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Groessl EJ, Kaplan RM, Rejeski WJ et al. Physical Activity and Performance Impact Long-term Quality of Life in Older Adults at Risk for Major Mobility Disability. Am J Prev Med 2019; 56 (1): 141-146. (DOI: 10.1016/j.amepre.2018.09.006).

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

The integrity and quality of scientific publishing rely heavily on the commitment, expertise, and dedication of peer reviewers. As editors of this journal, we are profoundly grateful for the time and effort that referees invest in evaluating manuscripts, often alongside their already demanding professional responsibilities.

In 2024, we received an impressive number of submissions, spanning a wide array of topics and methodologies. The task of assessing these manuscripts for originality, methodological rigor, relevance, and clarity is no small feat. It is thanks to the critical insights and constructive feedback of our referees that we can uphold the high standards our authors and readers have come to expect.

Reviewing is a selfless act that frequently goes unnoticed in the broader scientific community. Yet, it is the cornerstone of progress, ensuring that published work is both reliable and impactful. The thoughtful critiques and suggestions provided by our reviewers not only enhance individual manuscripts but also contribute to the overall advancement of science.

As members of the Editorial Board, we would like to express our sincere gratitude to the scientific referees; Hamdi AKAN, Özlem AKİ, Aysun ANKAY YILBAS, Berna ARDA, Sadık ARDIÇ, Didem ARSLANTAŞ, Vildan AVKAN-OĞUZ, Semih AYDEMİR, Pınar AYDIN, Tolga Reşat AYDOS, Okay BAŞAK, Terken BAYDAR, Mehmet BEYAZOVA, Sedat BOYACIOĞLU, Ahmet COŞAR, İlke COŞKUN BENLİDAYI, Alfonso CRUZ-JENTOFT, Aslı DÖNMEZ, Ufuk ERGÜN, Erhan ESER, Ayşe GELAL, Yeşim GÖKÇE KUTSAL, Gloria GUTMAN, Özlem GÜLBAHAR, Ceyda GÜLTER KABAROĞLU, Zafer GÜNENDİ, Rengin GÜZEL, Gülşen HASÇELIK, Kenan HIZEL, Önder İLGİLİ, Jale İRDESEL, Fuat KALYONCU, Sevilay KARAHAN, Ayşe KARS, Semih KESKİL, Pembe KESKİNOĞLU, Murat KOÇ, Mahir KUNT, Ali KUTSAL, Abdullah OLGUN, Serpil ÖCAL, Işıl ÖZKOÇAK, Zerrin ÖZKÖSE, Şerefnur ÖZTÜRK, Mihrimah ÖZTÜRK, Sercan ÖZYURT, Gülden PEKCAN, Reyhan POLAT, İskender SAYEK, Meral SAYGUN, Derya SOY BUĞDAYCI, Meltem ŞENGELEN, Tijen ŞENGEZER, Mehmet Ali TAŞKAYNATAN, Tugan TEZCANER, Zahide TUNA, Canan ULUOĞLU, Songül VAİZOĞLU, Neslihan YÜCEL and Murat ZİNNUROĞLU.

As we embark on another year of publishing, we remain committed to recognizing the invaluable contributions of our reviewers. We encourage authors, readers, and institutions to join us in celebrating the vital role referees play in the scientific process.

Together, let us continue fostering a culture of rigor, integrity, and collaboration in science.

Prof. Yeşim GÖKÇE KUTSAL, M.D.

EDITORIAL ARTICLE

OSTEOPOROSIS IN THE OLDEST OLD: TIME TO STAND UP AND TO ACT

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By the age of 50 years, the lifetime risk of sustaining a fracture is approximately 50% for women and 20% for men (1). For hip fracture, this risk is 23 and 7 % in women and men, respectively. These data are coming from a region with a particularly high longevity, indicating that such elevated lifetime fracture risk is a threat for many countries where life expectancy is growing and population aging. Since the median age for a hip fracture is above 80 years, 50 % of these fractures are occurring in the oldest olds (2). The term 'the oldest old' refers to the oldest subset of older adults and comprises a group of patients which may have substantial differences in pharmacokinetics and higher levels of co-morbidities and are often not included in pivotal randomised controlled trials. Chronological age cut-off values for this group vary, as the European Medicines Agency considers ≥85 years as 'oldest old', while the American Geriatrics Society and World Health Organisation set a chronological threshold at ≥80 years (3).

Fracture incidence varies according to type of fracture (4). There is an exponential increase in the incidence of fractures of the femoral neck and trochanter with increasing age (4). The incidence is much lower in men. In addition, there is variation in the distribution of incidence by age. With trochanteric fractures there is a fairly rapid increase from the age of 75 years, and, for fractures of the femoral neck, a more constant, almost linear increase in incidence from the age of 65 years (5). The exponential increase in trochanteric fractures continues in the 10th decade of life (those aged between 90-100 years). Fracture risk considerably varies according to the region (6). In addition, it also changes over time (7), with a decrease of secular trend for hip fracture in several places (8). Although Turkey was among the countries with low hip fracture rates in Europe, the incidence has increased markedly between 1989 and 2009 (9).

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Fragility fracture is the clinical expression of the disease osteoporosis (2). Among the complications of osteoporosis, hip fracture represents the most dramatic event, in terms of morbidity, mortality and medical costs. Increased mortality has been consistently demonstrated after hip or vertebral fracture. For instance, hip fracture is associated with a 20% excess mortality within the first year after surgery (2, 10,11). Reduced survival cannot be attributed directly to the fracture, but to underlying cardiovascular or pulmonary diseases, which might become decompensated because of the fracture event. By the prolonged handicaps they cause, fractures are a major threat for the quality of life of the elderly and represent a significant cause of health expenses. By one year after hip fracture, close to 20% of the patients still require rehabilitation in hospital.

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and in susceptibility to fracture risk (12). The diagnosis of the disease relies on the quantitative assessment of areal bone mineral density (aBMD) at hip or spine, using dual energy x-ray absorptiometry (DXA), which represents an important determinant of bone strength and thereby of fracture risk. Depending on the experimental model, aBMD accounts for about two thirds of the variance of bone strength as determined *in vitro* on isolated bones (13), as aBMD integrates the size of the bone and its thickness, as well as the true volumetric density, all being determinants of bone strength.

The operational definition of osteoporosis is based on aBMD lower than the lower limit of normal range of young healthy women, as defined in a World Health Organisation (WHO) document (12). The operational definition of osteoporosis (endorsed by the WHO) is aBMD T-score (T-Score = [measured BMD – Young Adult Women aBMD] / Young Adult Women SD) of -2.5 or lower (i.e. at least 2.5 standard deviations below average bone mineral density of healthy young women), where aBMD is assessed by dual X-ray absorptiometry (DXA) at spine or hip (12). A women database is also applicable to men. Between -1.0 and -2.5 standard deviations corresponds to low bone mineral mass or osteopenia. An osteodensitometry-based diagnosis of osteoporosis together with a prevalent fragility fracture defines severe osteoporosis. Indications to treatment depend on the evaluation of fracture risk, which also integrates other clinical risk factors than osteoporosis densitometric diagnosis (12). Above the age of 65, osteoarthritis makes the measurement of lumbar spine BMD is less reliable for diagnosis purpose. Femoral neck BMD appears to be a good predictor of fracture of the proximal femur (14), though up to 50% of hip fracture could occur in patients with aBMD above -2.5 T-score (15), emphasizing the need to take into consideration prevalent fracture (16, 17), as well as clinical risk factors in fracture risk assessment. Recently, it was also reported that after adjusting for age, sex, and site of initial fracture, an increasing number of frailty deficit items was associated with increased risk of subsequent fracture (18).

Moderate or severe vertebral fractures, even when asymptomatic, are strong risk factors for subsequent fracture (16). Vertebral fracture assessment should therefore be considered in high-risk individuals, using either lateral lumbar and thoracic spine radiographs or lateral spine DXA imaging. Vertebral fracture assessment should be considered in postmenopausal women if there is a history of ≥4cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, as well as in individuals with a history of non-vertebral fracture (12).

Of the various risk assessment tools developed in osteoporosis, the FRAX® model is the most widely used (12). FRAX® is a computer based algorithm (http://www.shef.ac.uk/FRAX) that integrates age, sex, clinical risk factors such as prevalent



fracture, parental hip fracture, current smoking, ≥3 alcoholic drinks/day, rheumatoid arthritis, current corticosteroid use, body mass index (BMI) <20 kg/m^2, or secondary osteoporosis, and calculates the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture, but is also capable of predicting asymptomatic vertebral fractures. It is calibrated for local fracture incidence and mortality. Assessment of fall risk predictors should be one of the major pillars in the physical evaluation of osteoporotic patients as recently reported in a Fracture Liaison Service of Turkey (19).

In addition to the risk factors included in the FRAX tool, malnutrition and particularly protein-energy malnutrition is a risk factor for osteoporosis, sarcopenia and frailty (20). In addition, malnutrition impairs the rehabilitation after fracture, leading to higher risk of medical complications and prolonged hospital stays (2). Protein-energy malnutrition is as high as 4-10% in oldest olds living at home, 15-38% in those in institutional care, and 30-70% in hospitalized older patients (21). Patients who have recovered from a major fracture are significantly more likely to fall. Intrinsic risk factors for falls include gait deficits, dizziness and orthostasis, visual impairment, depression, functional and cognitive impairment, low body mass index, urinary incontinence, chronic musculoskeletal pain, some drugs and age 80 years and older.

A diagnosis threshold as determined by aBMD, should not be automatically translated into a therapeutic threshold. Other factors such as those included in the FRAX tool, bone turnover level or treatment cost/benefits, should be considered in the treatment decision (12). Thus, the risk of fracture for an individual is related to BMD and to a series a number of factors independent from BMD. For instance, the same T-Score has a different significance at different ages. For any BMD, fracture risk is much higher in the oldest olds than in the young (12). The objective of the risk estimation is to identify the individuals at higher fracture risk, and to provide treatment accordingly, to reduce the risk of fracture. However, given the above epidemiology which emphasises the predilection for fractures in the oldest old, there is recognised undertreatment for those requiring anti-osteoporosis medication in this population (22). Many people at high risk of fracture receive no treatment or highly inadequate treatment (12). There is now sufficient evidence of the short-term benefits of treatment and of the long-term safety profile of anti-osteoporosis treatments particularly in the oldest old population (20). Many older people are under-nourished and vitamin D deficient. These are situations that should be easily improved. In order to promote awareness and encourage proactive treatment in high-risk patients, the *Capture the Fracture Campaign* of the International Osteoporosis Foundation and a wide implementation of fracture liaison services (23) to strengthen secondary fracture prevention should be strongly advocated (24). Since its launch in 2013 and as of November 15th, 2024, the Capture the Fracture® program (https://www.capturethefracture.org) has welcomed 1'043 FLS, spread across 60 countries and 6 continents, which constitutes a very important network across the world. The inclusion of patients with a recent fracture in such as pathway is associated with a decreased fracture risk and a lower mortality (25, 26), this with a favorable cost-effectiveness ratio (27-29).

Sufficient levels of vitamin D are a prerequisite for the efficacy of anti-osteoporosis medications as all studies on these agents have been conducted in calcium and vitamin D-supplemented patients. The recommendation of a dose of 800 IU/day (20µg/day) in older adults (>70 years) has been adopted by most European guidelines, as well as the International Osteoporosis Foundation (IOF) and the Institute of Medicine (IOM) and was also advised in ESCEO consensus paper (30). There is no strong necessity to systematically measure circulating levels of 25(OH) D in older patients with suspected high fracture

risk since the cost of testing far exceeds that of supplementation. Vitamin D supplementation should precede any anti-osteoporosis therapy. Overall, it can be concluded that (31) 1-Calcium and vitamin D supplementation may lead to a modest reduction in fracture risk, although population-level intervention has not been shown to be an effective public health strategy; 2-Supplementation with calcium alone does not reduce fracture risk; 3-Side effects of calcium supplementation include renal stones and gastrointestinal symptoms; 4-Vitamin D supplementation, rather than calcium, may reduce falls risk; 5-Increased cardiovascular risk consequent to calcium supplementation is not convincingly supported by current evidence, particularly if calcium is of dietary origin; 6-Calcium and vitamin D supplementation is recommended for patients at high risk of calcium and vitamin D insufficiency, and in those who are receiving treatment for osteoporosis.

Correction of protein insufficiency can lead to a rapid normalisation of IGF-I levels in frail older adults and in patients with a recent hip fracture (20). In view of the impaired protein assimilation of older individuals, the RDA (0.8 g/ kg body weight) should be increased to 1.0 or 1.2 g/kg per day in the older age group without adverse event (32, 33). Dairy products are a source of both protein and calcium, since one litre of milk provides 32 g of protein and 1,200 mg of calcium. Dairy products, some being fortified with calcium or vitamin D, decrease circulating PTH, increase IGF-I, and decrease bone resorption markers (34). Dairy products are associated with higher bone strength (35). Higher dairy products consumption, particularly fermented dairy products is associated with a lower hip fracture risk (34, 36).

Anti-osteoporosis drugs are either anti-resorbers or stimulators of bone formation. The efficacy of the available anti-osteoporosis agents in increasing bone strength and reducing osteoporotic fracture risk is well established thanks to randomized placebo-controlled trials with fracture incidence as primary outcome (2, 12). Reduction of fracture risk in patients with osteoporosis is as high as 50-70% for vertebral fractures (75-96% for multiple vertebral fractures) and 20-35% for non-vertebral fractures, as well as 40-50% for hip fractures with some drugs (37). Moreover, osteoporosis medication does not lose its efficacy among frail adults (38). There is a large variety of regimens with oral, Intravenous or subcutaneous administration, and daily, weekly, monthly, 3-monthly, 6-monthly or yearly schedules.

Agents that have been approved for the treatment of osteoporosis in postmenopausal women include selective estrogen receptor modulators (SERMs), bisphosphonates (alendronate, risedronate, zoledronic acid and ibandronate), denosumab as antiresorbers, and teriparatide, the PTH-related protein analog abaloparatide and the monoclonal antibody against sclerostin romosozumab as bone formation stimulators (2, 39).

Anti-osteoporosis treatments are frequently under-prescribed, even in patients who have sustained an osteoporotic fracture and are at increased risk of a subsequent fracture (22). Clinicians may be reluctant to prescribe treatment because of doubts they might have over the effectiveness of treatment in a short period of time in patients with a limited life expectancy. Clinically significant benefits in terms of fracture reduction have been demonstrated within the first year of treatment (20). Thus, even in an oldest old patient population, treatment with an anti-osteoporosis agent is worth to be introduced, because of an early onset of fracture risk reduction. Over the long-term, anti-osteoporosis treatments seem to maintain effectiveness and remain safe (2). For patients at very high risk of fracture or at imminent risk, a bone formation stimulator followed by an antiresorber is an efficacious option in terms of rapidity of action and magnitude of the fracture risk reduction (39). Various guidelines recommend



treatment re-evaluation every 3 years for parenteral bisphosphonate administration and 5 years for oral formulations (40).

The risk of osteoporotic fractures is a major healthcare concern. The impact of a major fracture on patients' lives is immense, often leading to frailty and dependence. The costs borne by society are also significant, both in terms of immediate care and rehabilitation, and possible dependence over the longer term. Pharmaceutical anti-osteoporosis treatments are generally cost-effective, and even cost-saving in the oldest old (41). When the costs threshold for one Quality-adjusted Life-Year (QALY) was set at twice the gross domestic product per capita and a first-line treatment with alendronate (original molecule) was evaluated, treatment was cost effective in women having a 10-year risk for a major osteoporotic fracture as low as 13.8% or more, whereas for men the risk estimate should exceed 15% (41).

In summary, osteoporosis increases the risk of fractures, which are associated with increased mortality and altered quality of life. Patients with prevalent fracture are at high risk to sustain another one. Optimal protein and calcium intakes, and vitamin D supplies, together with regular weight bearing physical exercise are the corner stones of fracture prevention. Evidence for anti-fracture efficacy of pharmacological interventions relies on results from randomised controlled trials in postmenopausal women with fractures as the primary outcome. Treatments with bone resorption inhibitors, like bisphosphonates or denosumab, and bone formation stimulator like teriparatide, abaloparatide or romosozumab reduce vertebral and non-vertebral fracture risk. A reduction in vertebral fracture risk can already be detected within a year after starting therapy, justifying to undertake treatments even in the oldest olds.

The International Osteoporosis Foundation has for vision of its action a world without fragility fracture in which healthy mobility is a reality for all.

