [38.2%]) of all the patients. The C-DISH prevalence was 6.3% (6.4% in males, 6.2% in females). The difference between genders regarding C-DISH prevalence was not statistically significant (p=0.908).

The data on all demographics, affected vertebrae and intervertebral distances are given in Table 1.

In the 110 patients with C-DISH, bridging was observed at 3 levels in 69 (62.7%), 4 levels in 27 (24.6%) and 5 levels in 14 (12.7%) patients.

In the study group, C-O was detected in 636 patients (C-O+), (in min. 1 and max. 7 levels). The prevalence of C-O was 36.5% in the study group (33.9% in males and 40.6% in females). High prevalence rate of C-O+ in females was statistically significant (p=0.004). The difference between age distributions in terms of genders was statistically significant among C-O+ patients (p=0.001). The

Table 1. Descriptive Statistics, C-Osteophyte and C-DISH Characteristics

	Study Group		C-O (+)			C-DISH (+)		
	n/%	Min.-Max.(y)	n/%	Min.-Max.(y)	p	n/%	Min.-Max.(y)	p
Gender Total	1744/100	20-96	636/36.57%	26-96		110/6.3	40-94	
Male	1069/61.3	20-95	362/33.96%	28-95	**0.004**	68/6.4	40-94	0,908
Female	675/38.7	20-96	274/40.69%	26-96		42/6.2	52-94	
	Mean ±SD(y)	Min.-Max.(y)	Mean ±SD(y)	Min.-Max.(y)	p	Mean ±SD(y)	Min.-Max.(y)	p
Age	48±19.7	20-96	64.9±19.7	26-96		72 ±19.8	40-94	
Male	45.7±19	20-95	63.1±19.7	28-95	**0.001**	71.8±19.8	40-94	0,355
Female	51.7±20.2	20-96	67.4±19.7	26-96		74±19.7	52-94	

Table 1 continued.

Table 1. Descriptive Statistics, C-Osteophyte and C-DISH Characteristics

Age Groups									
	Study Group			C-O (+)			C-DISH (+)		
	Total n/%	M. n/%	F. n/%	Total %	M. %	F. %	%	M. %	F. %
20-29	388/22.2	276/71.13	112/28.9	0,8	0,4	1,8	0	0	0
30-39	304/17.4	196/64.5	108/35.5	4,3	6,1	1	0	0	0
40-49	292/16.7	177/60.6	115/39.4	27,1	28,8	24,4	1.4	5,8	7,3
50-59	243/13.9	150/61.7	93/38.3	56,8	58	54,8	5.8	15,9	34,2
60-69	229/13.1	133/58.1	96/41.9	75,1	76,7	73	11.8	18,8	17,1
70-79	149/8.5	79/53	70/47	**81,2**	81	81,4	18.8	30,4	17,1
≥80	139/8	58/41.7	81/58.3	79,1	77,6	80,3	**26.6**	29	41,5
Total	1744/100	1069/61.3	675/38.7	36,5	33,9	40,6	6.3	6.4	6.2
Cervical Osteophyte and Intervertebral Bridge values									
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**		
n	1	47	130	276	498	533	367		
%	0.1	2.7	7.5	15.8	28.6	**30.6**	21		
	C1-2	**C2-3**	**C3-4**	**C4-5**	**C5-6**	**C6-7**			
n	0	26	73	153	295	285			
%	0	1.5	4.2	8.8	**16.9**	16.3			

(M.: Male, F.:Female, n:number, SD:standart deviation, C-DISH:Cervical diffuse idiopathic skeletal hyperostosis, C-O:Cervical osteophyte, Min.:Minimum, Max.:Maximum, y:year)

mean age of C-O+ patients was 65±19.7 years, whereas the mean was 38±19.7 years in patients who were not C-O+ (p=0.001). The lowest rate of C-O prevalence was detected in the 20-29 (0.8%) age group, whereas the highest rate was determined in the 70-79 (81.2%) age group (Figure 2). The C-O prevalence was 36.5% in the study group, whereas it was significantly higher in the groups aged over 40 and 60 years (58.9% and 78%, respectively) (p=0.001) (p=0.001).

In the study group, the lowest rates of osteophytes were found in C1 (0.1%) and the highest in C6 (30.6%). Intervertebral bridging was monitored in one or more intervertebral levels (min. 1 and max. 5) in 418 (24%) patients. No bridging was encountered in the C1-C2 level, whereas the largest number of bridging was monitored in the C5-C6 level (16.9%) (Figure 3). The C4-5 and C5-6 levels were affected in all of the C-DISH+ patients (Figure 3). When the localisations of osteophytes

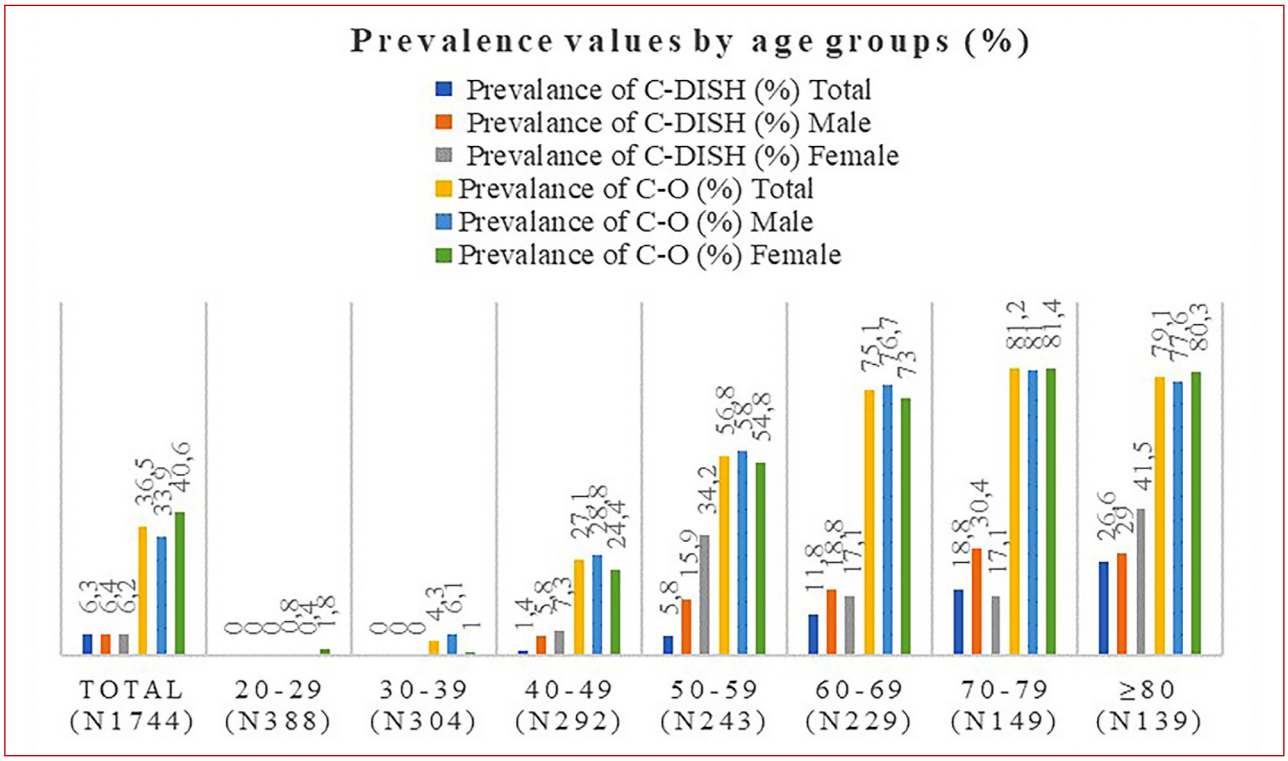

Figure 2. The prevalence values of the affected cervical vertebrae and intervertebral levels in the age groups

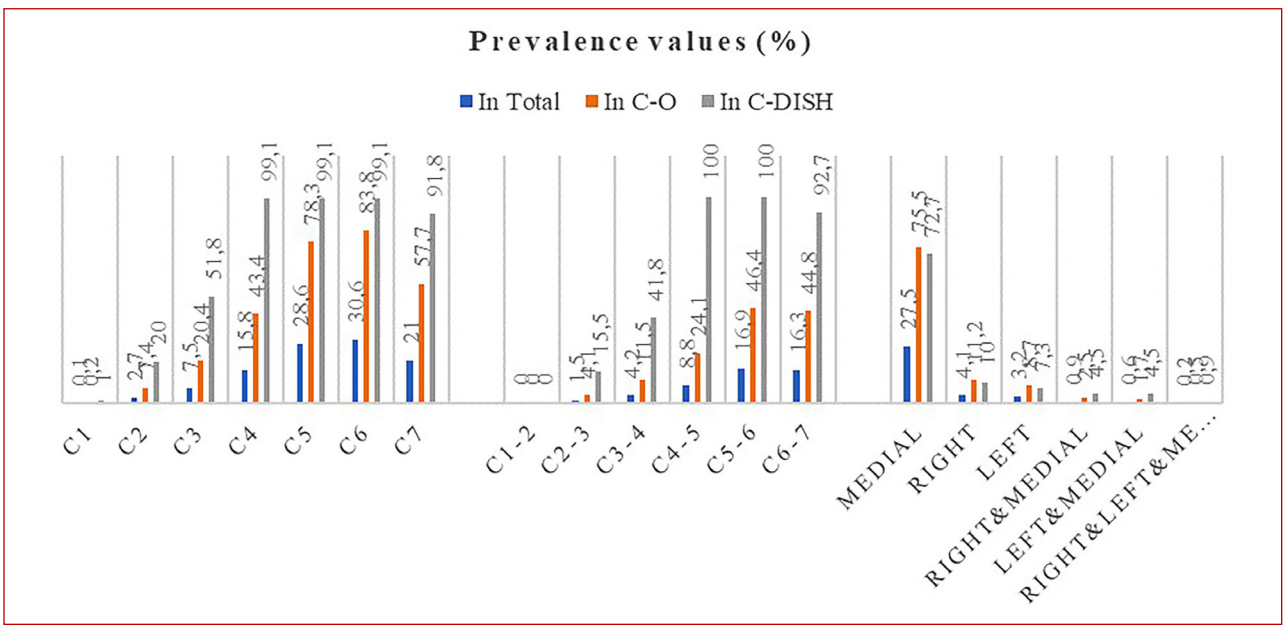

Figure 3. The prevalence values of the affected cervical vertebrae, intervertebral levels and the localisation distribution of osteophytes

were examined, 75.5% of osteophytes were in the midline (Figure 3).