Take home messages for osteoporosis management in the oldest old

- Correct or prevent vitamin D insufficiency (800-1000 IU/d)
- Ensure dietary calcium intake ≥ 1000 mg /d
- Ensure adequate dietary protein intake ≥ 1.2 g/kg body weight x d
- Promote tailored weight-bearing physical exercise
- Treat any disease that might cause bone loss
- Reduce the risk of falls
- Prescribe pharmaceutical treatment when indicated by risk assessment
- Follow-up patients to ensure compliance and persistence
- Re-evaluate therapeutic options after 3 or 5 years

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ORIGINAL ARTICLE

BONE MARROW BIOPSIES IN OLDER ADULTS: ASSESSING DIAGNOSTIC ACCURACY AND PRE-DIAGNOSIS CONCORDANCE

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Abstract

Introduction: Bone marrow biopsy is widely used for the diagnosis of hematological diseases and malignancies that increase with age. We aimed to show the contribution of bone marrow biopsies to the diagnostic process by comparing pathological diagnoses and clinical preliminary diagnoses in the patient group aged 65 and over.

Materials and Method: The study included 1,821 patients aged 65 and over who underwent bone marrow biopsy between 2019 and 2024. Clinical preliminary diagnoses, patient demographic information, and pathology reports of the departments requesting bone marrow biopsy were accessed through the patient information system. Pathological definitive diagnoses and clinical diagnoses were categorized and statistical analysis was performed.

Results: 30.8%(n=563) of the clinical pre-diagnoses were Multiple Myeloma, 18.5%(n=338) were Myelodysplastic Syndrome and 14.2%(n=258) were Chronic Myeloproliferative Disorders. Pathological examination was sufficient for diagnosis in 6.8%(n=124). Of these, 45.5%(n=772) were diagnosed with malignancy. Of the pathological diagnoses, 14.5%(n=265) were Multiple Myeloma, 7.4%(n=135) were Chronic Myeloproliferative Disorders and 2.9%(n=53) were diagnosed with Myelodysplastic Syndrome. When the diagnoses were compared, it was seen that there was a discrepancy rate of 38.1% (n=616). The highest discrepancy was in the Hematology department at a rate of 59.4% (n=366) and was statistically significant (p=0.024). The second highest discrepancy was in the Oncology department at a rate of 20.5% (n=126).

Conclusion: The high diagnostic discordance in clinics suggests that current diagnostic algorithms may not be sensitive enough. Our study showed that bone marrow biopsy should be performed in patients aged 65 years and older based on accurate clinical indications and that new diagnostic protocols should be focused on development.

Keywords: Bone Marrow Examinations; Aged; Pathology.



INTRODUCTION

Bone marrow biopsy (BMB) is a critical diagnostic procedure widely used in the evaluation of haematological diseases and certain non-haematological conditions (1). In addition to cytomorphological analysis, BMB facilitates advanced diagnostic assessments, such as immunophenotyping, flow cytometry, cytogenetic testing and molecular genetic tests (2). BMB plays a critical role in both the diagnosis and staging of leukemias and lymphomas, and it may need to be performed multiple times when clinically indicated (1). Furthermore, in chronic myeloproliferative diseases (CMPDs), essential findings such as bone marrow fibrosis, which can only be identified through BMB, hold significant diagnostic value (1). In the context of solid tumors, the detection of bone marrow metastases is crucial for staging and prognostic assessment, as these findings remain indispensable in guiding treatment strategies (1). The increased prevalence of haematological disorders and malignancies in older patients underscores the importance of BMB in this age group (3). The geriatric population, defined as individuals aged 65 years and older, represents a highly heterogeneous group. Notably, the physiological age of patients, rather than their chronological age, is a critical factor in determining the appropriateness of invasive procedures such as BMB. In frail or severely debilitated patients, particularly those aged 85 years and older, the risks associated with BMB, and other diagnostic interventions may outweigh the potential benefits. However, the diagnostic efficacy of BMB and its alignment with clinical predictions in the older population have not yet been thoroughly investigated (4).

The incidence of haematological disorders increases with age, often complicating the diagnostic process due to non-specific symptoms and multiple comorbidities (3). In cases of anaemia, thrombocytopenia and unexplained cytopenia, BMB stands out as a crucial tool for identifying underlying causes, particularly when traditional diagnostic methods fall short (5). For instance, Riley et al. demonstrated that BMB had high specificity in diagnosing haematological malignancies, such as acute leukaemia and lymphoma (6). A review by Bain revealed that BMB provided over 90% diagnostic accuracy for haematological malignancies (7), which is particularly significant given the increased incidence of malignancies in older patients (3).

Incorrect or insufficient clinical assessments may lead to unnecessary BMBs, exposing patients to the additional risks of invasive procedures (7). Unnecessary biopsies increase patients' anxiety, pain and complication risks, and they prolong the diagnostic process, imposing additional costs on the healthcare system (7-9). In older patients, these unnecessary interventions can lead to significant issues in terms of safety and efficient resource use (10). When appropriate, advanced diagnostic tests, such as immunophenotyping and molecular genetic analyses, can be used to supplement or even replace BMB when adequate peripheral samples are available. However, particularly in hematology and oncology, BMB remains an indispensable source of diagnostic material, especially for cytopenia evaluations. Therefore, it is crucial to ensure that BMBs are conducted based on accurate clinical indications and are aligned with clinical pre-diagnoses.

A retrospective study by Manion et al. analysed 119 bone marrow aspirates and biopsies from patients aged 85 or older. The study found that 43% of the procedures yielded specific diagnoses, particularly in cases involving haematological malignancies. However, the diagnostic yield was lower for non-specific symptoms, such as unexplained cytopenia (11). These findings emphasise the importance of conducting BMB with the correct indications and algorithms in the older population to avoid additional invasive procedures. Stratifying older patients based on physiological rather than chronological age can improve the accuracy and safety of invasive diagnostic interventions.

This study aimed to retrospectively evaluate the pathological results of BMBs performed in patients aged 65 or above and compare these results with the patients' clinical pre-diagnoses. We hope that our findings will provide guidance in establishing biopsy algorithms for older patients.

METHODS

In this retrospective study, BMBs evaluated in the pathology laboratory of a tertiary healthcare centre between 2019 and 2024 were analysed. The study included patients aged 65 or older who underwent BMB. The exclusion criteria were being a patient younger than 65 years and having incomplete data for a case. All the data for the included participants were retrospectively retrieved from the hospital's electronic medical records. Ethical approval for this study was obtained. Patient consent was not required.

Data Recording

Patient data were retrospectively accessed through the hospital's electronic database. Demographic data, including patient age and sex, were recorded. The departments that requested BMBs were categorised as follows:

- Medical departments (haematology, oncology, internal medicine, nephrology, geriatrics and rheumatology)
- Surgical departments (orthopaedics, surgical oncology, general surgery and urology)
- Intensive care units
- Other departments (pulmonology, cardiology, infectious diseases, physical therapy and rehabilitation)

The preliminary clinical diagnoses were categorised as follows:

- No preliminary diagnosis provided
- Multiple myeloma
- Myelodysplastic syndrome (MDS)
- Chronic myeloproliferative hematopathies (CMPHs)
- Chronic lymphocytic leukaemia (CLL)
- Lymphoma (Hodgkin and non-Hodgkin)
- Acute myeloid leukaemia (AML)
- Amyloidosis
- Anaemia
- Metastasis

The pathological diagnoses were recorded as follows:

- Insufficient sample
- Multiple myeloma
- MDS
- CMPHs
- CLL
- Lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin lymphoma, hairy cell leukaemia and mantle cell lymphoma)
- AML
- Acute lymphoblastic leukaemia (ALL)
- Hypercellular marrow
- Hypocellular marrow
- Non-specific findings

Definition of Concordance and Discordance

Concordance was defined as the alignment between preliminary clinical diagnoses provided by the requesting departments and the definitive pathological diagnoses obtained through BMB. Discordance, on the other hand, referred to cases where the pathological findings did not match the clinical pre-diagnoses. This discordance may highlight diagnostic challenges, the complexity of non-specific symptoms in elderly patients,



or insufficient clinical data provided during the diagnostic process. For the purposes of this study, discordance did not include insufficient samples, which were categorised separately.

Bone Marrow Processing Technique

BMB material was admitted to the pathology department, and routine tissue processing was performed. The samples were embedded in paraffin blocks, and 3 µm thick sections were taken for microscopic examination. These sections were stained with haematoxylin–eosin to prepare slides. If necessary, additional histochemical and immunohistochemical tests were performed to aid the diagnosis. The microscopic evaluation, conducted by expert pathologists, involved documenting the morphological findings and test results electronically. These findings were used to reach definitive diagnoses.

Statistical Analysis

All the data were analysed using the software SPSS Statistics. In this article, demographic data are expressed as means±standard deviations, while categorical variables are expressed as percentages. After excluding cases with no preliminary diagnosis and insufficient samples, the departments with the highest rates of malignancy diagnoses and the most common malignancy diagnoses were identified and expressed as percentages. The preliminary and pathological diagnoses for each department were categorised as either concordant or discordant, and interdepartmental comparisons were performed using chi-square and Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

RESULTS

In this study, a total of 1,821 patients were evaluated. The mean age of the participants was 74.8 years, with an age range of 65 to 95 years. The patient group comprised 44% (n=801) females and 56% (n=1,020) males. The majority of pathology requests originated from internal medicine departments, with haematology accounting for the highest proportion (57.3%, n=1,043), followed by medical oncology (21.8%, n=398) and general internal medicine (7.2%, n=132). Requests from nephrology, geriatrics and rheumatology each constituted less than 5% of the total (Table 1).

Regarding the initial clinical diagnoses, the most common was multiple myeloma, which accounted for 30.8% (n=563) of cases. This was followed by MDS (18.5%, n=338) and chronic myeloproliferative disorders (CMPDs) (14.2%, n=258). Less common diagnoses included CLL (3.1%, n=56), lymphoma (13.8%, n=251) and AML (6.9%, n=117).

The pathological evaluations yielded various diagnoses. A total of 6.8% (n=124) of the samples were deemed insufficient for a definitive diagnosis. Among the confirmed pathological findings, multiple myeloma was diagnosed in 14.5% (n=265) of cases, CMPDs in 7.4% (n=135) of cases and MDS in 2.9% (n=53). Lymphomas were further classified into subtypes, with diffuse large B-cell lymphoma identified in 7.1% (n=130) of cases. Other less common subtypes included follicular lymphoma, Hodgkin lymphoma, hairy cell leukaemia and mantle cell lymphoma. Among the types of acute leukaemia, AML and ALL were diagnosed at rates of 6% (n=110) and 0.5% (n=9), respectively (Table 1).

Non-specific bone marrow changes were categorised as hypercellular (21.8%, n=398) and hypocellular (2.4%, n=43), making these some of the most frequently observed findings. Additionally, non-specific pathologies were diagnosed in 25.7% (n=469) of cases.

A total of 1,624 samples from various departments were analysed in this study. Of these, 852 were diagnosed with non-specific findings, while malignancy was identified in 772 samples. When the malignancy rates were analysed by department, haematology had the highest rate at 59.6% (n=459),

Table 1. Characteristics of the study cohort (n=1821)

Age, mean (min-max)	74.8 (65-95)
Sex, n (%)	
Women	801 (44)
Men	1020 (56)
Medical department requesting biopsy, n (%)	
Internal Medicine	
Hematology	1043 (57.3)
Medical Oncology	398 (21.8)
General Internal Medicine	132 (7.2)
Nephrology	65 (3.6)
Geriatrics	18 (1.0)
Rheumatology	7 (0.4)
Intensive Care Unit	79 (4.3)
Surgical Departments	22 (1.2)
Others	57 (3.2)
Preliminary diagnoses	
Unspecified	82 (4.5)
Multiple Myeloma	563 (30.8)
Myelodysplastic Syndrome (MDS)	338 (18.5)
Chronic Myeloproliferative Hematopathies (CMPH)	258 (14.2)
Chronic Lymphocytic Leukemia (CLL)	56 (3.1)
Lymphoma	251 (13.8)
Acute Myeloid Leukemia (AML)	117 (6.9)
Amyloidosis	21 (1.2)
Anemia	71 (3.8)
Metastasis	64 (3.5)
Pathological diagnoses	
Insufficient sample	124 (6.8)
Multiple Myeloma	265 (14.5)
MDS	53 (2.9)
CMPH	135 (7.4)
CLL	32 (1.8)
Lymphoma	
Diffuse large B-cell lymphoma (DBBH) Lymphoma	130 (7.1)
Follicular lymphoma	6 (0.3)
Hodgkin Lymphoma	3 (0.2)
Hairy cell Leukemia	5 (0.3)
Mantle cell Lymphoma	7 (0.4)
AML	110 (6)
ALL	9 (0.5)
Hypercellularity	398 (21.8)
Hypocellularity	43 (2.4)
Nonspecific	469 (25.7)



which was statistically significant (p=0.026). This was followed by the oncology department, with a malignancy rate of 19.6% (n=151) (Table 2).

The malignancy rate in the samples from the general internal medicine department was 7.3% (n=56), while it was 4.0% (n=31) in the nephrology department. In the samples from the geriatrics and rheumatology departments, the malignancy rates were 0.8% (n=6) and 0.0% (n=0), respectively. The samples from the intensive care unit had a malignancy rate of 2.7% (n=43), while the rate was 1.0% (n=8) in the surgical departments.

When comparing the initial clinical diagnosis with the final pathological diagnosis, 61.9% (n=1,001) of diagnoses were found to be concordant, while 38.1% (n=616) were discordant. The highest discordance rate was observed in the haematology department (59.4%, n=366), which was statistically significant (p=0.024). The oncology department had a discordance rate of 20.5% (n=126), making it the second highest one (Table 3).

The discordance rates in the general internal medicine and nephrology departments were 5.8% (n=36) and 4.9% (n=30), respectively. The geriatrics department had a notably low discordance rate (0.5%, n=3), while no discordance was observed in the rheumatology department. The samples from the intensive care unit had a discordance rate of

Table 2. Malignancy diagnosis according to departments

Department, n (%)	Non-specific (n=852)	Malignity (n=772)	p
Hematology	482 (57.3)	459 (59.6)	
Oncology	211 (25.1)	151 (19.6)	
General Internal Medicine	52 (6.2)	56 (7.3)	
Nephrology	30 (3.6)	31 (4.0)	
Geriatrics	9 (1.1)	6 (0.8)	p=0.026
Rheumatology	4 (0.5)	0 (0.0)	
Intensive Care Unit	25 (3.0)	43 (2.7)	
Surgical departments	11 (1.3)	8 (1.0)	
Others	17 (2.0)	16 (2.1)	

Table 3. Concordance rates among the departments ordering the biopsies

Department, n, (%)	Concordant (n=1001)	Discordant (n=616)	p
Hematology	578 (57.8)	366 (59.4)	
Oncology	238 (23.8)	126 (20.5)	
General Internal Medicine	73 (7.3)	36 (5.8)	
Nephrology	31 (3.1)	30 (4.9)	
Geriatrics	12 (1.2)	3 (0.5)	0.024
Rheumatology	4 (0.4)	0 (0.0)	
Intensive Care Unit	32 (3.2)	36 (5.8)	
Surgical departments	13 (1.3)	6 (1.0)	
Others	20 (2.0)	13 (2.1)	

5.8% (n=36), whereas the rate was 1.0% (n=6) in the surgical departments. The other departments exhibited a discordance rate of 2.1% (n=13).

DISCUSSION

In our study, we retrospectively examined the concordance between clinical pre-diagnoses and pathological BMB findings in patients aged 65 years or older. Data from a total of 1,821 patients were analysed, and 1,624 biopsy samples from various clinics were evaluated. The findings indicate that BMB is a critical tool in diagnosing haematological disorders in the elderly population. Notably, biopsy requests from departments such as internal medicine, haematology and oncology were frequently associated with a high rate of malignancy diagnoses, underscoring the high diagnostic sensitivity of these departments (3, 4).

The high rate of malignancy detection (59.6%, p=0.026) in biopsies requested by the haematology department supports the accuracy of biopsies performed under suspicion of haematological diseases. As reported in the literature, the incidence of haematological malignancies increases with age, which prompts haematology clinics to request biopsies with greater caution (6). However, the high discordance rate (59.4%) between pre-diagnoses and pathological diagnoses in haematology suggests the need for significant improvements in the diagnostic process. This discordance not only leads to unnecessary biopsies but also poses a risk to patient safety due to the invasive nature of the procedures; it also generates unnecessary costs for the healthcare system (10).

Although the biopsy requests from the oncology department were largely based on a suspicion of malignancy, the discordance rate between clinical pre-diagnoses and pathological findings was relatively high (20.5%). This suggests that the diagnostic algorithms used in this department may need a thorough review. While the malignancy detection rate was 19.6% among oncology patients, which reflects the fact that biopsy requests are often based on malignancy pre-diagnoses, clinical evaluations should be conducted with greater precision (12, 13). These results emphasise the need for more effective use of advanced diagnostic tests (e.g., flow cytometry and molecular genetic tests) and a multidisciplinary approach (14).

The lower malignancy rates observed in departments such as general internal medicine, nephrology and intensive care (7.3%, 4.0% and 2.7%, respectively), coupled with the high proportion of non-specific findings, indicate that these clinics faced a broader spectrum of diagnostic uncertainties. In elderly patients, the prevalence of non-specific symptoms may lead to unnecessary BMB procedures It is essential to consider the heterogeneity of the geriatric population in these cases. While chronological age is often used as a benchmark, physiological age plays a more critical role in decision-making for invasive procedures. In frail or severely debilitated patients, particularly those aged 85 years and older, the risks associated with BMB and other diagnostic interventions may outweigh the potential benefits. However, it is important to note that in certain conditions such as chronic myeloproliferative diseases, critical findings like bone marrow fibrosis, which is detectable only via BMB, play a significant diagnostic role. Similarly, in solid tumours, while bone marrow biopsies are less frequently diagnostic compared to metastasis screening purposes, the absence of metastases in such cases cannot be interpreted as discordance, as this information is still highly relevant for oncological decision-making.

The low discordance rates between pre-diagnoses and pathological findings in the geriatrics and rheumatology clinics (0.5% and 0.0%, respectively) suggest that biopsy requests in these departments were made with greater caution and based on more specific criteria. Avoiding unnecessary invasive procedures in older patients



is crucial for patient safety and quality of life (11, 15). Our findings highlight that the discordance observed in certain cases originates from the misalignment between clinical pre-diagnoses and pathological outcomes. This discordance is not merely a diagnostic challenge but also increases the likelihood older individuals undergoing additional invasive tests or procedures, further complicating their clinical management. Efforts should be directed at minimizing such discrepancies through improved diagnostic algorithms and better communication of clinical indications on pathology request forms.

In our study, the high rates of non-specific bone marrow changes (21.8% hypercellular, 2.4% hypocellular) demonstrate that BMB in the elderly population is essential not only for malignancy diagnosis but also for evaluating various haematological disorders (2, 16). In particular, peripheral blood cytopenia warrant careful evaluation to ensure that appropriate diagnostic samples are obtained, and unnecessary invasive procedures are avoided. Non-specific findings such as hypo- and hypercellular bone marrow, while categorized as non-specific in this study, may still provide critical diagnostic insights when correlated with specific clinical scenarios, such as suspected multiple myeloma. However, the inadequacy of 6.8% of the samples highlights the need for improvements in biopsy techniques and the quality of specimens (17). Stratifying older patients based on physiological rather than chronological age can improve the accuracy and safety of invasive diagnostic interventions. Moreover, advanced diagnostic methods, such as immunophenotyping and molecular genetic analyses, may supplement or even replace BMB in certain cases when adequate peripheral samples are available, reducing the need for unnecessary biopsies. Future studies should consider stratifying elderly patients into more specific age groups to better evaluate the appropriateness of invasive procedures. For instance, distinguishing between patients aged 65-79, 80-85, and above 85 years could provide clearer insights into the risks and benefits of BMB in these subgroups.

The development of new diagnostic algorithms is critically needed to prevent unnecessary invasive procedures in the older population (18). Incorporating a multidisciplinary approach that includes geriatric assessments can aid in tailoring diagnostic and therapeutic interventions based on the patient's physiological capacity and expected benefit, particularly in advanced age groups. The high discordance rate (38.1%) identified in our study suggests that current clinical protocols may not be sensitive enough for elderly patients. More advanced non-invasive tests (e.g., imaging techniques and genetic analyses) should be used before performing BMB, particularly in haematology and oncology departments. This approach could better determine the need for biopsies, thus reducing unnecessary invasive procedures and enhancing patient safety (14, 19).

One of the key strengths of this study is its comprehensive retrospective analysis, which highlighted the importance of BMB in diagnosing haematological diseases in the elderly population. By evaluating samples from various clinical departments, the study effectively assessed both diagnostic processes and the concordance between clinical pre-diagnoses and pathological findings. Furthermore, the comparison of malignancy detection rates and interdepartmental diagnostic discrepancies provided valuable insights into the sensitivity of diagnostic algorithms, especially for older patients. This kind of analysis is crucial to optimise diagnostic procedures in this demographic. However, the study also has certain limitations. The retrospective design may have introduced bias in the data collection. Furthermore, the fact that 6.8% of biopsy samples were deemed insufficient indicates that biopsy techniques and sample quality should be improved. Another limitation is the potential impact

of incomplete or poorly documented pathology request forms. These inconsistencies may have contributed to the observed discordance between clinical pre-diagnoses and pathological findings, particularly in cases involving non-specific bone marrow changes. Ensuring better communication and comprehensive clinical details on pathology request forms is essential to improving diagnostic accuracy. Additionally, the classification of hypo- and hypercellular bone marrow findings as non-specific in this study may have underestimated their diagnostic significance. Future studies should aim to correlate such findings more closely with clinical indications to better evaluate their role in specific conditions, such as multiple myeloma. The high rates of discordance, particularly in the haematology and oncology departments, suggest that existing diagnostic algorithms may not be sufficiently sensitive for older patients. This highlights the need for the expanded use of advanced diagnostic tests (e.g., molecular genetic analyses and advanced imaging techniques) before resorting to invasive procedures in order to improve diagnostic accuracy and patient safety.

In conclusion, our study underscores the importance of performing BMB in the older population based on accurate clinical indications. In older patients, BMB should be performed with careful consideration of the benefit-to-risk ratio, especially in those aged 80 years and older. Optimising multidisciplinary assessments and diagnostic processes not only enhances patient safety but also contributes to the cost-effectiveness of the healthcare system. Future studies should focus on developing new protocols to optimise diagnostic processes in older patients. Age-specific stratification could further improve the safety and efficacy of BMB in this population. These measures may reduce the discordance between clinical pre-diagnoses and pathological findings, thereby streamlining the diagnostic process. Additionally, integrating a multidisciplinary approach that includes geriatric assessments into diagnostic algorithms could enhance decision-making and improve patient outcomes, particularly in frail and vulnerable older individuals.

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ORIGINAL ARTICLE

ELECTROCARDIOGRAPHIC CHANGES AND CLINICAL IMPORTANCE OF THE FRONTAL QRS-T ANGLE IN OPEN-HEART SURGERY

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Abstract

Introduction: The frontal QRS-T angle reflects the difference between ventricular depolarization and repolarization and is a marker of electrical remodeling. This study evaluates changes in the frontal QRS-T angle before and after open-heart surgery, especially in the geriatric population. It examines its association with left ventricular ejection fraction, cardiopulmonary bypass time, and aortic cross-clamp time.

Materials and Method: A retrospective analysis of 88 adult patients undergoing open-heart surgery was conducted. Preoperative and postoperative electrocardiographic data were compared, and frontal QRS-T angles were analyzed. Statistical analysis included paired t-tests and generalized linear modeling to identify factors influencing changes in the frontal QRS-T angle.

Results: After surgery, a significant increase in ventricular rate ($p<0.001$) was observed, accompanied by significant reductions in QRS duration ($p=0.024$) and QT interval ($p=0.011$). Higher preoperative left ventricular ejection fraction values were inversely associated with postoperative changes in the frontal QRS-T angle (odds ratio: 0.980; $p=0.017$).

Conclusion: Open-heart surgery leads to significant changes in ventricular conduction and repolarization, which are reflected in alterations in the frontal QRS-T angle. The preoperative frontal QRS-T angle emerged as a robust predictor of postoperative electrical remodeling dynamics. Higher preoperative left ventricular ejection fraction is associated with less pronounced postoperative changes in the frontal QRS-T angle, highlighting its importance in predicting postoperative electrical remodeling. Particularly in elderly patients, the frontal QRS-T angle may serve as a practical marker for perioperative risk stratification. The frontal QRS-T angle may be valuable for perioperative risk assessment, particularly in elderly patients. Further large-scale studies must validate these findings and explore the underlying mechanisms.

Keywords: Aged; Electrocardiography; Cardiopulmonary Bypass; Stroke Volume.

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INTRODUCTION

The spatial QRS-T angle, which indicates myocardial repolarization, represents the vectorial difference between ventricular depolarization and repolarization. Accurate measurement of this parameter requires sophisticated computational software. However, the frontal QRS-T (FQRST) angle, which also reflects the vectorial concordance between ventricular depolarization and repolarization and is more commonly used in clinical practice, can be automatically calculated using modern electrocardiography devices and has been shown to strongly correlate with the spatial QRS-T angle (1,2). The FQRST angle is the absolute difference between the QRS and T wave axes and is recognized as a marker of disrupted ventricular electrical activity. Numerous studies have demonstrated that a widened FQRST angle is significantly associated with increased cardiovascular mortality, all-cause mortality, and risk of arrhythmia. For instance, an enlarged FQRST angle has been linked to atrial fibrillation, postoperative complications, and sudden cardiac death (3). Furthermore, its prognostic significance has been validated in patients undergoing myocardial revascularization or cardiac valve surgery (4-6).

Recently, there has been a growing focus on the potential of pharmacological and surgical interventions to improve the FQRST angle. For example, certain pharmacotherapeutic agents have been shown to narrow a widened FQRST angle, positively influencing cardiac repolarization and reducing the risk of sudden cardiac death. Moreover, the association between an abnormal FQRST angle and complications such as postoperative atrial fibrillation has been demonstrated, highlighting its importance for predicting clinical outcomes following surgery (1,5,7).

This study aimed to evaluate changes in the FQRST angle before and after open-heart surgery and to analyze its relationship with parameters such as left ventricular ejection fraction (LVEF), cardiopulmonary bypass (CPB) duration, and aortic X-clamp time. Due to the limited number of studies conducted on this subject, particularly in elderly patients, it also aimed to investigate the prognostic value of the FQRST angle for postoperative risk stratification and patient follow-up.

MATERIALS AND METHOD

Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the Good Clinical Practice guidelines. Approval was obtained from the local ethics committee (approval No. 2024/660). All patients provided written informed consent for the use of their clinical and surgical data. Additionally, the surgeons performing the procedures granted permission to include the surgical data they generated. These surgeons also waived their right to be acknowledged as coauthors of this article.

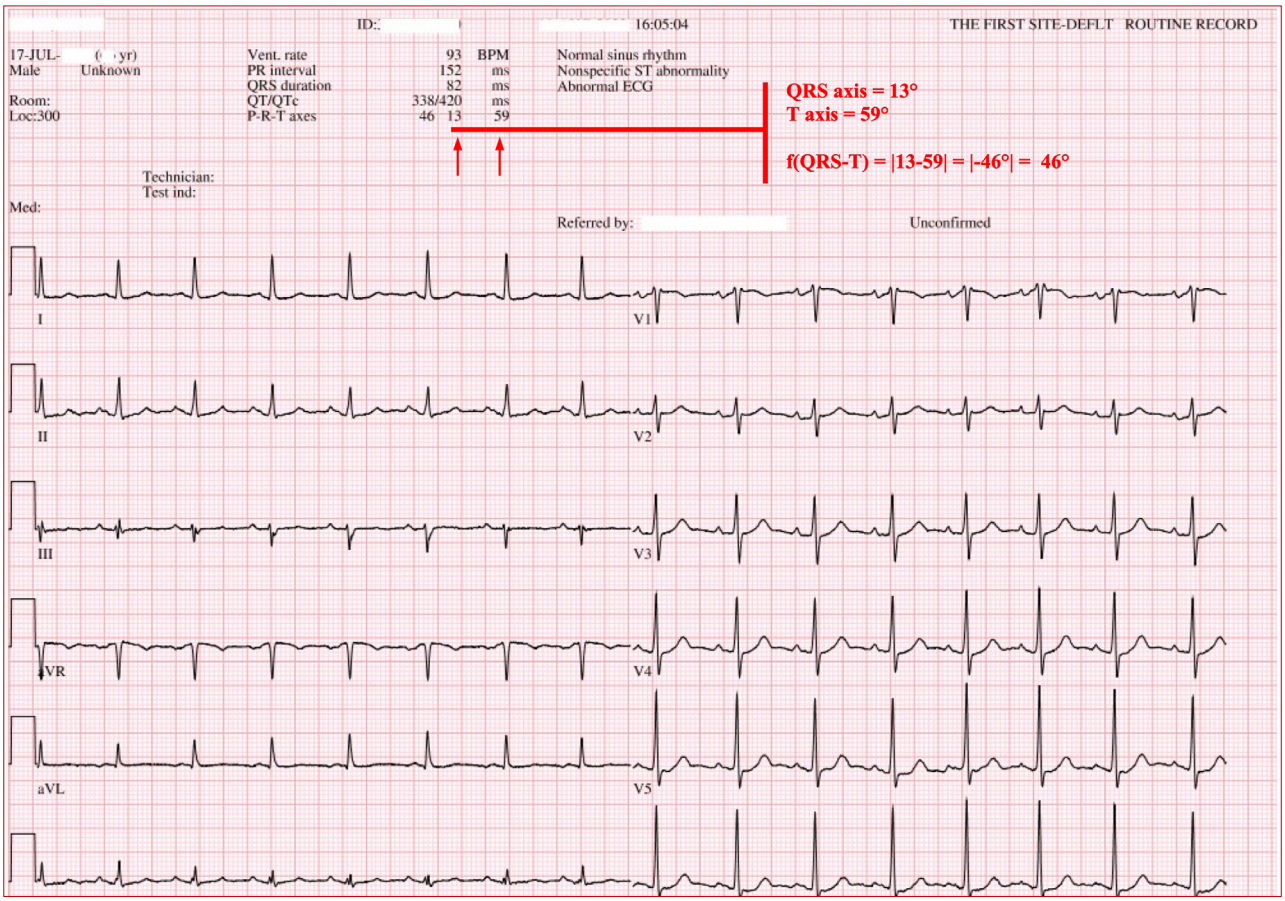
Population and Samples

A retrospective analysis of 600 patients undergoing open-heart surgery between March 2017 and March 2024 was performed. The electrocardiograms (ECGs) of 88 consecutive adult patients were analyzed. Specifically, preoperative ECGs were compared with ECGs obtained on the morning of postoperative day one. Patients with missing preoperative or postoperative ECGs and patients under the age of 18 years were excluded. Demographic, ECG, and echocardiographic data were collected from the patients' medical files and electronic databases.

ECG Measurements

The FQRST angle was calculated as the absolute difference between the QRS and T wave axes derived automatically from the ECG machine (Figure 1). The aim of using the QRS and T wave axes derived from the machine was to eliminate

Figure 1. Illustration of Frontal QRS-T Angle Calculation Method



measurement subjectivity. If the FQRST angle exceeded 180°, the value was subtracted from 360.

Statistical Analysis

Continuous variables were expressed as means and standard deviations, while categorical variables were expressed as frequencies and percentages. Preoperative and postoperative electrocardiographic indices, such as the QT interval, QTc interval, and FQRST angle, were compared using paired t-tests. To identify factors related to changes in the FQRST angle, a generalized linear model (GLM) was employed, in which the FQRST angle change was analyzed using a gamma distribution with a log-link function. Odds ratios with 95% confidence intervals (CIs) were calculated. Values of $p<0.05$ were considered statistically significant. All analyses were performed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of the study cohort are summarized in Table 1. The mean age of the patients was 66.32± 9.11 years. Female patients accounted for 34.09% of the study population. The mean body mass index was 28.27±3.98 kg/m², corresponding to an average body surface area was 1.86. The mean LVEF was



51.01±8.78, indicating that most patients had preserved to mildly reduced cardiac function. These baseline characteristics reflected a population at moderate cardiovascular risk, typical of patients undergoing cardiac surgery.

The differences between preoperative and postoperative ECG parameters are detailed in Table 2. A statistically significant increase was observed in the postoperative ventricular rate (VR; mean difference: −16.28, 95% CI: −21.18 to −11.38; p<0.001). This elevation was likely due to heightened sympathetic activation or autonomic dysregulation during recovery. In contrast, reductions in QRS duration (mean difference: 3.011, 95% CI: 0.406 to 5.617; p=0.024) and the QT interval (mean difference: 14.489, 95% CI: 3.434 to 25.543; p = 0.011) were noted postoperatively, suggesting improved ventricular conduction and reduced repolarization heterogeneity.