DISCUSSION

In the literature, the overall prevalence of DISH has been reported as between 2.6 and 30.8%. DISH is more common in men, and its prevalence increases in the elderly (even up to 44%). The thoracic spine is most commonly affected, and it has strong associations with metabolic diseases, such as obesity and type 2 diabetes mellitus (15). Studies report the prevalence of DISH belonging to different regions and ethnic groups from most parts of the world. This indicates that DISH is not geographically specific and is common despite differences (16). DISH prevalence may vary depending on age group distributions of study populations, gender, genetic and ethnic variability, imaging techniques used for scanning, lifestyle habits and frequency of examinations. The prevalence of DISH can be expected to increase in the coming years due to the increase of the elderly population and the worldwide increase in obesity and type 2 diabetes mellitus (2, 5, 14, 16). C-DISH prevalence has been reported between 0% and 7.9% in the limited number of studies on the topic (7, 8). Our study will be one of the first to examine the prevalence and characteristics of only C-DISH and C-O using CV-CT in detail.

In the past, direct radiography was used for the diagnosis of DISH, and lower prevalence rates were obtained (17). Today, studies have demonstrated that CT is more advantageous than plain radiography in the diagnosis of DISH and has high sensitivity in showing spinal ligament ossification; it may be the best imaging technique to encounter the exact prevalence (8, 18-20). Hirasawa et al. (19) compared direct radiography and CT evaluations and found a higher prevalence of DISH with CT.

As far as we know, the prevalence of C-DISH has also been reported in four studies using CT for general DISH screening (Table 2). Kim et al. (8), evaluated whole spine CT scans of patients over 16 years of age who were examined at Cheju Halla

Table 2. Previous Reports on C-DISH Prevalence

Author	Year	Modality	Country	n	Age (mean)	Min-max	C-O Prevalence % (Total/Male/ Female)	C-DISH Prevalence % (Total/Male/ Female)
Kagotani et al.	2014	Whole-Spine Radiography	Japan	1647	64.4	NA	NA	0
Kim et al.	2018	Whole Spine CT	Korea	164	NA	16- NA	NA	7.9
Liang et al.	2019	PET-CT	China	2000	48.5	20-95	6.6/7.9/4.1	2/ NA / NA
Hiyama et al.	2018	Whole Spine CT	Japan	1479	54.7	20- >90	NA	Low
Ahmed et al.	2022	Whole Spine CT	India	1815	47.5	20-98	>20/ NA / NA	0
This study	2022	Cervical Vertebra CT	Türkiye	1744	48	20-96	36.5/33.9/40.6	6.3/6.4/6.2

(NA: Not Available, n:number, Min.:Minimum, Max.:Maximum

General Hospital and reported the first and the highest C-DISH prevalence as 7.9%. Liang et al. (18), evaluated subjects who underwent PET/CT for the purpose of cancer screening in a single hospital and determined a C-DISH and C-O prevalence of 2% and 6.6%, respectively. Hiyama et al. (17), evaluated patients who had experienced trauma who had undergone whole-spine CT and stated, without specifying numbers, that C-DISH prevalence was low. In contrast, Ahmed et al. (21), evaluated whole-spine CT scans of polytrauma patients from 2018-2021 above the age of 20 years and found no C-DISH patients in their study. All these studies observed that prevalence increased with age, and it was significantly high in males.

We also used CV-CT to assess C-DISH prevalence. We utilised the criteria described by Resnick ve Niwayama for DISH diagnosis (3). Since our study has a retrospective design, we could not evaluate sacroiliac joint involvement, which was one of the diagnostic criteria. Although the mean age and age distribution of our study group were similar with studies in the literature, which reported C-DISH prevalence using CT, we found prevalence rates of 6.3% and 36.5%, respectively, for C-DISH and C-O, which were higher than the mean values found in the literature. Weinfeld et al. (22) reported that genetic or hereditary differences are the important predisposing factors regarding DISH. They also demonstrated that DISH prevalence was lower in Asian, Black and Indian populations. Kim et al. (8) obtained lower prevalence rates in Korean patients, whereas higher prevalence values were obtained in studies conducted with Japanese patients originating from the same race. Therefore, it is believed that genetic factors influence DISH prevalence more than race (21, 23). We consider that the prevalence values of our study were found to be higher than the other studies performed on mostly Asian study populations because of racial and genetic differences as well as lifestyle habits of the Turkish population. Since CV-CT is an imaging method mainly preferred in patients with cervical complaints in the clinic, the probability of detecting any pathology is higher in these patients. Also, for this reason, we may have found the prevalence rates of DISH to be high in our study.

Most of the previous studies denoted that DISH is more frequently seen in males independently of ethnic origin or genetic factors (2, 5, 7, 23). However, some authors showed that T-DISH prevalence was higher in female patients in the black race population (2). In our study group, the mean age of females was significantly higher than the males' ($p=0.001$). However, this difference decreased in the age groups over 40 and 50. This decrease probably resulted from the high number of hospital admissions in young males, since they work more actively in our population and, therefore, are exposed to more trauma. However, in the studies of Yoshihara et al. (2), Bateman et al. (15) and Pereira et al. (24), the T-DISH prevalence differences between male and female patients were not statistically significant. In our study, the higher prevalence rate of C-DISH in females was not significant ($p=0.908$), whereas the higher prevalence rate of C-O in females was statistically significant ($p=0.004$). In other words, we found that the probability of developing C-DISH in patients does not depend on gender. However, we determined that the difference between genders regarding prevalence rates of C-DISH increased in favour of males as age advanced (11.4% in males and 9.2% in females over 40 years, 20% in males and 15.4% in females over 60 years).

We concluded that advanced age caused an increase in prevalence rates of C-DISH and C-O. The lowest prevalence rates of C-O and C-DISH were identified in the 20-29 age group, and the highest prevalence rates were identified the 70-79 year group and older. The mean ages of the patients who did and did not have C-DISH were 72 and 46 years, respectively, and the mean ages of the patients who did and did not have C-O were 72 and 38 years, respectively ($p=0.001$), ($p=0.001$).

No C-DISH patients were found in males below 40 years old and females below 52 year old. There were no C-O+ patients below 26 year old. The C-DISH prevalence was 10.5% and 17.8% in the groups over 40 and 60 years old, respectively. The increase in the prevalence with advancing age was statistically significant (p=0.001), (p=0.001). Almost 90% of the C-DISH+ patients were 50 years old and over. Approximately 18% of patients 60 years and older had C-DISH, and 80% had C-O.

In their review, Verlaan et al. (16) evaluated the vertebrae affected by C-DISH on dysphagia and/or airway obstruction cases due to C-DISH and identified that C1 (2.9%) was the least affected vertebra, whereas C4 (95.9%) was most affected one. Symptoms were present in 25% of the patients without affecting four adjacent vertebrae. This study showed that essential symptoms may occur without an increase in the number of osteophytes. Some authors reported that slow-growing cervical osteophytes can be reasonably well tolerated by many individuals; however, fast onset complaints may emerge due to suddenly occurring soft tissue oedema due to a triggering condition, such as an upper respiratory tract infection (16). For this reason, we believe that the presence of osteophytes or bridging, even in small numbers, should be considered symptomatic at any time, and this should not be forgotten, especially in elderly patients with symptoms.

In our study group, C-O was present in 36.5% of the patients, whereas only 24% had intervertebral bridging. We consider that the high mobility of cervical vertebrae prevented more bridging. No bridging was monitored in C1-2, whereas the largest number of bridging was observed in C5-6. The least number of osteophytes was found in C1 whereas the largest number of osteophytes was found in C6, C5 and C7. We ascertained that most of the osteophytes (75.5%) were localised in the midline. We speculate that dysphagia most often occurs in the patients with C-DISH, since osteophytes predominantly form in the ventromedial aspect of the lower cervical vertebrae in the cervical region, and this region has a close association with the oesophagus. C-DISH and C-O are the important diagnoses that should be kept in mind, particularly for elderly patients admitted with cervical region complaints, primarily dysphagia, along with comorbid factors. Early diagnosis and an effective multidisciplinary approach can provide appropriate treatment.

Limitations

There are some limitations of our study. First, our study addressed only cervical vertebrae, and other spine regions were not examined. Second, sacroiliac joint involvement, one of the diagnostic criteria of DISH described by Resnick and Niwayama, could not be evaluated (3). Third, the patient's symptoms, comorbidities and etiopathogenetic data could not be obtained because of the study's retrospective design. Finally, our study is not a community screening study (that would be unethical due to radiation from CT). However, these are the scans of patients who applied to the hospital for any reason, and the clinician requested a CT scan. So it is expected that the prevalence is higher than the previous literature since most of them have evaluated patients that do not specifically have neck symptoms – they evaluated acute trauma cases or cancer screening patients.

CONCLUSION

In our study, we detected that C-DISH and C-O prevalence rates were 6.3% and 36.5%, respectively. There was no significant difference between genders in terms of C-DISH prevalence. Prevalence values significantly increased with age; cervical osteophytes were most often localised in the midline, and the most affected cervical vertebra and intervertebral levels were C6 and C5-6, respectively. Given all these data, we conclude that C-DISH is

a geriatric disease. Therefore this fact should be considered, particularly for patients admitted with cervical complaints. Furthermore, the follow-up and treatment of these patients should be performed with a multidisciplinary approach.

Declaration of Conflicting Interests

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RESEARCH

EVALUATION OF HOSPITALIZED YOUNGEST-OLD, MIDDLE-OLD AND OLDEST-OLD COVID-19 PATIENTS IN TERMS OF MORTALITY AND RISK FACTORS

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Abstract

Introduction: In the coronavirus disease 2019 (COVID-19) pandemic, severe disease is predominantly seen in advanced-aged patients. In our study, we evaluated hospitalized youngest-old (65–74 years), middle-old (75–84 years) and oldest-old (≥85 years) COVID-19 patients in terms of mortality and risk factors.

Materials and Methods: This retrospective study included hospitalized COVID-19 patients aged 65 years and older. Demographic characteristics, such as age, gender and comorbid conditions, baseline blood oxygen saturation levels, the necessity of oxygen treatments (nasal cannula,oxygen mask/reservoir oxygen mask), condition of the patients(mild, moderate, severe), baseline laboratory findings as C-reactive protein , white blood cell counts, thrombocyte counts, lymphocyte counts, D-dimer, alanine aminotransferase, aspartate aminotransferase and ferritin levels, pulmonary involvement on computerized tomography, the increase in oxygen requirements, the status of going to the intensive care unit and the status of receiving corticosteroids were recorded. Factors associated with mortality were analyzed.

Results: A total of 399 geriatric COVID-19 patients were included in this study: 214(53.6%) were female and 185 (46.4%) were male. The mean age of the patients was 75±7.87(min:65–max:96). In our study, the mortality rate was found to be higher in the middle-old and oldest-old groups than in the youngest-old group (p=0.01). Other factors associated with mortality were as follows: lower baseline oxygen saturation levels (p=0.03), necessity of higher oxygen treatment (p<0.01), higher pulmonary involvement on computerized tomography (p<0.01), corticosteroid use (p<0.01) and having Alzheimer's disease (p=0.03).

Conclusion: Our findings emphasize that older patients are more vulnerable to COVID-19 infection and require special attention.

Keywords: Geriatrics; SARS-CoV-2; Mortality.

INTRODUCTION

Today, people are living longer, especially in developed countries. Overall birth rates are decreasing and the elderly population has been rising. With the increase in life expectancy, the geriatric patient population accessing health services is also rising. Infectious diseases are the most common causes of hospitalization, morbidity and mortality among elderly individuals (1,2).

In the coronavirus disease 2019 (COVID-19) pandemic, which has been affecting the world since 2020, severe disease is predominantly seen in advanced-aged patients and/or in patients with underlying comorbidities (3). Physiological changes occurring with aging, such as the weakening of cellular and humoral immunity, have made elderly people more fragile throughout the pandemic. In some studies, it has been reported that the rates of hospitalization with the diagnosis of COVID-19 increase with age: 1% for those aged 20 to 29 years, 4% for those aged 50 to 59 years, and 18% for those over 80 years (4). A study in the United States showed that 80% of COVID-19-related deaths are over the age of 65 (5).

The geriatric population can be divided into three groups: ages 65–74 years, 75–84 years and≥85 years are named as youngest-old, middle-old and oldest-old, respectively (6).It should be noted that these elderly groups may vary and their responses to infections may be different. In our study, we evaluated hospitalized youngest-old, middle-old and oldest-old COVID-19 patients in terms of mortality and risk factors.

MATERIALS AND METHODS

This retrospective study included hospitalized COVID-19 patients aged 65 years and older between November 2021 and January 2022. The hospitalization rate of geriatric COVID-19 patients admitted to our hospital was 5.2%. Demographic characteristics, such as age, gender and comorbid conditions, were recorded. Ethical approval was obtained from the Izmir Bozyaka Training and Research Hospital Ethics Committee.

The patients' conditions were classified as having mild, moderate and severe during hospitalization (7). Mild cases were described as patients who had signs of COVID-19 but did not have dyspnea or abnormal chest imaging. Moderate cases were individuals who had pneumonia and whose blood oxygen saturation levels were over 94%. Severe cases had an oxygen saturation of ≤93%, respiratory frequency of ≥30 and/or lung infiltrates of more than 50%. Mild patients were hospitalized due to inadequate oral intake, need for isolation, lack of care and/or trauma.

At hospitalization, blood oxygen saturation levels and the necessity of oxygen treatments (nasal cannula, oxygen mask/reservoir oxygen mask) were recorded. Also, the increase in oxygen requirements, the status of going to the intensive care unit and the status of receiving corticosteroids (none, 0,5-1 mg/kg i.v. methylprednisolone for up to 10 days or pulse steroid, ≥ 250 mg i.v.) were recorded.

Before hospitalization, patients who had received three doses of Sinovac (0-1-4. months), two doses of BioNTech (0-1. months) and one dose of BioNTech three months after two doses of Sinovac were considered fully vaccinated (8). Those who could not complete one of these vaccination schedules were considered incompletely vaccinated, and those without any vaccination were considered unvaccinated.

All patients underwent radiological imaging before hospitalization. According to a semi-quantitative scoring system, patients who had pulmonary involvement in computerized chest tomography (CT) were classified as follows: <5%, 5–25%, 26–49%, 50–75% and>75% (9).

At hospitalization, laboratory findings such as C-reactive protein (CRP), white blood cell counts, thrombocyte counts, lymphocyte counts,

D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and ferritin levels were analyzed. The total length of hospital stay and mortality were also recorded.

Statistical Analysis

Descriptive statistics are given as numbers and percentages for categorical variables. Normal distribution was examined with visual (histogram and probability graphics) and statistical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Non-normally distributed continuous variables were compared with the Mann–Whitney U test. Categorical variables were compared using the Pearsonchi-square test or Fisher's exact test. We used univariate Cox proportional hazard regression models to identify the factors associated with in-hospital mortality. Additionally, we produced Kaplan-Meier survival curves to compare median or mean ± SE (standard error) survival times between groups. Double-sided p-values of less than 0.05 were considered significant. Visualizations and statistical analyses were performed with R version 4.1.2 (https://www.r-project.org/).

RESULTS

A total of 399 geriatric COVID-19 patients were included in this study: 214(53.6%) were female and 185 (46.4%) were male. The mean age of the patients was 75±7.87(min:65–max:96). Of these patients, 348 (87.2%) had at least one comorbid condition. Among the patients, the most common comorbid condition was hypertension (n:226, 56.6%). The ratio according to the geriatric classification of the patients was as follows: 184(46.1%) of them were in the youngest-old (65–74 years), 146 (36.6%) were in the middle-old (75–84 years) and 69 (17.3%) were in the oldest-old (≥85 years) groups. Sociodemographic features, vaccination status, baseline clinical spectrum and oxygen requirement status of the patients are given in Table 1. Comorbid conditions according to geriatric age classification are given in Table 2.

Table 1. Sociodemographic features, vaccination status, baseline clinical spectrum and oxygen requirement status

	All n=399
Gender	
Female	214 (53.6)
Male	185 (46.4)
Geriatric age classification	
Youngest-old (65-74 years)	184 (46.1)
Middle-old (75-84 years)	146 (36.6)
Oldest-old (≥85 years)	69 (17.3)
Comorbid conditions	348 (87.2)
Hypertension	226 (56.6)
Diabetes mellitus	161 (40.4)
Chronic heart disease	120 (30.1)
End-stage renal disease	44 (11.0)
Chronic obstructive pulmonary disease	41 (10.3)
Cerebrovascular disease	38 (9.5)
Alzheimer's disease	35 (8.8)
Solid cancer	16 (4.1)
Hematological cancer	12 (3.0)
Organ transplantation	9 (2.3)
Asthma	7 (1.8)
Rheumatological disease	5 (1.3)
Trauma	2 (0.5)
Acute kidney failure	1 (0.3)
Vaccination status, n=398	
Unvaccinated	83 (20.9)
Incompletely vaccinated	123 (30.9)
Fully vaccinated	192 (48.2)
COVID-19 clinical spectrum	
Mild	22 (5.51)
Moderate	119 (29.8)
Severe	258 (64.7)
Oxygen requirement	
None	84 (21.1)
Nasal cannula	100 (25.1)
Oxygen mask	70 (17.5)
Reservoir oxygen mask	145 (36.3)

Data were presented as numbers and column percentages, n (%)

Table 2. Comorbid conditions according to geriatric age classification

	All n=399	Youngest-old n=184	Middle-old n=146	Oldest-old n=69	p
Comorbid conditions	348 (87.2)	154 (83.7)	128 (87.7)	66 (95.7)	0.04
Hypertension	226 (56.6)	105 (57.1)	80 (54.8)	41 (59.4)	0.81
Diabetes mellitus	161 (40.4)	90 (48.9)	56 (38.4)	15 (21.7)	<0.001
Chronic heart disease	120 (30.1)	50 (27.2)	45 (30.8)	25 (36.2)	0.36
End-stage renal disease	44 (11.0)	14 (7.61)	19 (13.0)	11 (15.9)	0.11
Chronic obstructive pulmonary disease	41 (10.3)	16 (8.70)	17 (11.6)	8 (11.6)	0.63
Cerebrovascular disease	38 (9.5)	16 (8.70)	13 (8.90)	9 (13.0)	0.55
Alzheimer's disease	35 (8.8)	3 (1.6)	15 (10.3)	17 (24.6)	<0.001
Solid cancer	16 (4.1)	8 (4.4)	6 (4.1)	2 (2.9)	0.95
Hematological cancer	12 (3.0)	7 (3.80)	3 (2.1)	2 (2.9)	0.69
Organ transplantation	9 (2.3)	7 (3.80)	2 (1.37)	0 (0.0)	0.18
Asthma	7 (1.8)	2 (1.09)	3 (2.05)	2 (2.9)	0.54
Rheumatological disease	5 (1.3)	3 (1.63)	2 (1.37)	0 (0.0)	0.85
Trauma	2 (0.5)	0 (0.0)	1 (0.7)	1 (1.5)	0.16
Acute kidney failure	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0.54

Data were presented as numbers and column percentages, n (%)