The mean preoperative frontal QRS-T angle was 60.48± 50.61, while the postoperative value was 60.88 ± 49.89, showing no statistically significant difference (p=0.959). In the generalized linear model used to identify factors related to changes in the FQRST angle, the dependent variable, FQRST angle change, was modeled with a gamma distribution and a log-link function. The variables included in the analysis—based on their clinical relevance and the related literature—were the procedure at hospital admission, total CPB time, aortic X-clamp time, and preoperative LVEF. As

Table 1. Baseline Characteristics and Perioperative Metrics of the Study Cohort

Parameters	(n=88)
Age	66.32±9.11
Female, n (%)	30 (34.09%)
Body Mass Index, kg/m^2	28.27±3.98
Ischemic etiology	44 (50.00%)
Hypertension	54 (61.4%)
Diabetes mellitus	39 (44.3%)
Dyslipidemia	40 (45.5%)
Smoking	39 (44.3%)
Total Cardiopulmonary Bypass time (min)	109.89±31.02
Aortic X-clamp time (min)	76.38±25.08
Left Ventricle Ejection Fraction (%)	51.01±8.78

Table 2. Comparison of Pre- and Postoperative ECG Parameters in Open Heart Surgery

Parameters	Preoperative	Postoperative	P value
Frontal QRS-T angle (°)	60.48±50.61	60.88±49.89	0.959
Frontal QRS-T angle (°) (Age>65)	60.62±52.41	64.36±51.63	0.690
Ventricular rate (bpm)	75.59±15.59	91.88±15.71	**<0.001***
P wave axis (°)	41.99±40.13	42.71±47.53	0.915
R wave axis (°)	19.22±47.06	16.50±41.33	0.538
T wave axis (°)	48.57±77.13	52.15±75.18	0.762
PR interval, ms	166.14±35.57	164.19±48.07	0.715
QRS duration, ms	94.03±16.74	91.02±16.26	**0.024***
QT interval, ms	393.43±37.60	378.94±40.02	**0.011***
QTc interval, ms	422.33±59.87	415.44±77.80	0.440
Tp-e interval, ms	422.24±59.87	415.35±77.79	0.440
Tp-e/QT ratio	1.077±0.15	1.101±0.19	0.351
Tp-e/QTc ratio	0.999±0.00	0.999±0.00	0.285

shown in Table 3 and Figure 2, only the preoperative LVEF was found to be significantly associated with changes in the FQRST angle, showing an inverse relationship (odds ratio: 0.980, 95% CI: 0.964 to 0.996; p=0.017), thus suggesting that higher preoperative LVEF values were associated with less pronounced postoperative changes in the FQRST angle.

In a subgroup analysis of patients over 65 years old, the mean preoperative FQRST angle was 60.62±52.41, while the postoperative mean value was 64.36±51.63. The mean change in the FQRST angle was +3.73, indicating substantial interpatient variability in postoperative cardiac remodeling. The generalized linear model analysis for the ≥65 age subgroup demonstrated that preoperative FQRST angle was significantly associated with postoperative FQRST angle (β=0.2881, p=0.048). However, LVEF did not exhibit a statistically significant effect in this age group (β=0.0992, p=0.906). This suggests that factors other than LVEF may play a more significant role in postoperative electrical remodeling in elderly

Table 3. Analysis of Surgical and Cardiac Parameters Associated with the Frontal QRS-T Angle

	OR (95% CI)	p-value
Procedure (reference: CABG only)		
Valve Replacement alone	1.573 (0.866 – 2.859)	.137
Complex Procedure	0.762 (0.437 – 1.330)	.339
Total Cardiopulmonary bypass time	1.003 (0.995 – 1.011)	.490
Aortic X-clamp time	1.002 (0.990 – 1.014)	.718
Left Ventricle Ejection Fraction (%)	0.980 (0.964 – 0.996)	**.017***

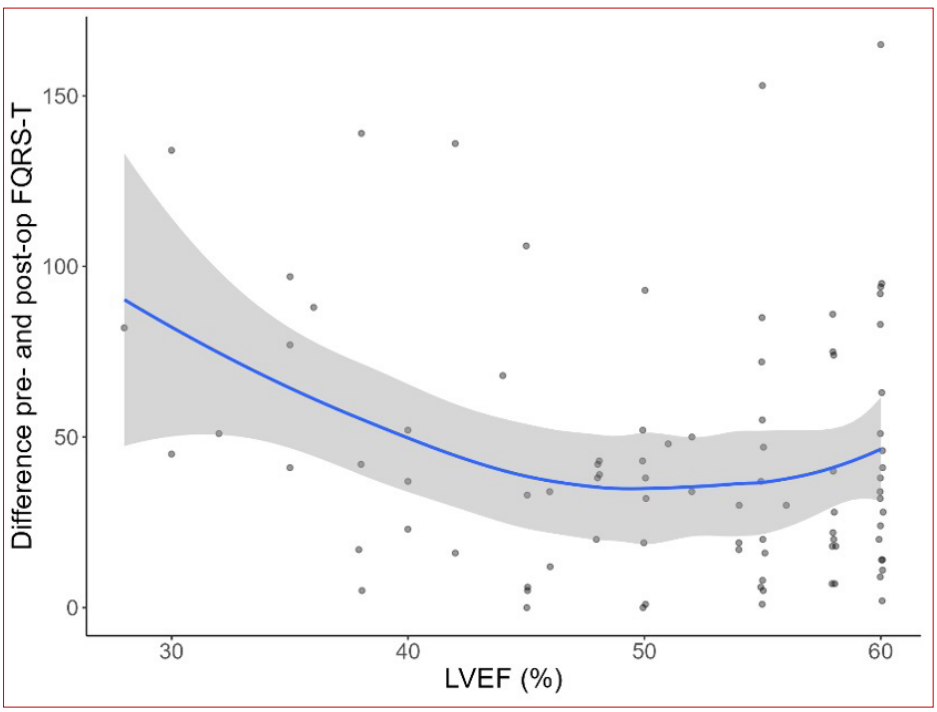


Figure 2. Relationship Between Left Ventricle Ejection Fraction (LVEF) (%) and Differences in Pre- and Postoperative Frontal QRS-T Angles

patients. The scatter plot in Figure 3 illustrates the relationship between LVEF and the difference in preoperative and postoperative FQRST angles, but it does not show a meaningful trend.

In subgroup analyses based on surgical procedures, patients undergoing complex procedures exhibited the highest mean preoperative FQRST angles (79.25±50.66), followed by those undergoing coronary artery bypass grafting (CABG) (58.46±49.79) and valve replacement (52.00±55.38). Postoperatively, complex procedures also demonstrated the highest FQRST angles (81.92±60.38), whereas CABG and valve replacement groups showed lower values (58.26±45.22 and 53.36±62.64, respectively). However, paired t-tests revealed no significant changes in FQRST angles between preoperative and postoperative measurements across all subgroups: CABG (p=0.98), valve replacement (p=0.95), and complex procedures (p=0.87) (Table 4). A GLM analysis demonstrated that the preoperative FQRST angle was a significant predictor of postoperative FQRST angle changes (β=-0.6674, p<0.001). This indicates that higher preoperative FQRST angles are associated with less pronounced postoperative changes. Importantly, the type of surgical procedure (CABG, valve replacement, or complex procedure) did not significantly influence

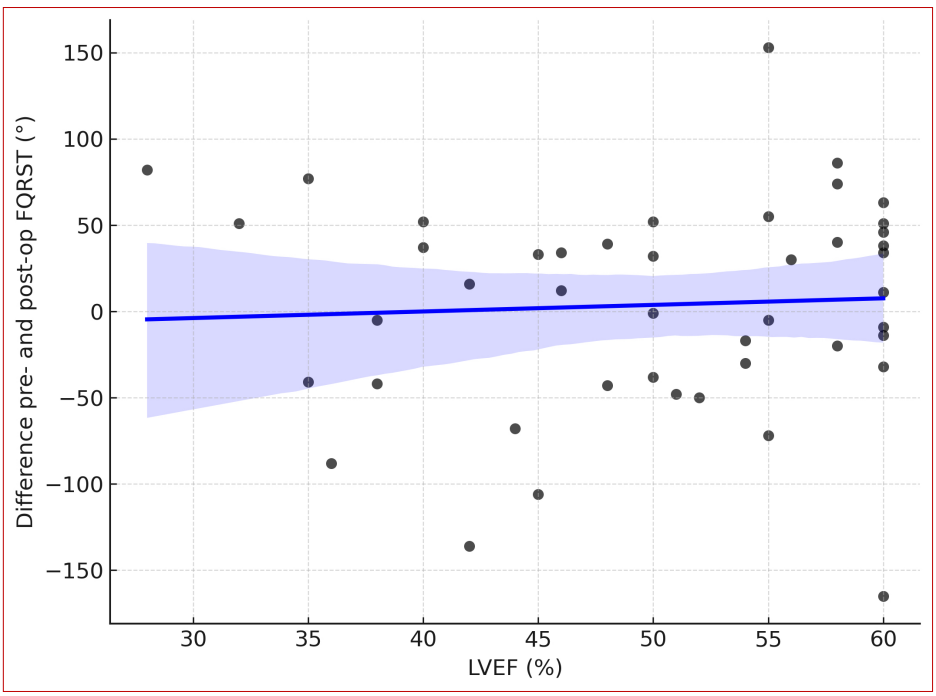
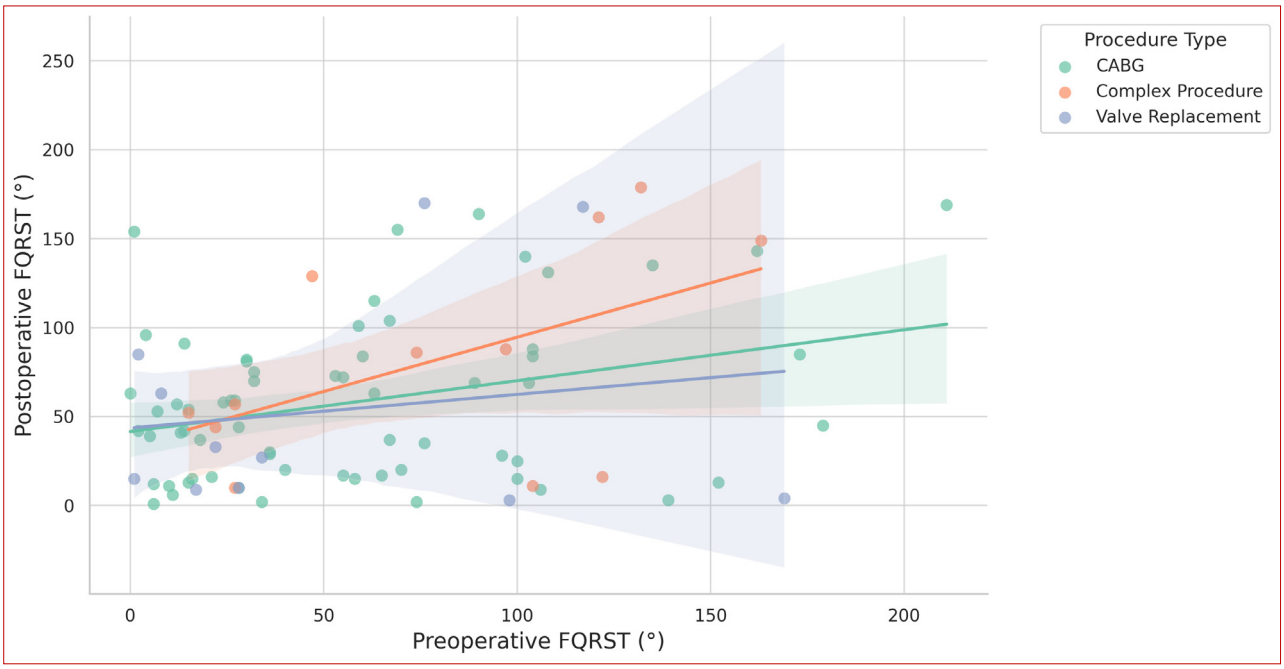


Figure 3. Relationship Between Left Ventricle Ejection Fraction (LVEF) (%) and Difference in Pre- and Postoperative Frontal QRS-T Angles (Age>65)

Table 4. Preoperative and postoperative Frontal QRS-T angles by procedure

Procedure	n	Preoperative	Postoperative	P value
CABG	65	58.46±49.79	58.26±45.22	0.98
Valve Replacement	11	52.00±55.38	53.36±62.64	0.95
Complex Procedure	12	79.25±50.66	81.92±60.38	0.87

Figure 4. Subgroup Analysis of the Frontal QRS-T Angles by Procedure (CABG: Coronary Artery Bypass Grafting)



this relationship (p=0.811), suggesting that preoperative electrical characteristics primarily drive postoperative remodeling. Figure 4 illustrates these findings, showing consistent trends across surgical subgroups, with a clear inverse relationship between preoperative FQRST angle and postoperative changes, irrespective of the procedure type. This emphasizes the potential role of preoperative electrical characteristics as dominant factors in predicting postoperative remodeling outcomes.

DISCUSSION

This study investigated the relationship between preoperative and postoperative ECG parameters and clinical outcomes in cardiac surgery patients. Our findings are consistent with previous studies showing that cardiac surgery leads to significant electrical remodeling, as evidenced by changes in ventricular conduction and repolarization processes (1,4,7). Specifically, the observed postoperative reductions in QRS duration and the QT interval suggest improved ventricular conduction and decreased repolarization heterogeneity. These findings provide valuable insights into how cardiac surgery may influence the electrical substrate and arrhythmic risk.

Aging is associated with structural and electrical remodeling of the heart, including myocardial fibrosis, conduction system disease, and increased arrhythmic vulnerability. Our findings indicate significant postoperative ventricular conduction and repolarization changes in geriatric patients following cardiac surgery. Age-related vascular changes, such as increased arterial stiffness, reduced nitric oxide bioavailability, and endothelial dysfunction, contribute to impaired myocardial perfusion and increased cardiovascular vulnerability. These changes are often compounded by comorbidities such as hypertension, diabetes, and chronic kidney disease, which are more prevalent in elderly populations. Consequently, postoperative cardiac outcomes in geriatric patients are significantly influenced by intrinsic myocardial changes and



systemic vascular aging processes that compromise overall cardiovascular resilience (8).

In line with prior reports (1,7,9), the marked increase in the VR observed postoperatively reflects increased sympathetic activation and autonomic dysregulation during recovery. In older adults, this increase may indicate heightened postoperative sympathetic activation combined with age-related autonomic dysfunction. The reduced QRS duration and QT interval suggest improved myocardial conduction and repolarization, although age-related myocardial stiffness may modulate these effects. The observed QRS duration and QT interval changes are noteworthy, as they suggest a potential reduction in arrhythmic vulnerability. Similar findings have been reported in the context of other cardiac interventions, highlighting the dynamic nature of electrical remodeling (1,4,7).

The prognostic significance of the FQRST angle has been well documented (1,2,6). To the best of our knowledge, this study is one of the first to investigate the relationship between these factors and clinical outcomes in patients undergoing cardiac surgery, where the majority of the study population consists of geriatric individuals. A wide QRS-T angle has consistently been linked to adverse cardiovascular outcomes, including ventricular arrhythmia and sudden cardiac death (10). The inverse relationship between the preoperative LVEF and postoperative changes in the FQRST angle observed in this study highlights the protective role of preserved cardiac function against adverse electrical remodeling.

Subgroup analyses demonstrated that complex procedures had the highest preoperative and postoperative FQRST angles compared to CABG and valve replacement. Despite this, no significant pre-to-postoperative changes in FQRST angles were observed across subgroups, suggesting that procedural type alone does not independently drive substantial electrical remodeling. Generalized linear model analysis revealed that preoperative FQRST angle was a robust predictor of postoperative values, with higher preoperative angles associated with attenuated postoperative changes. Notably, the type of surgical intervention did not significantly influence this relationship, emphasizing the preeminence of intrinsic preoperative electrical characteristics in shaping postoperative remodeling. These findings highlight the prognostic utility of the FQRST angle in assessing perioperative electrical remodeling dynamics. Future investigations should focus on elucidating the mechanistic underpinnings of this relationship, particularly in complex procedures, to refine risk stratification and improve personalized cardiac care.

Although paired t-tests revealed no significant difference in mean preoperative and postoperative FQRST angles, the GLM analysis demonstrated a significant relationship between the preoperative FQRST angle and its postoperative changes. This discrepancy highlights the strength of GLM in identifying predictive relationships and variability at the individual level, which comparisons of groups may not capture means. The findings suggest that while the overall mean FQRST angle remained stable, individual factors, particularly preoperative electrical characteristics, played a significant role in determining postoperative electrical remodeling.