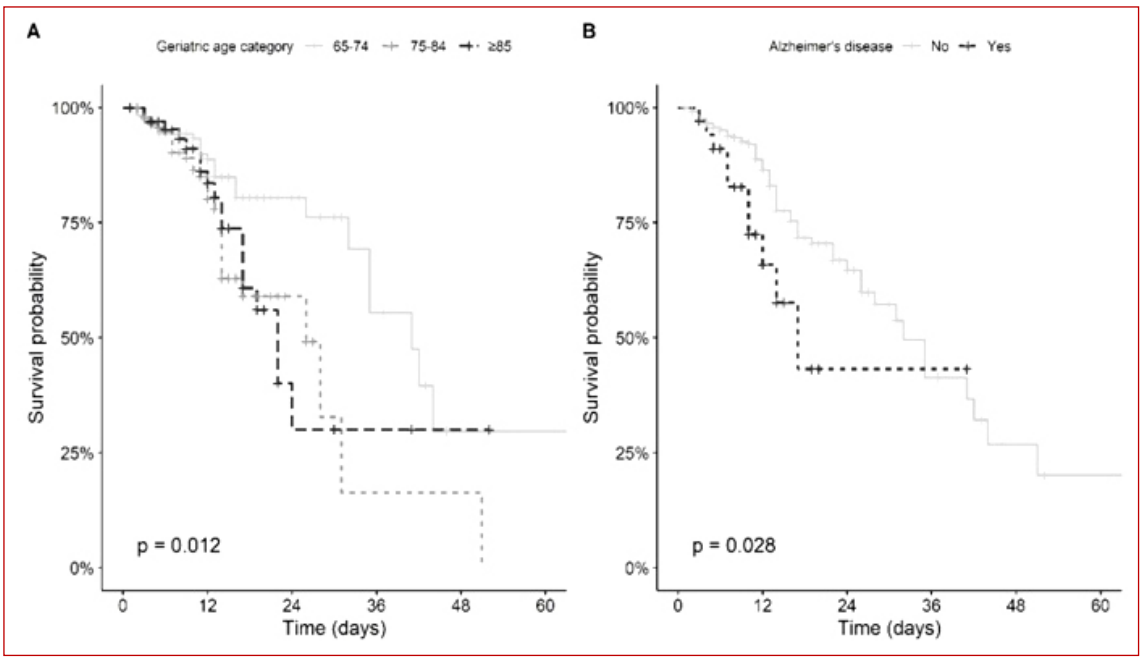

Figure 1. Kaplan–Meier survival curves

Figure 1 shows Kaplan Meier survival curves for in-hospital mortality in terms of age groups and Alzheimer's disease. There was a significant difference in the mean survival times between the youngest-old (mean±SE: 39.8± 3.53), middle-old (mean±SE: 25.3± 3.45) and the oldest-old (mean±SE: 30.7± 5.33) age groups (p=0.01). Also, patients with Alzheimer's disease had a lower mean survival time (mean±SE: 33.6± 7.56 vs 34.3± 2.57, p=0.03).

Table 3. Baseline radiological and laboratory findings

	All n=399
Pulmonary involvement on computerized chest tomography	
None	25 (6.3)
<5%	37 (9.3)
5–25%	155 (38.8)
25–50%	130 (32.6)
50–75%	49 (12.3)
75–100%	3 (0.8)
C-reactive protein (mg/L)	
<5	113 (28.3)
≥5	286 (71.7)
Lymphocyte count (103 /UL)	
≤0.8	122 (30.6)
>0.8	277 (69.4)
Thrombocyte count (103 /UL)	
<150	85 (21.3)
≥150	314 (78.7)
Aspartate aminotransferase (U/L),n=397	
<50	337 (84.9)
≥50	60 (15.1)
Alanine aminotransferase (U/L), n=397	
<50	368 (92.7)
≥50	29 (7.3)
D-Dimer (ng/mL), n=397	
<1000	313 (78.8)
≥1000	84 (21.2)
Ferritin (ug/L), n=393	
<500	236 (60.1)
≥500	157 (39.9)

Data were presented as numbers and column percentages, n (%)

Comorbid conditions were higher in the oldest-old group (n=66, 95.7%) compared to the youngest-old group (n=348, 87.2%), (p=0.04).The ratio of diabetes mellitus was higher in youngest-old group (p<0.001) while the ratio of Alzheimer's disease was higher in the oldest-old group (p<0.001).

Radiological and laboratory findings at hospitalization are given in Table 3.

A total of 111 (27.9%) patients had an increased oxygen requirement on the median day 2 (min:1–max:26) of hospitalization. A hundred and fourteen (28.6%) patients had gone to the intensive care unit on the median day 3 (min:1–max:26) of hospitalization. Of the patients, 323 (81%) were discharged from the hospital, whereas 76 (19%) died.

The factors affecting in-hospital mortality due to COVID-19 are given in Table 4.

Data were presented as numbers and row percentages n (%) or median with minimum-maximum

DISCUSSION

During the COVID-19 pandemic, elderly patients were the most vulnerable group in terms of morbidity and mortality. In our study, the mortality rate was found to be higher in the middle-old and oldest-old groups than in the youngest-old group. Other factors associated with mortality are as follows: lower baseline oxygen saturation levels, necessity of higher oxygen treatment, higher pulmonary involvement on CT, corticosteroid use and having Alzheimer's disease. Similarly to our work, another study evaluating clinical outcomes of geriatric patients found older age (85 years and older), abnormal chest CT findings and lower oxygen saturation levels to be significantly associated with mortality (10). Also, in two studies conducted in our country, low oxygen saturation levels on admission were found significantly associated with mortality among hospitalized geriatric COVID-19 patients (11,12).

A study by Covino et al. evaluated factors affecting mortality among COVID-19 patients aged ≥ 80 years and determined that worse clinical and radiological presentation, increasing age and dementia were significantly associated

Table 4. Factors affecting in-hospital mortality due to COVID-19

	Mortality		p	Hazard Ratio (95% CI)
	No, n=323	**Yes, n=76**		
Gender, n (%)			0.66	
Female	172 (80.4)	42 (19.6)		Ref.
Male	151 (81.6)	34 (18.4)		0.90 (0.57–1.42)
Geriatric age classification, n (%)			**0.01**	
Youngest-old (65–74 years)	157 (85.3)	27 (14.7)		Ref.
Middle-old (75–84 years)	115 (78.8)	31 (21.2)		2.12 (1.25–3.60)
Oldest-old (≥85 years)	51 (73.9)	18 (26.1)		1.89 (1.04–3.45)
Comorbid conditions, n (%)			0.17	
Not existing	44 (86.3)	7 (13.7)		Ref.
Existing	279 (80.2)	69 (19.8)		1.71 (0.78–3.72)
Hypertension, n (%)			0.87	
Not existing	139 (80.3)	34 (19.7)		Ref.
Existing	184 (81.4)	42 (18.6)		0.96 (0.61-1.52)
Diabetes mellitus, n (%)			0.29	
Not existing	196 (82.4)	42 (17.6)		Ref.
Existing	127 (78.9)	34 (21.1)		1.27 (0.81–2.00)
Chronic heart disease, n (%)			0.06	
Not existing	236 (84.6)	43 (15.4)		Ref.
Existing	87 (72.5)	33 (27.5)		1.55 (0.97–2.46)
End-stage renal disease, n (%)			0.66	
Not existing	286 (80.6)	69 (19.4)		Ref.
Existing	37 (84.1)	7 (15.9)		0.84 (0.39–1.84)
Chronic obstructive pulmonary disease, n (%)			0.10	
Not existing	295 (82.4)	63 (17.6)		Ref.
Existing	28 (68.3)	13 (31.7)		1.65 (0.90–3.03)
Cerebrovascular disease, n (%)			0.06	
Not existing	296 (82.0)	65 (18.0)		Ref.
Existing	27 (71.1)	11 (28.9)		1.84 (0.97–3.51)
Alzheimer's disease, n (%)			**0.03**	
Not existing	298 (81.9)	66 (18.1)		Ref.
Existing	25 (71.4)	10 (28.6)		2.09 (1.07–4.08)
Vaccination status, n (%)			0.12	
Unvaccinated	62 (74.7)	21 (25.3)		Ref.
Incompletely vaccinated	94 (76.4)	29 (23.6)		0.92 (0.52–1.62)
Fully vaccinated	166 (86.5)	26 (13.5)		0.58 (0.33–1.04)
COVID-19 Clinical spectrum, n (%)			0.20	
Mild	21 (95.5)	1 (4.5)		Ref.
Moderate	109 (91.6)	10 (8.4)		1.87 (0.24–14.6)
Severe	193 (74.8)	65 (25.2)		3.04 (0.42–22.0)

Table 4 continued.

Table 4. Factors affecting in-hospital mortality due to COVID-19

Baseline oxygen saturation levels	92 (45–99)	89 (73–98)	**0.03**	0.96 (0.93–1.00)
The necessity of oxygen treatment, n (%)			**<0.001**	
None	79 (94.0)	5 (6.0)		Ref.
Nasal cannula	98 (98.0)	2 (2.0)		0.25 (0.05–1.30)
Oxygen mask	45 (64.3)	25 (35.7)		2.68 (1.02–7.09)
Reservoir oxygen mask	101 (69.7)	44 (30.3)		2.52 (0.99–6.42)
Pulmonary involvement on computerized chest tomography, n (%)			**<0.001**	
None	23 (92.0)	2 (8.00)		Ref.
<5%	29 (78.4)	8 (21.6)		3.24 (0.69–15.3)
5–25%	137 (88.4)	18 (11.6)		1.22 (0.28–5.29)
25–50%	101 (77.7)	29 (22.3)		1.92 (0.46–8.09)
50–75%	32 (65.3)	17 (34.7)		1.91 (0.44–8.36)
75–100%	1 (33.3)	2 (66.7)		54.8 (7.35–409)
C-reactive protein (mg/L), n (%)			0.98	
<5	93 (82.3)	20 (17.7)		Ref.
≥5	230 (80.4)	56 (19.6)		0.99 (0.60–1.66)
Lymphocyte count (103 /UL), n (%)			**0.02**	
≤0.8	88 (72.1)	34 (27.9)		Ref.
>0.8	235 (84.8)	42 (15.2)		0.58 (0.37–0.91)
Thrombocyte count, (103 /UL), n (%)			0.16	
<150	63 (74.1)	22 (25.9)		
≥150	260 (82.8)	54 (17.2)		
Aspartate aminotransferase, (U/L), n=397			0.35	
<50	278 (82.5)	59 (17.5)		Ref.
≥50	43 (71.7)	17 (28.3)		1.30 (0.75–2.25)
Alanine aminotransferase, (U/L), n=397			0.35	
<50	298 (81.0)	70 (19.0)		Ref.
≥50	23 (79.3)	6 (20.7)		0.67 (0.29–1.56)
D-dimer, ng/mL, n=397			0.80	
<1000	253 (80.8)	60 (19.2)		Ref.
≥1000	69 (82.1)	15 (17.9)		1.08 (0.61–1.91)
Ferritin, ug/L, n=393			0.41	
<500	194 (82.2)	42 (17.8)		Ref.
≥500	125 (79.6)	32 (20.4)		1.22 (0.77–1.94)
Corticosteroid use			**<0.001**	
None	89 (95.7)	4 (4.30)		Ref.
Methylprednisolone (0.5–1 mg/kg i.v.) up to 10 days	189 (87.9)	26 (12.1)		1.75 (0.61–5.04)
Pulse steroid (≥ 250 mg i.v)	45 (49.5)	46 (50.5)		4.53 (1.60–12.8)

Data were presented as numbers and row percentages n (%) or median with minimum-maximum

with mortality (13). Consistent with this, we found a higher mortality rate among patients with more radiological involvement, those who were older and those with Alzheimer's disease. We also found that older patients had a higher rate of Alzheimer's disease. In another study evaluating risk factors for death and severe disease among COVID-19 patients over 70 years and older, it was found that older age and cognitive decline were associated with in-hospital mortality (14). Also other studies show COVID-19 associated mortality are increased in Alzheimer's disease patients (15,16).