In a subgroup analysis of patients aged ≥65 years, we observed that preoperative FQRST angle remained a significant predictor of postoperative changes in FQRST angle. However, LVEF did not exhibit a statistically significant association with FQRST angle changes. As shown in Figure 3, there was no meaningful relationship between LVEF and the degree of electrical remodeling, suggesting that other factors may play a more prominent role in geriatric patients. This association appears to be particularly relevant to geriatric patients, in whom age-related structural and functional changes may amplify the clinical implications of electrical remodeling. A previous study on primary percutaneous coronary interventions has also identified the FQRST angle as a strong predictor of mortality (11).

Although the Tp-e/QT and Tp-e/QTc ratios have been proposed as electrocardiographic markers of ventricular repolarization heterogeneity and arrhythmic risk (12), no significant differences were observed in these parameters before and after surgery in our study. This may be attributed to the differing etiologies and mechanisms of arrhythmogenesis in surgical and trauma populations.

The observed postoperative improvements in ventricular conduction are likely related to enhanced myocardial function following surgical intervention. Similar findings have been reported in populations undergoing myocardial revascularization or valve surgery, with the postoperative changes in the FQRST angle linked to reduced arrhythmic vulnerability (4). Both these findings and our results underscore the prognostic value of the FQRST angle and its potential to be used for perioperative risk stratification. The significant association between the preoperative LVEF and changes in the FQRST angle highlights the importance of baseline cardiac function as a determinant of postoperative electrical remodeling. However, the subgroup analysis of patients aged ≥65 years revealed that LVEF may not independently predict postoperative electrical remodeling in this age group. This finding suggests that other age-related structural or functional changes might be more significant in modulating postoperative electrical remodeling. Geriatric patients with impaired baseline cardiac function may require closer perioperative monitoring and targeted interventions to mitigate arrhythmic complications during recovery. The potential of dynamic ECG changes, such as alterations in the FQRST angle, to be used as biomarkers for predicting arrhythmic risk and cardiac dysfunction warrants further investigation in comprehensive studies (1,4,6).

This study has certain limitations that should be acknowledged. Its retrospective and single-center design inherently limits the generalizability of the findings. Moreover, although sufficient for early postoperative analyses, the relatively small sample size may not provide adequate statistical power to detect more nuanced associations or subgroup differences. Additionally, the absence of mid- and long-term follow-up data restricted the ability to evaluate the prognostic value of observed ECG changes, such as FQRST angle alterations, to arrhythmic events and clinical outcomes. Furthermore, the study population primarily consisted of patients with preserved or mildly reduced left ventricular ejection fraction (LVEF). This may have influenced the extent and generalizability of the observed electrical remodeling. Furthermore, this study did not evaluate key cardiovascular parameters such as left ventricular end-diastolic volume or left atrial diameter, which are known to influence electrical remodeling due to data limitations. The potential role of these parameters warrants further investigation in future studies.

Future studies should address these limitations by including larger and more diverse patient populations, focusing on geriatric subgroups. Incorporating advanced imaging techniques, biomarker analyses, and additional clinical variables would enable a deeper understanding of postoperative electrical remodeling mechanisms. Additionally, future research should explore the impact of different surgical procedures on long-term outcomes, such as mortality and arrhythmic events, to further delineate the role of electrical remodeling in perioperative risk stratification. Longitudinal studies with extended follow-up periods are essential to elucidate the interaction between structural and electrical remodeling and its long-term clinical implications, particularly in high-risk surgical populations.

CONCLUSION

This study highlights the dynamic nature of early postoperative electrical remodeling following cardiac surgery, with changes in the FQRST angle reflecting significant alterations in ventricular conduction and repolarization. Preoperative LVEF



was identified as a key predictor of these changes; however, in elderly patients, additional age-related structural and functional factors may influence the remodeling process, emphasizing its multifactorial complexity. The findings underscore the value of the FQRST angle as a biomarker for perioperative risk stratification and the need for further validation in larger cohorts with long-term follow-up to better understand its prognostic implications.

Ethics approval and consent to participate: The study was approved by the Local Ethical Committee. The ethics approval date and number is 17.12.2024-2024/660.

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AO: All stages, including conceptualization, investigation, literature search, analysis, interpretation, writing, editing, final draft review, and critical review, were carried out by the author.

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ORIGINAL ARTICLE

EVALUATION OF HAEMATOLOGICAL PARAMETERS IN PATIENTS AGED ≥85 YEARS: A RETROSPECTIVE SINGLE-CENTER STUDY FROM TURKEY

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Abstract

Introduction: We aimed to analyse complete blood count values in patients aged ≥85 and the potential differences in haematological parameters between age groups within this population.

Materials and Method: A retrospective analysis was conducted on 458 patients aged ≥85 who underwent complete blood count testing between 2 February 2005 and 11 October 2023. White blood cell count, neutrophils, lymphocytes, eosinophils, basophils, haemoglobin, platelets, mean corpuscular volume, mean platelet volume, red cell distribution width, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration levels were recorded, and their median and mean values were calculated. Patients were stratified into three age groups: 85–89, 90–99, and ≥100 years. The impact of age and sex on complete blood count parameters was assessed. A subgroup analysis was also performed, excluding patients with a history of factors potentially affecting haematological parameters and those with abnormal mean corpuscular volume levels.

Results: Excluding patients with abnormal mean corpuscular volume and a history of factors potentially affecting haematological parameters, we found a notably high prevalence of anaemia (85% in men and 76% in women). No significant differences in haemoglobin values were observed across the age groups. The median platelet, lymphocyte, and white blood cell counts remained within the hospital's normal reference ranges.

Conclusion: The presence of anaemia in older patients aged ≥85, based on the current World Health Organization criteria, with no apparent cause after etiologic investigations, may be considered normal in some older individuals.

Keywords: Anaemia; Blood Cell Count; Geriatrics.

INTRODUCTION

There is no standardised age-specific reference level for blood count readings in older patients. The World Health Organization defines anaemia as haemoglobin levels < 12 g/dL in women and < 13 g/dL in men (1). Determining the limits of anaemia may also be decisive for developing a treatment plan. In a study conducted on patients aged ≥60 years, Hermann et al. reported that platelet levels were higher in women than in men (2). They also found that the lower platelet reference limit decreased in men with increasing age, whereas the upper reference limit remained constant (2). A German study by Röhrig et al. on patients aged ≥60 years showed that the levels of all leukocyte subtypes other than monocytes remained unaffected with advancing age (3). They also reported that platelet levels were higher in women than in men and that these values decreased with advancing age (3).

This study sought to analyse the complete blood count values of patients aged ≥85 years to establish both median and mean values for this cohort. Furthermore, we aimed to determine whether there were variations in haemogram parameters across different age subgroups within this older population. We also investigated the potential impact of advancing age on blood count values in patients aged ≥85. Additionally, our study explored whether haemogram parameters differed between men and women within this age group. The availability of age-specific standardised upper- and lower-limit blood count values for this demographic has the potential to contribute to avoiding unnecessary testing and wasting time in hospitals for certain geriatric patients.

MATERIALS AND METHOD

Research Protocol

This retrospective study analysed data from 458 patients aged ≥85 years who underwent complete blood count (CBC) testing at Süleyman Demirel University Medical Faculty Hospital (SDU Research and Teaching Hospital) between 2 February 2005 and 11 October 2023 inclusive. Patients aged < 85 years were excluded.

The patients included in the study were also divided into two groups, men and women and all analyses were performed separately.

The following CBC parameters were recorded for all patients: white blood cell (WBC) count, neutrophil count, lymphocyte count, eosinophil count, basophil count, haemoglobin concentration, platelet (plt) count, mean corpuscular volume (MCV), mean platelet volume (MPV), red blood cell distribution width (RDW), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC). Descriptive statistics, including median and mean values, were calculated for each CBC parameter in the entire cohort. These data were then stratified by sex, and separate descriptive analyses were performed for men and women the results are presented in separate tables by sex. Subsequently, sex-based differences in WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, platelet, MCV, MPV, RDW, MCH, and MCHC values were also investigated.

Patients were further stratified into three age groups: 85–89 years, 90–99 years, and ≥100 years. We analysed the differences in haematological parameters (WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, platelet count, MCV, MPV, RDW, MCH, and MCHC) across these age groups. Subsequently, men and women were separately categorised according to the same age stratification (men: 85–89, 90–99, and ≥100 years; women: 85–89, 90–99, and ≥100 years). Within each age group, sex-based differences in haematological parameters were examined. Age-related variations in these parameters were analysed within each sex group.

Subgroup analysis was conducted on patients with normal MCV values, defined as 80–100 fL. Patients with MCV outside this range (<80 or >100

fL) were excluded from the analysis. Subgroup analysis was performed on patients with normal MCV values, because other potential untested cytopenic factors could effect the MCV values. Our study was a retrospective study and to reduce bias we prefered to make subgroup analysis on patients with normal MCV values.

For this subgroup, haematological parameters, including WBC, neutrophils, lymphocytes, eosinophils, basophils, haemoglobin, platelet count, and MPV, were recorded. The mean and median values of these parameters were calculated and are presented in separate tables. Patients with MCV values between 80–100 fL were included in this group; however, additional exclusion criteria were applied to patients with normal MCV values (Table 1). Exclusion criteria are shown in Table 1. After applying the exclusion criteria in table 1 , the remaining patients were analyzed as a subgroup.

The WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, platelet, and MPV values of all patients with MCV values of 80–100 fL were

Table 1. Exclusion criteria for subgroup analysis performed on patients with normal MCV values

Patients with known high CRP levels (above the upper reference limit of the laboratory) on the day of the haemogram	Who were found to have active infections on the day of the haemogram
Patients who were on immunosuppressive drugs, had a history of chemotherapy, had a history of inflammatory connective tissue disease, and had a known history of organ transplantation	Patients with known active malignancies (“basal cell skin cancer/ low grade lymphomas with no known bone marrow involvement/ early stage cancers that did not need treatment and were followed only with observation/ early stage cancers that achieved remission only with surgery and received no other treatment” were included)
Patients on thyroid replacement therapy	Patients known to be on routine dialysis
Patients with a known history of chronic viral hepatitis	Patients with a disease infiltrating the bone marrow
Patients with a history of aplastic anaemia, myeloproliferative disease, lysosomal storage disease, myelodysplastic syndrome (MDS) myeloid neoplasm or stem cell transplantation	Patients with premalignant clonal cytopenia, idiopathic hypereosinophilic syndrome or spleen length of ≥18 cm
Patients with a diagnosis of NSAID-derived drug use on the day of the haemogram test or in the last 2 days before the day of the haemogram test	Patients whose files showed that they were on parasitosis treatment
Patients who had systemic steroid treatment on the day of the haemogram test or in the previous five days	Patients with a history of colchicine / methotrexate / azathioprine use on the day of the haemogram test or in the previous 7 days
Patients with a history of leflunomide use on the day of the haemogram test or in the previous 30 days	Patients who were under TNF inhibitor therapy on the day of the haemogram or in the previous 90 days
Patients with a diagnosis of adrenocortical insufficiency	Patients with a diagnosis of pituitary insufficiency
Patients with a diagnosis of systemic mastocytosis	Patients with decompensated liver cirrhosis
Patients with platelet levels that were permanently decreased to <150 thousand/microliter due to immune thrombocytopenia	Patients with both liver cirrhosis and oesophageal varices
Patients receiving active treatment for immune thrombocytopenia	Patients with active autoimmune haemolytic anaemia or those receiving treatment for autoimmune haemolytic anaemia
Patients receiving active treatment for immune thrombocytopenia or microangiopathic haemolytic anaemia	Patients with DIC (disseminated intravascular coagulation), TTP(thrombotic thrombocytopenic purpura, HUS (haemolytic uraemic syndrome) or active haemolytic anaemia
Patients with a disease that infiltrated the bone marrow, those with known AIDS or those with HIV infection	Patients who had “ferritin level test result <15 ng/mL or folic acid level test result <2 ng/mL or vitamin B12 test result below the lower reference limit in our hospital’s laboratory” on the day of haemogram analysis, within the last 30 days before the day of haemogram analysis, or the first 30 days after the day of haemogram analysis



recorded after applying the exclusion criteria in table 1. The means and medians of these values were calculated and the findings are shown in a separate table. Patients included in the subgroup analysis were divided into two groups: men and women. The WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, platelet, and MPV values of the men and women were recorded separately. The means and medians of these values were calculated and the findings are presented in separate tables for men and women. We also examined whether there was a difference in WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, plt, MPV values between "men and women". Patients included in the subgroup analysis were also divided into 3 different age groups in terms of age ranges (85–89, 90–99, and ≥100-year-old patients). We also investigated whether there were any differences in WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, platelet, and MPV values between the three age groups. Furthermore, "men and women" were classified separately according to these 3 age groups (men and women aged 85–89 years, 90–99 years and ≥100 years). Subsequently, we also investigated the presence of sex-based differences in WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, plt, MPV values in the same age groups were also determined in these patient groups.

Finally, to complete the analysis of the subgroup with normal MCV values, we also examined potential differences in WBC, neutrophil, lymphocyte, eosinophil, basophil, haemoglobin, plt, and MPV values between the three age groups within each sex (i.e., (85–89, 90–99, and ≥100-year-old men and women).

This study used a retrospective file-review design. No identifying information was published to ensure patient confidentiality. Data were extracted from the hospital's electronic file system and patient notes archived at the SDU Medical Faculty Hospital. Relevant data were collected and analysed according to the methodology described above.

Ethics Committee Approval

The research protocols were approved by the Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (Ethics Committee Decision dated 29 December 2023 number 289).

Statistical Analyses

Data presentation: Descriptive, categorical, and grouped data are presented using frequency (number) and percentage values, and numerical (measurement) data are presented using mean, median, standard deviation, and minimum-maximum values. Tables and graphs are used to present the data. Box and scatter plots were used for graphics.

Statistical analysis: All collected data were analysed using the SPSS 22 software package (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). In addition to descriptive statistics, the Independent Sample t-test, a parametric hypothesis test, was used to investigate whether there was a statistical difference in the haemogram values obtained between the groups. The Mann–Whitney U test and Kruskal–Wallis tests, which are nonparametric hypothesis tests, were employed to analyse the data that did not meet the parametric criteria. Pearson's correlation test was performed to compare the relationship between age and haemogram parameters.

When a statistically significant difference was detected using the Kruskal–Wallis test for the comparison of more than two groups (comparison of age groups and haemogram parameters), pairwise comparisons were performed using the Independent Sample t-test and Mann–Whitney U Test to determine which group or group this significant difference originated from. Statistical significance was set at $p < 0.05$.

As this was a retrospective study, data were obtained from the "electronic/old type file"

archive records of SDU Research and Application Hospital. With the approval of the hospital chief physician, we requested access to relevant patient information, including findings, diagnoses, patient characteristics, examination results, follow-up notes, and other pertinent patient information. Data were screened to identify eligible patients based on the inclusion and exclusion criteria. Patients with documented exclusion criteria were excluded from this study. Patients were included if their medical records did not meet any of the exclusion criteria.

RESULTS

Of the 458 patients included in the study, 53.3% (n=244) were women and 46.7% (n=214) were men. The mean age of the entire cohort was 88.9 ± 3.8 years (range: 85–109 years). The mean age of women and men was 88.9 ± 3.8 years (range: 85–109 years) and 88.8 ± 3.7 years (range: 85–108 years), respectively. The majority of patients (71.4%, n=327) were 85–89-years-old, followed by 27.3% (n=125) aged 90–99 years, and a small proportion (1.3%, n=6) aged ≥100 years. The CBC parameters of the patients are shown in Table 2.

The analysis in Table 3 reveals a statistically significant difference in the mean MCH values across the three age groups (p=0.010). Pairwise comparisons using independent sample t-tests and Mann–Whitney U tests indicated that this difference was attributable to lower mean MCH values in patients aged 100 years and older than in those aged 85–89 years (p=0.005) and 90–99 years (p=0.005).

The analysis of Table 3 also shows a significant difference in the mean MCHC values across age groups (p=0.032). Pairwise comparisons (independent sample t-tests and Mann–Whitney U tests) revealed that this difference was also due to lower mean MCHC values in patients aged ≥100 years compared to those aged 85–89 years (p=0.012) and 90–99 years (p=0.008). No statistically significant differences were observed in the other CBC parameters across the three age groups (p>0.05). Table 4 presents the CBC values of the

Table 2. Results of complete blood count tests of patients

Hemogram Parameters (Unit)	N	Mean ± SD	Median	Min-Max
WBC (Leukocytes) (x10³/mm³)	458	12650.2 ± 23036.3	8750.0	200–289600
Neutrophils (x10³/mm³)	458	9041.1 ± 13343.5	6200.0	0.0–214200
Lymphocytes (x10³/mm³)	458	2367.5 ± 11696.1	1100.0	100–197000
Eosinophils (x10³/mm³)	458	122.5 ± 198.3	100.0	0.0–1800
Basophils (x10³/mm³)	458	62.9 ± 189.3	0.0	0.0–1900
Hemoglobin (g/dL)	458	10.3 ± 2.1	10.2	3.5–17.6
MCV (fl)	458	87.0 ± 8.6	87.3	55.6–126.5
MCH (pg)	458	29.1 ± 3.3	29.4	17.8–41
MCHC (g/dL)	458	33.5 ± 1.5	33.5	27.6–40.2
RDW (%)	458	18.3 ± 4.1	17.2	12.4–34.9
Platelet (x10³/mm³)	458	197751.1 ± 125128.7	188000.0	3000–941000
MPV (fl)	458	8.5 ± 1.4	8.3	0.0–15.2

WBC, white blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RDW, red blood cell distribution width; MPV, mean platelet volume.



Table 3. Comparison of hemogram values according to age groups

Hemogram Parameters (Unit)	Age Groups						p*
	Age 85–89		Age 90–99		Age ≥100		
	N	Mean ± SD (Median Value)	N	Mean ± SD (Median Value)	N	Mean ± SD (Median Value)	
WBC (Leukocytes) (x10³/mm³)	327	12246.2 ± 18481.9 (8900)	125	13619.2 ± 32458.1 (8600)	6	14483.3 ± 8166.1 (13050)	0.207
Neutrophils (x10³/mm³)	327	8711.6 ± 8671.4 (6200)	125	9761.6 ± 21335.4 (6100)	6	11983.3 ± 7185.9 (10850)	0.213
Lymphocytes (x10³/mm³)	327	2315.0 ± 11438.0 (1200)	125	2567.2 ± 12652.4 (1000)	6	1066.7 ± 403.3 (1150)	0.576
Eosinophils (x10³/mm³)	327	124.8 ± 203.0 (100)	125	120.0 ± 190.5 (100)	6	50.0 ± 54.8 (50)	0.726
Basophils (x10³/mm³)	327	66.4 ± 198.2 (0)	125	54.4 ± 168.7 (0)	6	50.0 ± 54.8 (50)	0.597
Hemoglobin (g/dL)	327	10.2 ± 2.2 (10.2)	125	10.4 ± 2.1 (10.2)	6	11.4 ± 1.1 (11.4)	0.224
MCV (fl)	327	86.9 ± 8.6 (87)	125	87.4 ± 8.7 (88.2)	6	82.6 ± 3.5 (81.5)	0.142
MCH (pg)	327	29.1 ± 3.2 (29.3)	125	29.4 ± 3.3 (29.6)	6	26.1 ± 1.6 (26.1)	**0.010****
MCHC (g/dL)	327	33.4 ± 1.5 (33.5)	125	33.6 ± 1.5 (33.5)	6	31.6 ± 1.9 (31.4)	**0.032****
RDW (%)	327	18.4 ± 4.0 (17.2)	125	18.0 ± 4.2 (16.9)	6	21.5 ± 6.4 (19.8)	0.190
Platelet (x10³/mm³)	327	192042.8 ± 123408.5 (186000)	125	212168.0 ± 128647.7 (190000)	6	208500.0 ± 142061.6 (207000)	0.433
MPV (fl)	327	8.5 ± 1.4 (8.3)	125	8.5 ± 1.3 (8.3)	6	8.6 ± 1.4 (9.1)	0.922

*Kruskal–Wallis Test

**Mann–Whitney U Test, Independent Sample t-test

WBC, white blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RDW, red blood cell distribution width; MPV, mean platelet volume.

115 patients with normal MCV values (80–100 fL) that remained after exclusion.

To assess the influence of sex on CBC parameters, we compared the haemogram values of 115 patients with normal MCV values after applying the exclusion criteria. The comparisons are presented in Table 5.

When the haemogram values of the 115 patients with normal MCV values were compared according to sex, no statistically significant differences were

Table 4. Hemogram values in eligible patients with normal MCV

Hemogram Parameters (Unit)	N	Mean ± SD	Median	Min-Max
WBC (Leukocytes) (x10³/mm³)	115	9016.5 ± 2969.9	8600	1600–16400
Neutrophils (x10³/mm³)	115	6577.4 ± 2736.5	6100	1100–14800
Lymphocytes (x10³/mm³)	115	1521.7 ± 1204.7	1200	200–8300
Eosinophils (x10³/mm³)	115	139.1 ± 149.1	100	0.0–600
Basophils (x10³/mm³)	115	41.7 ± 104.3	0.0	0.0–900
Hemoglobin (g/dL)	115	11.0 ± 1.7	10.8	8.0–15.4
Platelet (x10³/mm³)	115	247191.3 ± 102984.7	219000	108000–544000
MPV (fl)	115	8.4 ± 1.3	8.1	6.2–12.9

WBC: white blood cell, MPV: mean platelet volume

Table 5. Comparison of hemogram values by sex in eligible patients with normal MCV

Hemogram Parameters (Unit)	Sex				p*
	Men		Women		
	N	Mean ± SD (Median)	N	Mean ± SD (Median)	
WBC (Leukocytes) (x10³/mm³)	48	9360.4 ± 2645.1 (9050)	67	8770.1 ± 3178.9 (8200)	0.295
Neutrophils (x10³/mm³)	48	6993.8 ± 2529.9 (6200)	67	6279.1 ± 2856.7 (5800)	0.168
Lymphocytes (x10³/mm³)	48	1391.7 ± 976.7 (1100)	67	1614.9 ± 1343.9 (1200)	0.329
Eosinophils (x10³/mm³)	48	133.3 ± 156.2 (100)	67	143.3 ± 144.8 (100)	0.726
Basophils (x10³/mm³)	48	64.6 ± 148.0 (0)	67	25.4 ± 50.3 (0)	0.083
Hemoglobin (g/dL)	48	11.0 ± 1.8 (10.7)	67	11.0 ± 1.6 (10.9)	0.973
Platelet (x10³/mm³)	48	260375.0 ± 113858.2 (229500)	67	237746.3 ± 94183.5 (218000)	0.247
MPV (fl)	48	8.2 ± 1.0 (8.0)	67	8.6 ± 1.5 (8.2)	0.116

*Independent Sample t-test

WBC: white blood cell; MPV: mean platelet volume



found (p>0.05). Table 6 presents the comparison of haemogram parameters across the three age groups (85–89 years, 90–99 years, and ≥100 years) in these 115 patients.

In the subgroup of 115 patients with normal MCV values, no statistically significant differences in haemogram parameters were observed across the three age groups (85–89 years, 90–99 years, and ≥100 years) (p>0.05).

Similarly, within each age group, no statistically significant differences in haemogram parameters were found between men and women (p>0.05). However, a comparison of haemogram parameters by sex in the ≥100 years age group was not performed due to the small sample size (only one men).

No statistically significant difference was found between the haemogram parameters in men with MCV within the normal range after the exclusion criteria were applied when compared according to the age groups of the patients (p>0.05).

No statistically significant differences were observed in haemogram parameters across age groups among women with normal MCV values who met the inclusion criteria (p>0.05).

Table 6. Comparison of hemogram values by age groups in eligible patients with normal MCV

Hemogram Parameters (Unit)	Age Groups						p*
	Age 85–89		Age 90–99		Age ≥100		
	N	Mean ± SD (Median Value)	N	Mean ± SD (Median Value)	N	Mean ± SD (Median Value)	
WBC (Leukocytes) (x10³/mm³)	81	8971.6 ± 2784.9 (8500)	33	9039.4 ± 3430.5 (8700)	1	11900.0 ± -(11900)	0.519
Neutrophils (x10³/mm³)	81	6523.5 ± 2645.3 (6100)	33	6618.2 ± 2981.6 (6000)	1	9600.0 ± -(9600)	0.501
Lymphocytes (x10³/mm³)	81	1540.7 ± 1265.4 (1200)	33	1487.9 ± 1076.7 (1100)	1	1100.0 ± -(1100)	0.933
Eosinophils (x10³/mm³)	81	150.6 ± 155.0 (100)	33	112.1 ± 134.1 (100)	1	100.0 ± -(100)	0.436
Basophils (x10³/mm³)	81	28.4 ± 61.7 (0)	33	75.8 ± 165.9 (0)	1	0.0 ± -(0)	0.117
Hemoglobin (g/dL)	81	10.9 ± 1.7 (10.7)	33	10.9 ± 1.7 (10.9)	1	12.9 ± -(12.9)	0.483
Platelet (x10³/mm³)	81	240765.4 ± 92263.8 (219000)	33	256818.2 ± 122541.4 (218000)	1	450000.0 ± -450000)	0.335
MPV (fl)	81	8.5 ± 1.3 (8.1)	33	8.3 ± 1.2 (8.1)	1	8.6 ± -(8.6)	0.775

*Kruskal–Wallis Test

WBC: white blood cell, MPV: mean platelet volume

DISCUSSION

Previous studies by Tettamanti et al. (4), Guralnik et al. (5), Artz et al. (6), Artz et and Thirman MJ (7), Price et al. (8), and McLennan et al. (9) reported that the prevalence of unexplained anaemia in older populations was 26.4%–45%. In our study, after excluding patients with an abnormal MCV and those meeting the other exclusion criteria, the prevalence of anaemia was notably higher (85% in men and 76% in women). This high prevalence raises critical questions about the applicability of current anaemia criteria, specifically the WHO definition (1), to individuals aged 85 years and older.

In an Italian study, Inelmen EM et al. (10), reported that the mean hemoglobin value in the group over 85 years of age was 13.83 ± 1.13 in men and 13.34 ± 1.61 in women. Besides, Zauber NP and Zauber AG (11) evaluated 110 patients who were at least 84 years old and found the mean Hb to be 14.8 +/- 1.1 g/dL in men and 13.6 +/- 1.0 g/dL in women. On the other hand, in our study, we found mean hemoglobine level 11.0±1.8 g/dL in men and 11.0±1.6 g/dL in women in the subgroup over 85 years old. The differences between these studies and our study might be attributed to the different ethnicities.

In our cohort of patients aged ≥85 years, after applying the exclusion criteria, the median haemoglobin level was 10.7 g/dL in men and 10.9 g/dL in women. Furthermore, we did not observe any significant differences in haemoglobin values between age groups within this population. These findings suggest that the lower limit of the Hb reference range for defining anaemia in this age group may need to be revised downward. While our study provides valuable insights, the small sample size of centenarians (≥100 years old) limits the generalisability of our findings to this specific age group. Future studies with larger cohorts of centenarians are required to establish more accurate reference ranges for this population. Based on our findings, we propose that the lower reference limit for haemoglobin in older patients aged 85–100 years may be as low as 10.7 g/dL in men and 10.9 g/dL in women. To validate this proposal, we recommend conducting multicentre studies with large populations to reassess and potentially update the Hb reference ranges for defining anaemia in this age group. This could lead to revisions in the WHO and other guidelines, ensuring a more accurate diagnosis and management of anaemia in older individuals.

Nagel et al. (12) observed a slight decrease in total lymphocyte count with advancing age, whereas Ferguson et al. (13) reported a negative correlation between age and total lymphocyte levels. In our study of patients with normal MCV values, mean lymphocyte counts were 1540.7 ± 1265.4 in the 85–89 age group and 1487.9 ± 1076.7 in the 90–99 age group. Sex analysis revealed median lymphocyte counts of 1100 in men and 1200 in women over 85 years. All median lymphocyte counts remained within the normal reference ranges, according to the available follow-up data.

Hermann et al. (2) reported sex-specific differences in age-related platelet counts. In their study, women showed no significant differences across age groups (60–69, 70–79, and ≥80 years), while men demonstrated significant differences between these age groups (p=0.02) with a significant negative trend (p=0.006). In our study of patients aged > 85 years with normal MCV values who met the inclusion criteria, the median platelet count was 229,500 in men and 218,000 in women. Both values were within the normal reference range according to the current clinical follow-up data. Unlike previous findings, our analysis of patients ≥85 years showed no statistically significant differences in platelet counts when compared across sex or age groups.

Timiras and Brownstein (14) stated that MCV does not change with age in either sex. In our study, we found the median MCV as 87.3 fL in all patients. We also found no significant differences



in the MCV across age groups. Salive et al. (15) reported no age-related changes in the WBC count, platelet count, and MCV. In our study, the median WBC level was 9050 in men and 8200 in women, respectively. The median WBC count was within the normal range according to the current clinical patient follow-up. Furthermore, we did not detect a statistically significant difference between the groups in terms of WBC value among the older age groups in patients aged ≥85 years with normal MCV and remaining after applying the exclusion criteria.)

In our study, among the median values of WBC, neutrophil, platelet, lymphocyte, eosinophil, basophil, haemoglobin, and MPV in patients with normal MCV, only the median haemoglobin values (for both men and women) fell within the ranges considered low in current clinical practice. The other median values (WBC, neutrophils, platelets, lymphocytes, eosinophils, basophils, and MPV) were within the normal ranges. Further studies, such as those exploring the levels of hormones and cytokines involved in erythropoiesis, assessing bone marrow reserve and activity, and conducting comparative studies with younger individuals, may yield more definitive data on the aetiology of low median haemoglobin levels observed in individuals aged ≥85 years.

Limitations of our study were the patient number and retrospective design. This was a unicenter study. And the number of the elder population applicable to the study criteria was limited. Besides , because of the retrospective design of the study , there might be selective bias in the study. The advantages of our study were the high specificity of the exclusion criteria. Our exclusion criteria were much selective and this would decrease the bias by helping to increase the accuracy of the findings.

In conclusion, our findings suggest that the current WHO definition of anaemia may not be entirely appropriate for individuals aged ≥85 years. Lowering the reference limit for haemoglobin in this population, as suggested by our data, could prevent unnecessary diagnoses of anaemia and reduce the burden of further investigations. When clinicians encounter mild anaemia in patients aged ≥85 years that cannot be explained after thorough etiologic investigations, it is important to recognise that such a condition may be a normal variant in some older individuals.

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Author Contributions: Alparslan Merdin: Study design, conceptualisation, methodology, supervision, writing, review, and editing. Kağan Dündar: Data collection, writing the original draft, formal analysis, investigation, literature search.

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ORIGINAL ARTICLE

ANALYSIS OF ORAL AND MAXILLOFACIAL PATHOLOGIES AMONG A SAMPLE OF THE ELDERLY PATIENTS FROM A SINGLE INSTITUTE IN TURKEY: A RETROSPECTIVE STUDY

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Abstract

Introduction: The global elderly population is increasing and becoming more susceptible to oral and systemic diseases. Therefore, comprehensive clinical and histopathological examinations of the oral and maxillofacial area to assess the oral health of this population are crucial. This study aimed to increase the knowledge base regarding the prevalence of biopsied oral and maxillofacial lesions among a sample of the elderly Turkish population (≥ 65 years of age).

Materials and Method: The clinical records of geriatric patients ≥ 65 years of age, who underwent biopsy for a pathological formation(s) in the oral region between January 2017 and January 2020 at Ege University School of Dentistry, Department of Oral and Maxillofacial Surgery (İzmir, Türkiye), were reviewed. Clinical follow-up data including demographic information, anatomical localization of the pathological mass, preliminary diagnosis, and biopsy results were evaluated. In order to ascertain the relationship between lesion formation and the independent variables, univariate analysis was employed.

Results: Data were collected from 353 of 400 patients over a three-year period. There was a high prevalence of odontogenic lesions (42.5%), and pathological diagnosis revealed an increased number of cases (43.1%). Pathological lesions were reported mostly in the posterior mandible (33.4%), followed by the anterior maxilla (21%), anterior mandible (13.3%), and posterior maxilla (7.1%).

Conclusion: These findings are in accordance with those of previous studies based on histopathological data, emphasizing their importance in guiding public health policies for this patient population.

Keywords: Biopsy; Pathology, Oral; Epidemiology; Geriatrics.

INTRODUCTION

The oral and maxillofacial regions are susceptible to a wide range of lesions encompassing both inflammatory processes and malignant neoplasms. These lesions exhibit various manifestations including pain, paresthesia, swelling, tooth loss, root resorption, and facial deformities. Such occurrences can manifest at any stage of a patient's lifespan, potentially leading to significant aesthetic and functional loss. Therefore, it is crucial to implement a comprehensive treatment plan and histopathological diagnosis to ensure optimal outcomes (1,2).