We did not find any significant association between vaccination status and mortality. Contrary to this, another study found that being unvaccinated and not being fully vaccinated were both significantly associated with increased risk of death among elderly patients in Hong Kong during the fifth COVID-19 wave in 2022 (17).

We found that receiving corticosteroid treatment was associated with mortality among elderly patients. In a work evaluating the relationship between in-hospital mortality and corticosteroid treatment among elderly COVID-19 patients, the factors associated with mortality were as follows: corticosteroid use, increasing age, oxygen saturation levels <90% and lowest lymphocyte counts(Odds Ratio = 0.49 [0.38–0.63]) (18).In our study, we showed that patients with lymphocyte counts higher than 0.8x103 /UL had (Hazard Ratio=0.58 [0.37-0.91]) decreased the risk of death. In a study by Gulec-Balbay E et al, predicting mortality risk in hospitalized geriatric patients with COVID-19 pneumonia, the need for corticosteroid and pulse corticosteroid therapy increased the mortality (19).

CONCLUSION

In conclusion, our findings demonstrated that patients in the oldest-old and middle-old groups have a higher mortality risk than those in the youngest-old group. Increasing age, lower baseline oxygen saturation levels, the necessity of higher oxygen, higher radiological involvement, use of corticosteroids and having Alzheimer's disease were found to be strong risk factors for in-hospital mortality.

Our findings emphasize that older patients are more vulnerable to COVID-19 infection and require special attention.

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RESEARCH

COVID-19 VACCINE REFUSAL AND ASSOCIATED FACTORS: A POPULATION-BASED DESCRIPTIVE STUDY

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Abstract

Introduction: Since the declaration of coronavirus disease as a pandemic, the focus was shifted to developing a vaccine for combatting the pandemic. However, it is believed that the most significant obstacle to community immunity against COVID-19 is vaccine hesitancy and refusal. Therefore, we aimed to identify the proportion of COVID-19 vaccine refusal and associated factors in a population aged 55 years and over in the central district of Burdur Province.

Materials and Methods: In order to increase the rate of Covid 19 vaccination, the Ministry of Health has issued a declaration on the establishment of "vaccine persuasion teams." Accordingly, health personnel were assigned to call the people who were not vaccinated, to learn their opinions about the vaccine, to inform them about the vaccine and to persuade them to get vaccinated. According to the records, there were 1303 unvaccinated people aged 55 years and over as of June 2021 at survey site, namely Burdur Province-Turkey. A total of 349 people could not be contacted and 146 people hesitated to get vaccinated. Dependent variables were vaccine acceptance or strict refusal.

Results: We found that vaccine refusal was 1.75 (CI= 1.148-2.664) times higher among those with more than eight years of education and 2.37 (CI= 1.341-4.178) times higher among those obtaining vaccine information from sources other than their family physicians.

Conclusion: Overall, we discovered that the vaccine acceptance level was quite high among our participants. Relevant bodies may engage in community-based works to ensure public confidence in COVID-19 vaccines.

Keywords: Aged; COVID-19 Vaccine; Persuasive Communication; Vaccination Refusal.

CORRESPONDANCE

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INTRODUCTION

Many of the diseases that have negatively affected human societies for thousands of years have begun to be treated, especially with the Industrial Revolution and the scientific tools that came with it, making it available to medicine. Many new approaches have been introduced in the field of preventive medicine. One of the revolutionary innovations is undoubtedly the vaccine. Thanks to the vaccination technique and vaccination policies developed during the twentieth century, it has become possible to combat epidemic diseases, most of which negatively affect children, especially smallpox. Massive application of vaccination has become one of the most basic functions of modern state organization, and it has become possible to fight the disease, to control the disease, and even to eradicate some of them completely from the world. However, since the 1990s in the world and the 2000s in Turkey, it is observed that parents have an attitude of hesitation, resistance or total refusal to have their children vaccinated (1).

When the massive spread of the coronavirus (COVID-19) was declared a pandemic, research shifted its focus to developing an effective vaccine to fight against the disease. Many vaccines were developed and approved at unprecedented speeds by the relevant bodies (2). Then, two main problems emerged: access to the vaccine and the capacity to create community immunity (vaccination of at least 60.0%–70.0% of the population) with vaccination (3,4). However, as in other pandemics, the most notable obstacles to creating community immunity against COVID-19 emerged as vaccine hesitancy and refusals. Insufficient information and conspiracy theories have been suggested as possible reasons for both vaccine hesitancy and refusal (5-7).

Since the vaccine cannot be supplied at once to cover the entire target population, the order of the groups to be vaccinated against COVID-19 was determined by Turkish Ministry of Health by evaluating the exposure to the disease, the risks of heavy transmission and transmission of the disease, and the negative impact of the disease on the social functioning.Vaccination studies in Turkey started on January 13, 2021 with the Sinovac vaccine. Biontech vaccine arrived in Turkey on March 24, 2023. The vaccination process was carried out through the Public Health Management System (HSYS) developed by the Ministry of Health and the AŞILA mobile application. The first Covid 19 vaccinations in Turkey were started from healthcare workers and people aged 85 and over. The vaccination of this age group was performed by the physician and allied health personnel by visiting house to house. In the following period, hospitals were included in the process by creating vaccine rooms, since the cold chain requirement of the Biontech vaccine was not suitable for mobile application. Vaccination applications continued according to age groups, and on April 16, 2021, the 55 age group was granted the right to be vaccinated (8, 9). However, vaccination levels did not reach the expected rates. In order to increase the rate of Covid 19 vaccination, the Ministry of Health has issued a declaration on the establishment of "vaccine persuasion teams."

The present study aims to investigate the proportion of COVID-19 vaccine refusal and its associated factors in adults aged 55 years and older.

MATERIALS AND METHODS

Study Design: Descriptive

A brief organisational framework of healthcare services in Turkey: The primary healthcare units operating to provide healthcare services in Turkey are family medicine units (FMUs). While FMUs provide primary health care to approximately 4,000 people, they have become the fundamental units for the COVID-19 vaccination. The FMUs are affiliated with community health centres (CHCs), CHCs are affiliated with presidencies of public healthcare services (PPHS), PPHS are affiliated with Provincial

Directorates of Health (PDH), and PDH are affiliated with the Ministry of Health (MoH).

Presentation of the Research Area

With a population of 267,092 people, Burdur is a city located in the Mediterranean region of Turkey. The population of the central district where we conducted the research was 111,984. The population of people aged 55 years and over was 26,768 (10). The main livelihood of the province is agriculture and animal husbandry (11). There is a secondary care hospital, an oral and dental health centre, a CHCs and a total of 36 FMU in the central district (12).

Research Design and Sample: According to the Burdur PPHS data, Among 26,768 people aged 55 and over living in the city center, 1,303 (4.9%) were not vaccinated for COVID as of June 2021. These individuals constituted the target population of this descriptive study. A total of 349 (26.8%) people could not be contacted because of refusal to answer phone calls, incorrect contact numbers, and deaths. Following persuasion efforts, 658 participants agreed to be vaccinated while 150 participants absolutely refused to be vaccinated and 146 people hesitated to get vaccinated (Table 1).

Variables: The dependent variables were vaccine acceptance (n=658) or absolute objectors (n=150) following persuasion attempts, while the independent variables were sex, age, education, occupation, place of residence and sources of vaccine information.

Persuasion process and data collection: Vaccination applications continued according to age groups, and on April 16, 2021, the 55 age group was granted the right to be vaccinated. However, vaccination levels did not reach the expected rates. In order to increase the rate of Covid 19 vaccination, the Ministry of Health has issued a declaration on the establishment of "vaccine persuasion teams" within the CHCs. Accordingly, in every CHC, health personnel were assigned to call the people who were not vaccinated, to learn their opinions about the vaccine, to inform them about the vaccine and to persuade them to get vaccinated. The teams were able to access the list of unvaccinated people in their area of responsibility via HSYS. Data such as contact information, age, sex, and chronic disease were accessed via HSYS. It is envisaged that the teams will call people via their contact number, question the reason for not vaccinating, give information about the reason for refusal, and vaccinate those who decide to vaccinate, if necessary, by going to their homes (8,9). In the persuasion studies, information notes prepared for the common causes of vaccine refusal were used. If a participant had any of the responses in Table 2 to the questions asked, they were provided with information regarding their response. In addition, the persuasion teams tried to convince the participants to accept vaccinations by providing information on other vaccine-related subjects they were curious about. In the study, the data of the interviews conducted by the vaccine persuasion teams between 28 June – 1 July 2021 were used. Total of 349 (26.8%) people could not be contacted because of refusal to answer phone calls, incorrect contact numbers, and deaths.

Statistical Analysis: Statistical analyzes were carried out among 150 people who refused to be vaccinated absolutely and 658 people who were persuaded to be vaccinated. We analysed the data using the chi-square test on IBM SPSS Version 23.0 (SPSS; IBM Corp., Armonk, NY, USA). The participants' descriptive characteristics are shown as numbers and percentages. Independent variables found to be statistically significant in the chi-square test were included in the logistic regression analysis. A p value <0.05 was accepted as statistically significant.

Ethical Considerations: Vaccine persuasion teams gave information to the people they called on the phone about the reasons for the call and interviewed those who agreed to be interviewed. In order for the data collected at CHC to be used

scientifically within the scope of vaccine persuasion studies, an application was made to the Health Scientific Research Platform, which is authorized to allow research to be carried out within the scope of Covid 19. Following the response that the data could be used, the ethics committee approval of the study was obtained from the Mehmet Akif Ersoy University Non-Invasive Clinical Research Ethics Committee (GO 2021/10).

RESULTS

The mean age of the participants was 65 ± 9.5 years (55–102 years) About 56.1% of them were males, 80.1% educated 8 years and below, 67.5% living in the city center and 80.7% obtained vaccine information from social media, television and newspapers. Despite participants' right to vaccination, as of the research date, the rate of unvaccinated individuals was 4.9% of the total 55-years or older population. After the interviews, 50.5% agreed to be vaccinated.

Table 2 shows the reasons for vaccine refusal. The most common reason for not receiving the vaccine was "distrust" (28.7%), while 11 (7.3%) participants reported that "they required no vaccination since they were healthy".

Table 1. Distribution of the aged 55 and over people following persuasion efforts (Burdur-Turkey, 2021)

Persuation efforts	N/n	%
Status of COVID vaccination (N=26,768)		
Vaccinated	25.465	95.1
Not vaccinated	1303	4.9
Persuation process involvement status (N=1303)		
Out of contact	349	26.8
Involved	954	73.8
Persuation Status (n=954)		
Persuaded	658	69.0
Hesitated	146	15.3
Absolute objectors	150	15.7

Table 2. Distribution of reasons for refusal of Vaccine among participants (Burdur-Turkey, 2021)

Reasons for Vaccine Refusal	n	%
"The vaccines are newly developed, so I do not trust them."	43	28.7
"I have a chronic disease"	40	26.7
"COVID-19 is overrated."	39	26.0
"I have seen it in the news; I am afraid of its side effects."	17	11.3
"I am healthy, so I do not need vaccination."	11	7.3
Total	**150**	**100.0**

Table 3. Vaccine refusal status of participants by some demographic characteristics and sources of vaccine information (Burdur-Turkey, 2021)

Characteristics		IVaccine refusal status				
		Accepted	Refused	Total	X2	p
		n (%)**	n (%)**	n (%)***		
Age	55-64 years	436 (82.3)	94 (17.7)	530 (65.6)	3.712	0.294
	65-74 years	125 (81.7)	28 (18.3)	153 (18.9)		
	75-84 years	69 (81.2)	16 (18.8)	85 (10.5)		
	85 and + years	28 (70.0)	12 (30.0)	40 (5.0)		
Sex	Male	365 (80.6)	88 (19.4)	453 (56.1)	0.506	0.477
	Female	293 (82.5)	62 (17.5)	355 (43.9)		
Education	8 years and below	541 (83.6)	106 (16.4)	647 (80.1)	**10.217**	**0.001**
	Over 8 years	117 (72.7)	44 (27.3)	161 (19.9)		
Profession**	Retired/Unemployed	478 (81.6)	108 (18.4)	586 (72.5)		
	Private sector	78 (78.8)	21 (11.2)	99 (12.3)	6.654	0.099
	Civil servant	26 (70.3)	11 (29.7)	37 (4.6)		
	Farmer	76 (88.4)	10 (11.6)	86 (10.6)		
Place of residence	City center	432 (79.3)	113 (20.7)	545 (67.5)	**5.213**	**0.022**
	Rural area	226 (85.9)	37 (14.1)	263 (32.5)		
Source of vaccine information	Family physician	141 (90.4)	15 (9.6)	156 (19.3)	**10.241**	**0.001**
	Other*	517 (79.3)	135 (20.7)	652 (80.7)		
Total		**658 (81.4)**	**150 (18.6)**	**808 (100.0)**		

*social media, television, newspaper etc.** row percentage, *** column percentage ****Korkut Boratav's "Class Profiles from Istanbul and Anatolia" is referenced (Boratav, K. (2004). İstanbul ve Anadolu'dan Sınıf Profilleri. 2nd Edition. Ankara: İmge Bookstore p:23-28).

Statistical analyzes were conducted between 150 people who were outspoken and 658 who were persuaded to get vaccinated (808 people in total). The participants did not significantly differ in vaccine refusal by age (p = 0.294), sex (p = 0.477), and occupation (p = 0.099). However, they significantly differed by place of residence (p = 0.022), educational attainment (p = 0.001), and source of vaccine information (p = 0.022). Then, the variables showing statistically significant differences were included in the logistic regression analysis.

It has been determined that vaccination refusal is 1.749 (95% CI= 1.148–2.664) times higher in those with an education level of 8 years and above. Vaccine refusal was also 2.367 (95% CI=1.341–4.178) times more prevalent among participants who obtained vaccine information from other sources (social media, TV, newspapers, etc.) compared to those who obtained vaccine information from their family physicians (Table 4).

Table 4. Results of logistic regression analysis of factors affecting vaccine refusal status (Burdur-Turkey, 2021)

Dependent variable: Vaccine refusal status						
Independent variables		**B**	**SE.**	**Wald**	**Odds Ratio**	**95% CI**
Educational attainment	Over 8 years	.559	0.215	6.774	**1.749**	1.148-2.664
	8 years and below				1 (Reference)	
Source of vaccine information	Other	.861	0.290	8.824	**2.367**	1.341-4.178
	Family physician				1 (Reference)	

DISCUSSION AND CONCLUSION

The highly contagious nature of COVID-19, its heavy burden on healthcare systems, and the lack of a robust treatment that can improve its prognosis make the use of a vaccine inevitable (13). However, ensuring COVID-19 vaccine acceptance prevails over the effective and equitable distribution of vaccines. Although vaccination is considered indispensable by healthcare professionals, it is a known fact that anti-vaccination is an increasing problem worldwide (14).

We found that only 4.9% of the participants remained unvaccinated within our target population (55 years and above) in June 2021. This means that vaccine acceptance among older adults was about 95.0%. The literature reports varying results on vaccine acceptance in populations aged 55 years and over. It was previously found to be 79.0% in low/low-middle income countries, 40.0% in Russia, and 69.4% in the USA (15). A European-based study revealed that vaccine refusal was 5.0% among people aged 55 years and over (16). Another study discovered that vaccine refusal was 14.3% among older adults (17). Overall, while the percentage of unvaccinated older adults in this research region overlaps that of Europe, it is considered better when compared with other studies. Possible reasons for this situation may be that the population was easily accessible because of the city's geographical structure and that the number of healthcare workers per capita in Burdur was above Turkey's average.

Vaccination refusal was found to be statistically significantly higher in those with an education level above 8 years (OR= 1.749). Despite overlapping results in the literature (15,18,19), some studies showed that low educational attainment incited vaccine refusal among people (20-22). Educated parents with a modern worldview believe that immunity should occur naturally; therefore, they do not want to have their children vaccinated, proposing that vaccination means intervening in an immunity mechanism that should occur spontaneously (1). This may apply to educated adults regarding vaccination. It is also possible that people with higher educational attainments are more concerned about the possible side effects and risks of novel vaccines. Furthermore, the nature of the patient–physician relationship may also facilitate vaccine refusal among educated individuals. In classical medicine practices, physicians may prefer to communicate with their patients based on an activity-passivity model where physicians mostly decide on behalf of their patients (23). However, highly educated individuals are dissatisfied with such relationships in which they perceive that their right to be informed is usurped; therefore, they may refuse the practices dictated to them.

The internet and smartphones have enabled more and more people to access social media, which appears to be a good tool for self-education in the vaccine decision-making process. On the other hand, the virtual environment increases the risk of encountering complex or incomplete scientific knowledge, conspiracy theories, and anti-vaccine messages, which may increase vaccine refusal among individuals. Many studies on adult vaccination have suggested that the level of vaccination is higher when recommended by healthcare providers, especially family physicians (23-25). In our study, the proportion of acceptance of the vaccine was 2,367 (95% CI= 1.341–4.178) times higher among the participants who received information about vaccination from their family physicians than those who received information from other sources.

At the time of this research, although the vaccine acceptance level was quite high among our participants compared to international and national data, a substantial number of people remained unvaccinated. Distrust of vaccines and feeling of being subjected to clinical trials were shown to be the greatest reasons for vaccine refusal, as in many studies (16,21). Thus, community-based studies should be planned to overcome such factors and ensure vaccine confidence. Moreover, family physicians should be given feedback on how effectively they provide the population with vaccine information. On the other hand, we found that vaccine refusal was high in the educated group. Therefore, vaccine education should be designed in accordance with individuals' educational attainment. Another issue that needs to be considered is the patient–physician relationship. A patient–physician relationship based on the activity-passivity model with old habits may cause resistance not only to vaccination but also to other medical interventions. It may be helpful to establish a participation-based relationship in which the physician and the patient make decisions together on all applications, from diagnosis to treatment options.

Limitations of the Study

One of the limitations of this study is that it is a descriptive ; therefore, it is limited in explaining the cause-and-effect relationship. In addition, only people who are included in the software of the Ministry of Health and who have a phone number in the system were interviewed. Variables for vaccine rejection are the limited number of variables shown in other vaccine rejection studies. Also 26% of the population could not be reached.

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Conflict of Interest

There is no conflicts of interest or disagreements between the authors.

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RESEARCH

EFFECTS OF THE *STAY AT HOME—TAKE A STEP* PROJECT FOR SEDENTARY ELDERLY PERSONS IN THE COVID-19 PANDEMIC: A RANDOMIZED CONTROLLED STUDY

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Abstract

Introduction: During the Covid-19 pandemic, a program was developed to encourage older adults, the population likeliest to become sedentary due to stay-at-home policies, to remain active. The aim of the current study was to investigate the effects of the average number of steps taken daily on quality of life and stress levels.

Materials and Methods: A randomized controlled study selected 69 participants aged 65 and over (mean 69.39 ± 4.61)—35 in the intervention group and 34 in a control group—and their sociodemographic data were collected. The stay-at-home step program was applied to the intervention group. Quality of life, stress level, and body mass index were assessed pre- and post-test, and their daily step counts were recorded.

Results: A significant correlation was found between number of steps and the quality of life scores in the intervention group ($p<0.05$). There was a significant difference between the groups in favor of the intervention group in the mean number of steps in weeks 4 and 8 of the intervention ($p<0.05$). The mean number steps 2024.71±605.18 in intervention, 1946.63±511.37 in control group.