Over the last decade, the proportion of people aged ≥ 60 years has increased at a faster rate globally than any other age group. Despite the prevalence of oral and dental diseases in this patient population, there have been few efforts to address their treatment needs. Oral health has received less attention than systemic health in the geriatric patients ≥ 65 years of age, and patients in this demographic who require assistance with the numerous activities of daily living may be less inclined to prioritize oral health (3,4).

The number of individuals> 65 years of age was 524 million in 2010; however, this number is projected to exceed 1 billion by 2050 (5). In response to the ageing population and increasing interest in the oral health of older adults, a significant number of scientific studies have been conducted, many of which have analysed clinical data (6). A number of studies have demonstrated that older people are about 10 times more likely to have potentially malignant oral lesions than younger people (6,7,8). However, geriatric patients ≥ 65 years of age have a significantly higher incidence of reactionary and inflammatory lesions, malignant epithelial neoplasms, premalignant lesions, autoimmune diseases, and salivary gland tumors than younger individuals (7).

Although lesions in the oral, dental, maxillofacial, and facial regions are similar worldwide, their incidences may vary regionally. Based on this information, a statistical study conducted in the ≥ 65 years of age population of our region will help dentists make preliminary diagnoses of the lesions they encounter to inform treatment planning and timing.

MATERIALS AND METHOD

The study protocol was approved by the Ege University Clinical Research Ethics Committee (date, approval number, 20-9T/71). In consideration of the retrospective nature of this study and the utilisation of anonymised patient data, the necessity for informed consent was not required. The study was in accordance with the Declaration of Helsinki.

In this study, biopsy records of oral maxillofacial lesions obtained from geriatric patients ≥ 65 years of age and histopathologically diagnosed between January 2017 and July 2022 at Ege University Faculty of Dentistry (Bornova, Türkiye) were evaluated.

A retrospective examination of medical records was performed on patients who had undergone biopsy for any pathological mass in the oral or maxillofacial region(s), whose clinical notes were complete and available in the file, and who had received a pathological diagnosis pertaining to the maxillofacial region. Patient data were transferred to a spreadsheet database (Excel, Microsoft Corporation, Redmond, WA, USA). Patients with insufficient clinical data and those for whom pathological results were not available in the system were excluded.

The dataset comprised information regarding age, sex, preliminary pathological diagnosis, final pathological diagnosis, site of the pathological mass, and systemic disease. Biopsy sites included the anterior and posterior maxillae, anterior and posterior mandibles, and other soft tissues (tongue, cheek, and palate). The biopsied lesions were evaluated according to 5 main categories: odontogenic cysts; reactive and inflammatory lesions; osteonecrosis; malignant soft and hard



tissue tumors; and others. Consideration was given to lesions frequently observed in the geriatric patient population.

Statistical analysis

The statistical analysis was performed using the 20.0 Statistical Package For The Social Sciences (SPSS) version (IBM Corporation, Armonk, NY, USA). Frequency values were calculated for the distribution of variables related to the descriptive characteristics, disease information, and pathological conditions of the patients in the study, and are expressed as number of cases (n) and percentage (%). The distribution of the final histopathological results according to region is presented in the cross-tabulations. Furthermore, the McNemar–Bowker test was used to assess the agreement between the preoperative diagnoses of the patients and the distribution of the final histopathological results. Statistical significance level was set at $p<0.05$.

RESULTS

Data from 400 patients were retrospectively reviewed; however, 22 with inadequate clinical notes and 14 without histopathological results were excluded. Among the remaining 353 patients, 165 (46.7%) were male and 188 (53.3%) were female, with a mean (± SD) age of 71.15 ± 5.21 years (range 65 to 89 years) (Table 1).

The most commonly diagnosed pathological masses were odontogenic cysts (43.1%), followed by reactive and inflammatory lesions (32.0%). The most common biopsy site was the posterior mandibular region (33.4%) and the least common was the posterior maxillary region (7.1%). Of the patients included, 60.9% exhibited evidence of systemic disease, the most prevalent of which was hypertension, observed in 120 (55.8%) (Table 1).

Preliminary diagnosis indicated that odontogenic cysts accounted for 150 (42.5%) cases. However, pathological diagnosis revealed that the number of cases increased to 152 (43.1%). Similarly, preliminary diagnosis indicated that 118 (33.4%) patients were affected by reactive and inflammatory lesions. However, pathological diagnosis indicated that the

Table 1. Description of patients regarding to age, gender, medical conditions, and diagnosis

Variables	Overall (n=353)
Gender n (%)	
Male	165 (46.7)
Female	188 (53.3)
Age, mean	71.15 ± 5.21 (65.0-89.0)
Preliminary diagnosis n (%)	
Odontogenic cysts	150 (42.5)
Reactive and inflammatory lesions	118 (33.4)
Osteonecrosis	51 (14.5)
Malignant hard-and soft-tissue tumors	29 (8.2)
Other	5 (1.4)
Patological diagnosis n (%)	
Odontogenic cysts	152 (43.1)
Reactive and inflammatory lesions	113 (32.0)
Osteonecrosis	51 (14.5)
Malignant hard-and soft-tissue tumors	34 (9.6)
Other	3 (0.8)
Region n (%)	
Anterior maxilla	74 (21.0)
Posterior maxilla	25 (7.1)
Anterior mandible	47 (13.3)
Posterior mandible	118 (33.4)
Other (Tongue, Buccal, Lip)	89 (25.2)
Medical Conditions n (%)	
Diabetes mellitus	67 (31.2)
Hypertension	120 (55.8)
Cardiovascular diseases	34 (15.8)
Onkology	54 (25.1)
Other	30 (14.0)

number of cases decreased to 113 (32.0%). There was no discrepancy in data pertaining to osteonecrosis when the preliminary and pathological diagnoses were evaluated. Malignant soft- and hard-tissue tumors constituted 29 (8.2%) preliminary diagnoses and 34 (9.6%) pathological diagnoses (Table 2 and Figure 1).

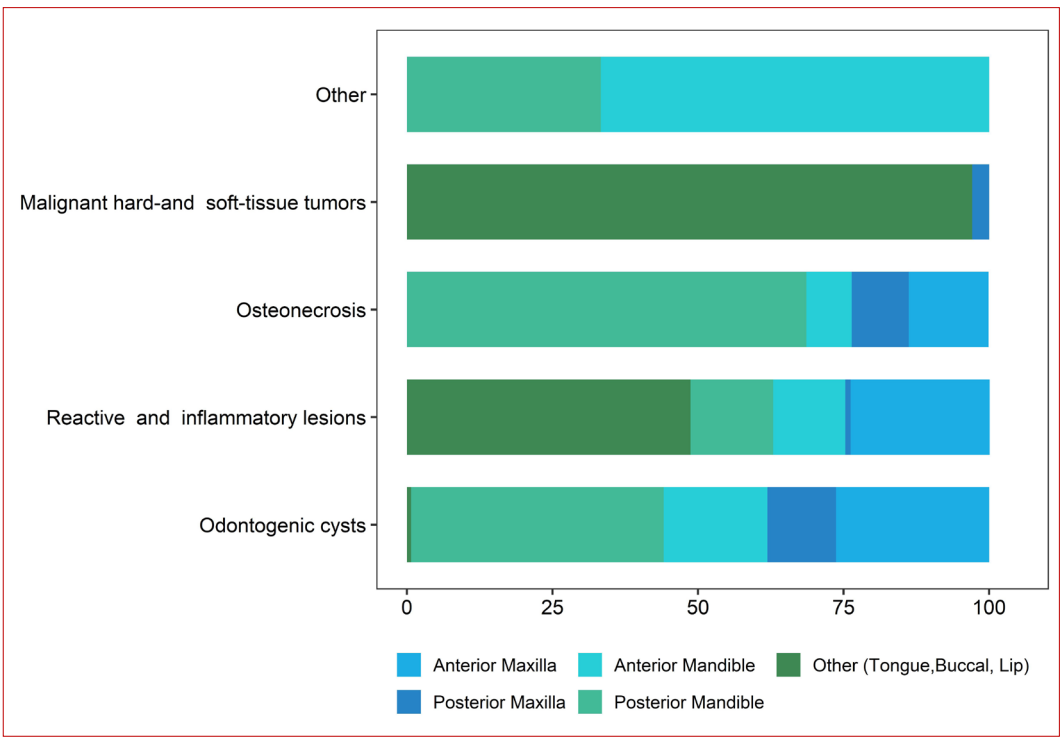
Seventy-four (21%) lesions were located in the maxillary anterior region, 40 (26.3%) of which were odontogenous. Twenty-five (7.1%) were located in

Table 2. Distribution of preliminary and pathological diagnoses

	Preliminary Diagnosis (n=353)	Pathological Diagnosis (n=353)	p
	n (%)	n (%)	
Odontogenic cysts	150 (42.5)	152 (43.1)	0.050
Reactive and inflammatory lesions	118 (33.4)	113 (32.0)	
Osteonecrosis	51 (14.5)	51 (14.5)	
Malignant hard-and soft-tissue tumors	29 (8.2)	34 (9.6)	
Other	5 (1.4)	3 (0.8)	

*<0.05: McNemar-Bowker Test.

Figure 1. The bar chart presents the distribution of patient population according to preliminary and pathological diagnoses. Data were summarized with percentages (%), and these columns were categorized in different colors

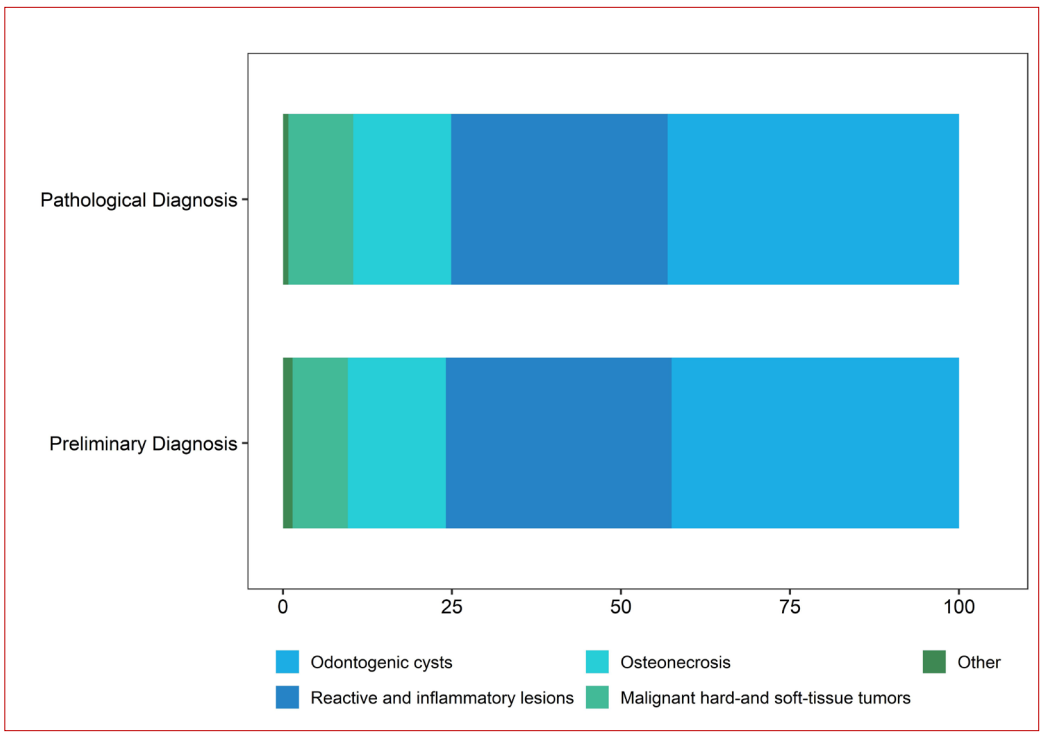


the anterior region of the maxilla, 18 (11.8%) of which were odontogenous cysts. A total of 47 (13.3%) lesions were located in the anterior mandibular region, of which 27 (17.8%) were odontogenic cysts. In the posterior mandibular region, 118 (33.4%) lesions were identified, of which 66 (43.4%) were odontogenic cysts. A total of 89 (25.2%) lesions were located in other regions, including the tongue, cheeks, and lips. Of these patients, 55 (48.7%) had reactive and inflammatory lesions (Table 3 and Figure 2).

Table 3. Distribution of pathological diagnosis according to region

Region	Pathological Diagnosis					
	Odontogenic Cysts (n=152)	Reactive and inflammatory lesions (n=113)	Osteonecrosis (n=51)	Malignant hard-and soft-tissue tumors (n=34)	Other (n=3)	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anterior Maxilla	40 (26.3)	27 (23.9)	7 (13.7)	0 (0)	0 (0)	74 (21)
Posterior Maxilla	18 (11.8)	1 (0.9)	5 (9.8)	1 (2.9)	0 (0)	25 (7.1)
Anterior Mandible	27 (17.8)	14 (12.4)	4 (7.8)	0 (0)	2 (66.7)	47 (13.3)
Posterior Mandible	66 (43.4)	16 (14.2)	35 (68.6)	0 (0)	1 (33.3)	118 (33.4)
Other (Tongue, Buccal, Lip)	1 (0.7)	55 (48.7)	0 (0)	33 (97.1)	0 (0)	89 (25.2)

Figure 2. The bar chart presents the distribution of patient population based on pathological diagnosis in region. Data were summarized with percentages (%), and these columns were categorized in different colors.



DISCUSSION

Numerous studies have investigated the incidence and prevalence of oral lesions in geriatric patients ≥ 65 years of age. However, many were based solely on clinical diagnoses, which can result in inaccurate findings and inappropriate treatment strategies. In many cases, a definitive diagnosis necessitates a histopathological analysis, which is regarded as the gold standard for the identification of numerous pathological conditions. It is thus important to stress that the discordance between clinical and histopathological diagnoses can lead to treatment errors and adverse patient outcomes. Consequently, healthcare professionals should implement the practice of sending all biopsied specimens for histopathological analysis to facilitate a more precise and comprehensive assessment of a patient's condition (4,8).

It is vital for dental professionals to be aware of the most prevalent conditions affecting the geriatric patients ≥ 65 years of age in their daily clinical practice. This enables them to diagnose simple diseases, conditions, and more complex conditions. Therefore, it is important to conduct epidemiological studies to determine the frequency and predominant features of oromaxillofacial lesions (9).

Results of the present study revealed a slightly higher prevalence of oral maxillofacial lesions in females versus males, which is consistent with findings reported in other studies (10,11). Nevertheless, some studies have identified a higher prevalence of oral lesions among males, which can be affected by several factors, including demographic, geographical, social, and cultural variables. For example, a higher prevalence of oral lesions has been reported in China, where males constitute > 50% of the population (12). Furthermore, inequalities in access to and use of health services between males and females may affect the identification and diagnosis of these lesions (4).

The prevalence of oral lesions is reportedly higher in the geriatric patients ≥ 65 years of age versus the young(er) population (13, 14). It has been reported that the epithelium of the oral cavity becomes thinner with age. Furthermore, it is reported that, the oral mucosa is rendered more vulnerable to harmful substances and more susceptible to external carcinogens due to reduced immunological reactivity, impaired DNA repairing capacity and impaired carcinogenic metabolism. However, age alone is not the only contributor; others, including systemic/dental conditions, medications used, poor nutritional status and poor oral hygiene may also affect the development of oral lesions (13, 14, 15, 16). Although both clinical- and biopsy-based studies have demonstrated that the reactive/inflammatory category is the most prevalent diagnostic category in this age group, the results of this study are consistent with those of biopsy-based studies. Reactive and inflammatory soft tissue lesions are the most commonly diagnosed pathological masses in soft tissue regions such as the tongue, cheek, and lips.

Oral lesions can be observed in various anatomical regions of the body. The tongue and labial/buccal mucosa are the most commonly affected soft-tissue sites, and intraosseous lesions mostly occur in the mandible. These findings were consistent with those of previous studies. The tongue and labial/buccal mucosa are the most common anatomical sites because the 5 most commonly diagnosed lesions (fibrous/fibroepithelial hyperplasia, squamous cell carcinoma, epithelial dysplasia, hyperkeratosis/acanthosis, and lichen planus) are primarily observed at these sites (14,16). The distribution of the data in the present study was similar to that reported in previous studies. Of these, 118 (33.4%) were located in the posterior mandibular region and 66 (43.4%) were odontogenic cysts. The remaining 89 (25.2%) were located in other (tongue, cheek, and lip) regions, 55 (48.7%) of which were reactive and inflammatory lesions.