Conclusion: The study found that the *Stay at Home—Take a Step* program was effective in increasing the number of steps taken daily by elderly participants who were inactive during the Covid-19 pandemic and initiated an improvement in their quality of life. Healthcare professionals who play a central role in supporting the elderly can be advised to use the program to promote healthy aging and physical activity.

Keywords: Aged; Physical Activity; Exercise; Quality of Life.

INTRODUCTION

Old age, the last stage of human life, is the period following development in which physiological and psychological changes occur and chronic diseases and losses are experienced (1). Changes in this period can bring about a decline in physical activity and a sedentary lifestyle (2). In 2022, the World Health Organization's global status report on physical activity reported that 47% of men and 65% of women over the age of 70 in the United States were classified as sedentary; in Turkey, 34% of men and 55% of women over age 70 are sedentary (3). A study by Kaplan and Demirçay (2021) conducted during the pandemic found that although 52% of elderly individuals over the age of 65 engage in physical activity in their free time, a very high rate (48%) remains who do not (4).

In older adults, a sedentary lifestyle is associated with an increased incidence of all-cause mortality, cardiovascular disease, cancer, and type 2 diabetes. In addition, studies have shown that many health problems, such as psychological and mental regression, occur more frequently in sedentary elderly people and that their quality of life is negatively affected (2,5,6). Encouraging older people to engage in more physical activity is an important strategy for healthy and active aging (2).

For sedentary seniors, regular physical activity can reduce the risk of health problems, improve quality of life, reduce healthcare costs, and help improve cognitive function. It also facilitates socialization by reducing social isolation, which is beneficial for physical and mental health (2). Increasing physical activity in sedentary elderly people has been targeted by government programs and non-state actors in accordance with the UN Decade of Healthy Aging, the WHO Global Action Plan on Physical Activity 2018–2030, and Turkey's Physical Activity Guide 2014 (2,7,8,9).

Ricci et al. (2020) defined physically inactive individuals, in the context of the Covid-19 pandemic, as those with low-intensity activities of daily living and moderate-intensity activities of less than 10 minutes per day, and suggested that it may be appropriate to focus on reducing their sedentary behavior (6). The World Health Organization report stated that walking can be a good way for sedentary elderly people to start and gradually increase their physical activities (2). No expensive equipment or gym membership is required to walk; most people can incorporate it into their daily lives. In addition, people can easily change the amount of energy they exert by adjusting the frequency, intensity, and duration of their walks according to their needs. Rather than compelling physical exercise in sedentary elderly people, even providing a change in walking behavior will contribute significantly to their healthy aging processes (1).

Previous studies have determined that to achieve behavioral change in the elderly, the important determinants of commitment are self-efficacy, social support and communication, self-monitoring, past exercise behavior, location of exercise, easy access, and reasonable cost (10). These predictors point to the need for programs that incorporate motivation, effective communication/interaction, and follow-up. With the goal of encouraging elderly individuals who had become sedentary at home during the pandemic, the Stay at Home—Take a Step program was developed, which is based on motivational interviews, mobile reminders, follow-up-based self-monitoring, and interactions with young people. This community-centered study evaluated the effects of the program on the elderly. We hypothesized that the Stay at Home—Take a Step intervention would increase the daily number of steps of the elderly, enhance their quality of life, and decrease their stress levels.

MATERIALS AND METHODS

This study was designed as a double-blind randomized controlled trial. The study period coincided with the Stay at Home Turkey campaign,

which was carried out to minimize contact during the Covid-19 pandemic. Individuals over the age of 65 comprised the study population. To recruit participants, information was distributed between May 15 and June 1, 2021, to university undergraduate students who were continuing their studies through distance education, asking them to invite people aged 65 and over of their acquaintance who met the inclusion criteria to participate in the study (*n* = 116). All potential participants were contacted by phone, and their conformity with the inclusion and exclusion criteria was evaluated. The inclusion criteria were willingness to participate in the study, no cognitive problems that impede communication, literacy in Turkish, familiarity with a smartphone, no muscle or joint problems that interfere with physical activity, no neuropsychiatric disorder, no Covid-19 diagnosis, ability to carry out activities of daily living independently, sedentariness (2,500 or fewer steps per day), and being 65 years old or older. Participants were excluded from the study if they had insulin-dependent type 2 diabetes, hypertension not controlled with medication, or had been diagnosed with heart failure, chronic obstructive pulmonary disease, asthma, or cancer.

The sample size was calculated using the G Power program and considering previously published research (11) in which similar interventions were applied. The amount of type 1 error was 0.05, test power was 0.95, and effect size was 0.83. The minimum number of participants required was 64—32 each in the experimental and control groups. Post-hoc power analysis resulted in the following findings for groups of 35 controls and 34 tested: power (1-β) was 0.947 with α=0.05 and effect size = 0.79 (according to t-test in independent groups for number of steps). The power suggests that this sample size was sufficient (12). All participants who met the inclusion criteria during the data collection period were included in the study. A simple randomization method was performed using the Random Online Allocation Software program (www.Graphpad.com), with a 1:1 randomization between the two groups (intervention, *n*=45; control, *n*=45) performed by a statistician not involved in the study. The participants did not know whether they belonged to the intervention group or the control group. The double-blind method was applied by enabling a statistician outside the study to analyze the data.

Ethics committee and institutional permissions for the research were obtained, and the participants provided voluntary informed consent using a consent form prepared in accordance with the Declaration of Helsinki. For pre-testing, the "Socio-demographic information form," "EQ-5D-3L General Quality of Life Scale," and "Perceived Stress Scale (PSS)" questionnaires were administered online to all participants who met the inclusion criteria. In addition, height and weight information for the previous week were recorded. A pedometer device was provided to all participants in both groups, and the details of its usage were explained in a video. Participants were asked to record the number of their daily steps for 2 months on the chart provided. Only the intervention group attended the four-week Stay at Home—Take a Step (SHTS) program. A post-test that included EQ-5D-3L and PSS was applied to both groups immediately after the program. One month after the intervention was completed, changes in the step counts and weight values of the participants were calculated.

Stay at Home—Take a Step (SHTS) program

The aim of the SHTS initiative is to increase the number of steps taken daily by the elderly, to avoid the negative effects of being sedentary, to adopt a more active lifestyle, to enhance the quality of life during the pandemic, and to reduce stress. The opinions of five experts were obtained regarding the suitability of the program's content. To test the comprehensibility of the program, a pilot study was conducted with five elderly people,

and the study was adjusted according to their feedback. Participants in the pilot study were not included in the study. The initiative was intended to take one month and be supported in different ways, including via mobile messages, videos, and phone calls. Motivational mobile interviews were conducted once a week in line with a guide prepared by researchers with motivational interviewing technique certificates. SMS messages containing reminders to encourage walking were sent to the participants by four university students between the ages of 20–24. Daily step count and weight were discussed to ensure the interaction of the participants with young people.

Data collection tools

1. Sociodemographic information form

The descriptive questionnaire was developed by the researchers in line with the relevant literature. The form includes questions about the sociodemographic characteristics of the participants.

2. EQ-5D-3L general quality of life scale

This scale was developed to assess health-related quality of life. The EQ-5D-3L scale consists of two parts: a descriptive system and the EQ VAS. The descriptive system focuses on five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension contains three responses according to difficulty. The responses for the five dimensions can be combined into a five-digit number that describes the respondent's health status in the descriptive system (13). In this study, we applied the value set obtained for Europe because there was no value set for Turks. The second part presents a scale (EQ VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health), on which respondents rate their current state of health. The Cronbach's alpha coefficient of the scale was 0.860.

3. Perceived stress scale (PSS)

The validity and reliability of the PSS was conducted by Erci (2006), who determined that it was adapted to Turkish society and appropriate. The scale consists of 10 items, and each item is ranked with 1, 2, 3, 4, or 5 points, thus total scores range between 10 and 50. A score of 30 or above indicates stress. Higher scores reflect increasing stress levels. The validity and reliability analysis of the scale determined that the test–retest correlation was 0.88 (14). The Cronbach alpha coefficient of the scale was 0.808.

Statistical analysis

The SPSS 21.0 (Statistical Package for Social Sciences, version 21) program was used for the statistical analysis of the data obtained in the study. Descriptive statistics for the continuous variables considered in the study were mean and standard deviation; categorical variables were expressed as numbers and percentages. For statistical significance, the paired sample t test, an independent sample t test, and analysis of variance in repeated measurements were performed to compare continuous numerical variables within and between groups. A chi-square test was used to compare categorical variables within and between groups. The results were evaluated at the 95% confidence interval and $p < 0.05$ was considered significant.

Ethical approval

The study was approved by the Republic of Turkey Ministry of Health, and ethics committee approval was obtained from the Faculty of Medicine's Non-invasive Clinical Research Ethics Committee (No. 2021.148.05.21). Written and verbal informed consent was obtained from each participant. It was registered with the U.S. National Library of Medicine Registry of Clinical Trials (NCT05110560).

RESULTS

In this community-centered study, 116 elderly people volunteered to participate. They were evaluated with regard to the inclusion and exclusion criteria, and 22.41% were excluded. Ninety participants were randomized into intervention and control groups. The eight-week study program was completed by 76.66% of the participants. Participant flow through the trial is summarized in a CONSORT flow diagram (Fig. 1).

The mean age of the participants was 69.39 ± 4.61, the mean age they perceived was 53.06 ± 14.41, and the average number of people in their households was 2.51 ± 1.09. The intervention group consisted of 52.9% women, and the control group consisted of 54.3% men. The marital status of 82.6% of the participants was married/living together,

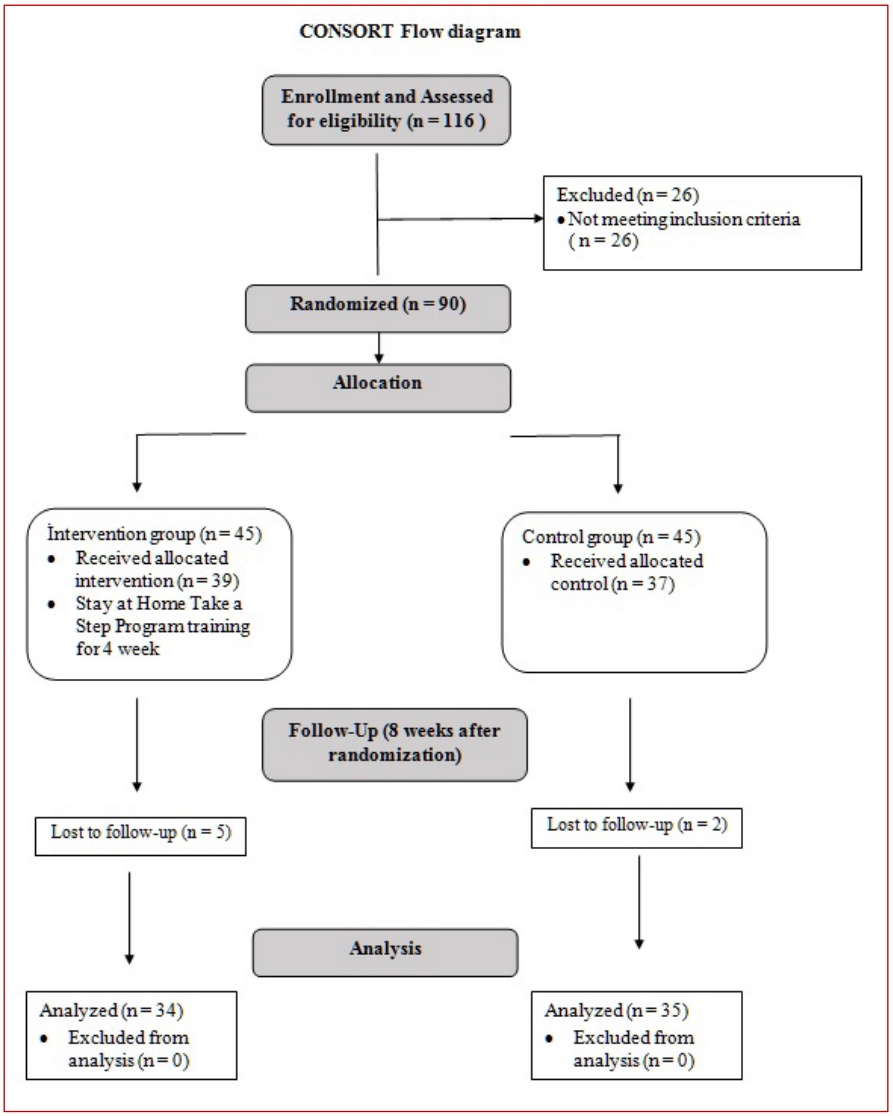

Figure 1. CONSORT flow diagram

Table 1. Baseline socio-demographic characteristics

	Total (n = 69)	İntervention Group (n = 34)	Control Group (n = 35)	p value
Age (Mean±SD)	69.39±4.61	69.94±4.80	68.86±4.41	.332[a]
Perceived age (Mean±SD)	53.06±14.41	53.68±15.83	52.46±13.08	.728[a]
Gender				.360[b]
Female	35 (50.7%)	18 (52.9%)	16 (45.7%)	
Male	34 (49.3%)	16 (47.1%)	19 (54.3%)	
Marital status				.603[b]
Widowed /Divorced	12 (17.4%)	6 (17.6 %)	6 (17.2%)	
Married/ Living together	57 (82.6 %)	28 (82.4%)	29 (82.9%)	
Educational Status				.190[b]
Primary school and below	36 (52.2%)	21 (61.8 %)	15 (42.9 %)	
Middle School	12 (17.4%)	6 (17.6 %)	6 (17.1 %)	
High school and university	21 (30.4%)	7 (20.6 %)	14 (40.0 %)	
Income level				.064[b]
Income less than expenses	14 (20.3%)	7 (20.6%)	7 (20%)	
Income more than or equal to expenses	55 (79.7%)	27 (79.4%)	28 (80%)	
Number of people living together	2.51±1.09	2.53 ±1.23	2.49±0.95	.870[a]

[a]: independent sample t test
[b]: ki kare

52.2% had primary school education or less, and 79.7% reported that their income meets or exceeds their expenses.

There were no significant differences between the groups in terms of age, perceived age, gender, marital status, educational status, household income, and number of people living with them (Table 1).

There were significant differences in the mean scores of the number of steps, EQ-5D-3L General Quality of Life Scale descriptive system, and the EQ VAS within the intervention group ($p < 0.05$). Within the control group, significant differences were found in the mean number of steps ($p < 0.00$). In comparing the groups, there was a significant difference in favor of the intervention group in the mean number of steps in post-intervention weeks 4 and 8 ($p < 0.05$). In addition, when the mean EQ VAS scores of the groups were compared at week 4 after the intervention, a significant difference was found in favor of the intervention group ($p < 0.05$, Table 2).

DISCUSSION

The mobility restrictions during the Covid-19 pandemic drove many people into loneliness and

Table 2. Intra-group and inter-group trends in variables of body mass index. Number of steps. PSS. EQ-5D-3L and EQ VAS

Variable	Group	Baseline Mean±SD	Post 4 weeks Mean±SD	Post 8 Weeks Mean±SD	Within group p value	Between group post intervention 4. week p value	Between group post intervention 8. week p value
Body mass index	İntervention	29.51±3.65	-	29.27±3.67	.125[a]	-	.454[b]
	Control	29.02±4.96	-	28.49±4.82	.055[a]		
Number of steps	İntervention	2024.71±605.18	4469.18±1732.91	4558.25±1859.69	**.000**[c]	**.002**[b]	**.001**[b]
	Control	1946.63±511.37	3212.55±1416.05	3158.41±1298.15	**.000**[c]		
PSS	İntervention	34.91±6.40	35.411±4.50	-	.700[a]	.364[b]	-
	Control	35.63±4.75	34.40±4.69	-	.179[a]		
EQ-5D-3L	İntervention	0.753±0.212	0.795±0.179	-	**.022**[a]	.541[b]	-
	Control	0.766±0.180	0.823±0.192	-	.095[a]		
EQ VAS	İntervention	7.76±1.72	8.38±1.46	-	**.016**[a]	**.027**[b]	-
	Control	7.74±1.65	7.60±1.42	-	0.586[a]		

EQ-5D-3L: EQ-5D-3L General Quality of Life Scale descriptive system points; EQ VAS: EQ-5D-3L General Quality of Life Scale EQ VAS points; PSS: Perceived Stress Scale; SD: Standard deviation

[a]: paired sample t test

[b]: independent sample t test

[c]: Analysis of variance test in repeated measurements

triggered physical health problems related to inactivity, especially among the elderly (1). A study by Kaplan and Demirçay (2021) of elderly individuals during the pandemic revealed that a very high rate (48%) of their participants over the age of 65 did not engage in any physical activity (4). The current study evaluated the effectiveness of the SHTS program, which was implemented to increase the number of daily steps taken by sedentary elderly participants through motivational interactions. The main contribution of this study is validation of the strategy adopted by the SHTS program to strengthen the active aging process during current or future pandemics by enhancing the psychosocial wellbeing of the elderly through intergenerational interaction.

Although the effects of the Covid-19 epidemic on physical activity are not fully known, a sharp decline in the number of steps, ranging from 12% to 38%, has been reported in many countries (15). A worldwide study based on a smartphone app showed that within 10 and 30 days after the declaration of the Covid-19 outbreak, average daily steps decreased by 5.5% to 27.3% in different regions (16). The most important finding obtained in this study was the significant increase in the number of steps taken

daily by participants in the SHTS intervention group. Moreover, this significant increase continued in the 4th week follow-up. It can be surmised that the motivational interviews and follow-up with young people offered by the SHTS program promoted interaction and self-management and increased the direct communication between practitioners and participants. Therefore, if problems arose that could affect behavior change commitment, they could be addressed and resolved in a timely manner. Another study demonstrated that collaborative interaction centered on counseling elderly people, encouraging mutual participation, and focusing on problem solving tends to increase their commitment to behavior change (10).

The current study also noted a significant increase in the number of steps in the control group. In parallel with our work, a study of 68 elderly women in Japan found that accelerometer feedback on physical activity intensity helped increase physical activity levels (17). Similarly, a study conducted with overweight adults at risk of type 2 diabetes concluded that tracking with mobile applications and pedometers increased the number of steps taken by their participants (18). Another study using pedometers observed that total sedentary time decreased and minutes spent walking increased in sedentary elderly individuals (19). All three systematic reviews concluded that the number of steps/day of pedometer users increased by 2,000–2,500 (20,21,22). This suggests that the reason for the significant increase in the number of steps in this study's control group was because they were given pedometers and asked to record their daily step counts.

It is widely acknowledged that the significant decline in the physical activity levels of the elderly during the Covid-19 pandemic negatively affected their quality of life (5). Moreover, a study conducted in Japan revealed that psychological problems resulted from decreased physical activity due to Covid-19, and that the public health measures enforced to prevent transmission created increasing concern among the elderly, which also adversely affected their quality of life (23). An important finding in this study was the significant increase in quality of life in the intervention group. In addition, there was a significant difference between the groups in favor of the intervention group in the quality of life visual comparison scores. This finding can be interpreted as reflecting the positive relationship between physical activity and quality of life; the level of physical activity positively influences quality of life. Studies investigating the effect of exercise on quality of life in the Covid-19 pandemic found that individuals who exercise enjoy a richer quality of life than those who do not (5).

On the other hand, the study found that the SHTS program had no effect on body mass index. A similar study conducted on young adults with a healthy and physically active lifestyle (>10,000 steps/day) reported that reducing the daily number of steps to approximately 1,500 steps/day for 14 days did not cause any change in body weight (24). The short follow-up period in this study is thought to be the reason for the lack of effect of the SHTS program on body mass index. A study by Richardson et al. (2008), based on pedometers, underscored that longer intervention and follow-up had a greater effect on weight loss (25). Furthermore, the SHTS program produced no observable effect on the stress levels of the elderly. Similar studies have likewise shown no effect of increased physical activity on depression or anxiety (19).

CONCLUSION

The Stay at Home—Take a Step initiative was found to be an effective intervention that succeeded in increasing the number of daily steps taken and improving the quality of life of sedentary elderly persons. Healthcare professionals who play a central role in supporting older adults can be advised to include the SHTS program in their practice to motivate daily physical activity for healthier aging.

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