Several studies have reported that reactive and inflammatory lesions are most common in geriatric patients ≥ 65 years of age (4,16,17). The high prevalence of reactive and inflammatory lesions may be related to the increased use of removable prostheses in geriatric patients ≥ 65 years of age. The quality of removable prostheses, anatomical factors, and duration of use of removable prostheses may affect the development of these lesions. Therefore, healthcare professionals should provide appropriate instructions to patients using removable prostheses (4,17). It is also important to note that Alzheimer's disease, Parkinson's disease, seizures and other neurodegenerative conditions, which are more prevalent in older individuals, may also influence the formation and development of these lesions (4, 14).

It has been established that clinically reactive and inflammatory lesions should be part of the differential diagnosis of malignant formations, and an accurate diagnosis of malignant diseases is contingent on the use of histopathological methods (16). According to previous studies, the incidence of premalignant and malignant lesions was higher in geriatric patients ≥ 65 years of age (16, 18). In our study, 34 patients were diagnosed with malignant soft or hard tissue tumors, 29 of whom were sent for histopathological examination with a preliminary diagnosis of malignancy. Considering the prognosis of malignant formations and morbidity rates in the geriatric population, it is important to subject all biopsy specimens to histopathological examination for definitive diagnosis, even if they are not clinically considered to be malignant.

The limitation of the present study is that it is based on a small sample of the Turkish geriatric patients ≥ 65 years of age. Therefore, further studies are needed on this topic to represent the entire population in Turkey.

In conclusion, due to high prevalence of malignancies and potentially malignant diseases, geriatricians and dentists should perform comprehensive periodic oral examinations for early detection of these lesions to reduce morbidity and mortality and contributing to better patient quality of life. In addition, the moderate agreement observed between the clinical and histopathological diagnoses reinforces the importance of histopathological analysis of all biopsy materials. This practice is essential, considering that clinical evaluations alone may not be sufficient to reach a correct diagnosis.

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ORIGINAL ARTICLE

THE EVALUATION OF ZINC, COPPER, AND SELENIUM TEST RESULTS IN GERIATRIC PATIENTS: THE FIVE-YEAR EXPERIENCE

Abstract

Introduction: People aged 65 and above constitute 9% of the world's population and 9.1% of the population in Türkiye. Age-related changes in trace element content occur. In the present study, researchers aimed to evaluate the zinc, copper, and selenium test results in geriatric patients.

Material and Methods: Data on geriatric patients' serum zinc, copper, and selenium tests between 01/02/2019 and 28/02/2024 were acquired from the laboratory information system at Ankara Bilkent City Hospital. Zinc and copper tests were performed using the Shimadzu AAS 7000 Atomic Absorption Spectrophotometer device, and selenium tests were performed using the Agilent 7700 Inductively Coupled Plasma—Mass Spectrometer device. Patients aged 65 and over were evaluated in age groups (youngest-olds: 64 to 74 years, middle-olds: 75 to 84 years, and oldest-olds: 85 years and over), gender, and preliminary diagnoses. Diagnoses were presented with International Classification of Diseases codes.

Results: 4231 zinc, 2180 copper, and 135 selenium test results were evaluated. Zinc levels grouped according to reference ranges showed a statistically significant difference among age intervals ($p < 0.001$), while no statistically significant differences were observed for copper tests ($p = 0.790$) and selenium tests ($p = 0.700$). Age intervals of copper showed a statistically significant difference among genders ($p = 0.019$), while no statistically significant differences were observed for zinc ($p = 0.657$) and selenium ($p = 0.326$) tests.

Conclusion: We evaluated zinc, copper, and selenium levels in geriatric patients according to different age groups, ICD codes, and gender. Our findings may serve as a useful reference for future research.

Keywords: Zinc; Copper; Selenium; Trace Elements; Aging; International Classification of Diseases.

INTRODUCTION

Aging in the human body occurs over time (1). People aged 65 and above constitute 9% of the world's population and 9.1% of the population in Türkiye (2). The dynamic, physiological, and continuous aging process is complex. In biological aging, changes occur progressively in the metabolism and physicochemical properties of cells as age increases. Impairments in cell self-regulation and regeneration can lead to structural changes in the cell and functional disorders in tissues and organs (3). Chronic inflammation, progenitor cell dysfunction, and damaged macromolecules may play a role in the cellular and molecular changes that occur with aging (4). Furthermore, age-related changes in trace element content occur (5).

Trace elements are dietary minerals, required in trace amounts for the body's physiological functions. In the body, each trace element constitutes less than 0.01% of body mass, while the total amount of all trace elements is less than 1% of total body mass (6). Trace elements have the following properties: They are found in living beings, and interact with living substances, and additionally, the biological effects that occur due to lower levels of the optimum levels of trace elements can be reversed when they reach their optimum levels (7). Trace elements are components of certain enzymes and structural factors that play roles in preventing nutritional deficiencies, chronic diseases, and in supporting immunity, regulating gene expression, and antioxidant defense (6).

Zinc (Zn) is involved in protein, lipid, and nucleic acid metabolism, immune system functions, wound repair, and activation of macrophages, neutrophils, and natural killer cells in the human body. Zn cannot be synthesized in the human body, and its adequate levels must be maintained in humans. Hereditary malabsorption, inadequate zinc intake, and increased metabolic requirements can cause Zn deficiency. Zn deficiency can be seen in Crohn's disease, pancreatic insufficiency, small intestinal malabsorption, anorexia nervosa, short bowel syndrome, certain strict vegetarian diets, and hookworm infections (8).

It has been suggested that Zn deficiency might be prevalent in elderly people. There are also studies showing a relationship between zinc deficiency and various diseases in the elderly (9).

Copper (Cu), a transition element, is abundant in the human body. This trace element is necessary for collagen synthesis, skin pigmentation, oxygen and iron metabolism, and the synthesis of some neurotransmitters. It also plays a role in antioxidant defense. It is involved in many cellular pathways. It is important for neuronal functions. Both excessive high and low Cu levels are harmful to humans. (10).

Selenium (Se) has antioxidant and anti-inflammatory properties. It plays a role in the production of active thyroid hormone. Low Se levels lead to an increased risk of death, weakening of the immune system, and decline in cognitive functions. High Se levels have antiviral effects, positively affect reproductive system functions in women and men, and reduce the risk of autoimmune thyroid disease (11). The strategic status of Se against aging and age-related diseases is still unclear (12).

In this study, the aim was to evaluate serum zinc, copper, and selenium levels in geriatric patients admitted to Ankara Bilkent City Hospital between 01/02/2019 and 28/02/2024. To the best of our knowledge, this is the first retrospective study to evaluate serum Zn, Cu, and Se levels of geriatric patients across different age groups and genders, using five years of data.

MATERIALS AND METHOD

The present study included serum Zn, Cu, and Se test results of patients aged 65 and over. Disease diagnoses are expressed with the International Statistical Classification of Diseases and Related Health Problems codes (ICD) in the Ankara Bilkent City Hospital laboratory information system.



For each test, only the first result of each patient was included. In this retrospective study, all the evaluations were conducted according to gender and age groups, including the ICD codes (13).

In our study, patients aged 65 and over were evaluated in three groups according to their ages, based on the study conducted by Lee et al. (14). The age groups in our study were as follows: youngest-olds aged between 64 and 74 years, middle-olds aged between 75 and 84 years, and oldest-olds aged 85 years and over. For the population included in our study, the reference ranges of Zn and Se do not vary according to gender, and they are as follows: 70-120 µg/dL for Zn and 63-163 µg/L for Se. The reference range of Cu is 80-155 µg/dL for females and 70-140 µg/dL for males.

Samples were taken into gel-free tubes for zinc and copper tests and into trace element tubes for selenium tests. In the present study, before the analyses of trace elements the devices were first calibrated. Then, internal quality controls were performed for each test. The analysis was performed after biochemistry experts found the internal quality controls appropriate. External quality controls for the tests were performed at periodic intervals depending on the test. The measurement procedure for each of the serum Cu and serum Zn tests was the same and was as follows: A 500 µL serum sample was taken, diluted to 10 mL with distilled water, and measured using the flame atomic absorption spectrophotometer method with the Shimadzu AAS 7000 Atomic Absorption Spectrophotometer device. Serum Se tests were performed at the external laboratory contracted with our hospital using the Agilent 7700 Inductively Coupled Plasma—Mass Spectrometer device.

All the data registered between 01/02/2019 and 28/02/2024 were acquired from the laboratory information system of Ankara Bilkent City Hospital. Ethics committee approval was obtained from Ankara Bilkent City Hospital's Ethics Committee (Number: TABED 2-24-448, Date: 04/09/2024). All the researchers worked in line with the Helsinki Declaration in every process of the present study.

Statistical Analysis

Frequency, percent, median, and interquartile ranges (IQR) were used to express the data. Statistical analyses were performed with Chi-square and Kruskal-Wallis tests. A p-value < 0.05 was regarded as statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The present study included the data of geriatric patients' serum zinc, copper, and selenium tests, completed between 01/02/2019 and 28/02/2024, and available in the hospital laboratory information system. A total of 4231 Zn, 2180 Cu, and 135 Se test results were evaluated. The quantitative variables are presented in Table 1.

The data of serum Zn, Cu, and Se tests among age intervals are presented in Table 2. Only serum Zn levels grouped according to reference ranges showed a statistically significant difference among age intervals ($p < 0.001$), while no statistically significant differences were observed for Cu ($p = 0.790$) and Se ($p = 0.700$) tests (Table 2).

The data of serum Zn, Cu, and Se tests across age intervals by gender are presented in Table 3. Only the age intervals of Cu showed a statistically significant difference among genders ($p = 0.019$), while no statistically significant differences were observed for the Zn ($p = 0.657$) and Se ($p = 0.326$) tests (Table 3).

In the present study, preliminary diagnoses were grouped and presented with ICD codes. The numbers and percentages of the ICD codes among the reference intervals of Zn, Cu, and Se are reported (Table 4).

Table 1. Quantitative Variables

	Zn (µg/dL)		Cu (µg/dL)		Se (µg/L)	
	N	(%)	N	(%)	N	(%)
Gender						
Female	2526	(59.7)	1146	(52.6)	98	(72.6)
Male	1705	(40.3)	1034	(47.4)	37	(27.4)
Age (Years)						
65-74	2766	(65.4)	1389	(63.7)	97	(71.8)
74-84	1173	(27.7)	636	(29.2)	34	(25.2)
85 and over	292	(6.9)	155	(7.1)	4	(3)
Test Results						
Below the Reference Range	390	(9.2)	286	(13.1)	23	(17)
Within the Reference Range	3720	(87.9)	1858	(85.2)	111	(82.3)
Above the Reference Range	121	(2.9)	36	(1.7)	1	(0.7)

Zn: Zinc, Cu: Copper, Se: Selenium

Table 2. Serum Zn, Cu, and Se Test Data For Age Intervals

		Age Intervals (years)						p
		65-74		75-84		85 and over		
		N	(%)	N	(%)	N	(%)	
Zn (µg/dL)	Below the Reference Range	195	(7.05)	140	(11.9)	55	(18.8)	<0.001*
	Within the Reference Range	2482	(89.73)	1005	(85.7)	233	(79.8)	
	Above the Reference Range	89	(3.22)	28	(2.4)	4	(1.4)	
Cu (µg/dL)	Below the Reference Range	186	(13.3)	82	(12.9)	18	(11.6)	0.790
	Within the Reference Range	1180	(85.0)	542	(85.2)	136	(87.7)	
	Above the Reference Range	23	(1.7)	12	(1.9)	1	(0.7)	
Se (µg/L)	Below the Reference Range	12	(12.4)	10	(29.4)	1	(25)	0.700
	Within the Reference Range	85	(87.6)	23	(67.7)	3	(75)	
	Above the Reference Range	0	(0)	1	(2.9)	0	(0)	

p: Chi-square test, *: Statistical significance, Zn: Zinc, Cu: Copper, Se: Selenium

Table 3. Serum Zn, Cu, and Se Tests for Age Intervals with respect to Gender

		Gender				p
		Female		Male		
	Age Intervals (years)	N	(%)	N	(%)	
Zn (µg/dL)	65-74	1660	65.7	1106	64.9	0.657
	75-84	688	27.2	485	28.4	
	85 and over	178	7.0	114	6.7	
Cu (µg/dL)	65-74	702	61.3	687	66.4	0.019*
	75-84	350	30.5	286	27.7	
	85 and over	94	8.2	61	5.9	
Se (µg/L)	65-74	67	68.3	30	81.1	0.326
	74-84	28	28.6	6	16.2	
	85 and over	3	3.1	1	2.7	

p: Chi-square test, *: Statistical significance, Zn: Zinc, Cu: Copper, Se: Selenium

Table 4. Preliminary Diagnosis of Serum Zn, Cu, and Se Tests

Zn Tests								
Below the Reference Range			Within the Reference Range			Above the Reference Range		
ICD Codes	N	%	ICD Codes	N	%	ICD Codes	N	%
ICD 1	13	3.3	ICD 1	41	1.1	ICD 1	1	0.8
ICD 2	25	6.4	ICD 2	133	3.6	ICD 2	6	5.0
ICD 3	21	5.4	ICD 3	101	2.7	ICD 3	2	1.7
ICD 4	79	20.3	ICD 4	1108	29.8	ICD 4	36	29.8
ICD 5	5	1.3	ICD 5	33	0.9	ICD 6	2	1.7
ICD 6	18	4.6	ICD 6	105	2.8	ICD 7	1	0.8
ICD 7	5	1.3	ICD 7	34	0.9	ICD 9	10	8.3
ICD 9	21	5.4	ICD 8	10	0.3	ICD 11	8	6.6
ICD 10	6	1.5	ICD 9	144	3.9	ICD 12	3	2.5
ICD 11	21	5.4	ICD 10	37	1.0	ICD 13	11	9.1
ICD 12	8	2.1	ICD 11	278	7.5	ICD 14	5	4.1
ICD 13	21	5.4	ICD 12	102	2.7	ICD 18	17	14.0
ICD 14	10	2.6	ICD 13	311	8.4	ICD 21	19	15.7
ICD 18	58	14.9	ICD 14	81	2.2			
ICD 19	4	1.0	ICD 16	1	0.0			
ICD 20	2	0.5	ICD 18	383	10.3			
ICD 21	72	18.5	ICD 19	5	0.1			
ICD 22	1	0.3	ICD 20	5	0.1			
			ICD 21	795	21.4			
			ICD 22	13	0.3			

Table 4. Continued...

Cu Tests								
Below the Reference Range			**Within the Reference Range**			**Above the Reference Range**		
ICD Codes	**N**	**%**	**ICD Codes**	**N**	**%**	**ICD Codes**	**N**	**%**
ICD 1	15	5.2	ICD 1	13	0.7	ICD 1	1	2.8
ICD 2	16	5.6	ICD 2	117	6.3	ICD 2	4	11.1
ICD 3	5	1.7	ICD 3	33	1.8	ICD 3	1	2.8
ICD 4	34	11.9	ICD 4	235	12.6	ICD 4	1	2.8
ICD 5	6	2.1	ICD 5	22	1.2	ICD 6	3	8.3
ICD 6	54	18.9	ICD 6	247	13.3	ICD 9	3	8.3
ICD 7	4	1.4	ICD 7	22	1.2	ICD 10	1	2.8
ICD 9	13	4.5	ICD 8	2	0.1	ICD 11	1	2.8
ICD 10	2	0.7	ICD 9	73	3.9	ICD 12	2	5.6
ICD 11	18	6.3	ICD 10	15	0.8	ICD 18	11	30.6
ICD 12	3	1.0	ICD 11	151	8.1	ICD 21	8	22.2
ICD 13	13	4.5	ICD 12	4	0.2			
ICD 14	3	1.0	ICD 13	116	6.2			
ICD 18	55	19.2	ICD 14	35	1.9			
ICD 21	45	15.7	ICD 17	1	0.1			
			ICD 18	449	24.2			
			ICD 19	3	0.2			
			ICD 20	2	0.1			
			ICD 21	306	16.5			
			ICD 22	12	0.6			
Se Tests								
Below the Reference Range			**Within the Reference Range**			**Above the Reference Range**		
ICD Codes	**N**	**%**	**ICD Codes**	**N**	**%**	**ICD Codes**	**N**	**%**
ICD 2	1	4.3	ICD 2	2	1.8	ICD 21	1	100
ICD 3	2	8.7	ICD 3	9	8.1			
ICD 4	7	30.4	ICD 4	43	38.7			
ICD 6	1	4.3	ICD 6	4	3.6			
ICD 8	1	4.3	ICD 7	4	3.6			
ICD 13	2	8.7	ICD 8	3	2.7			
ICD 14	1	4.3	ICD 9	1	0.9			
ICD 21	8	34.8	ICD 11	1	0.9			
			ICD 12	1	0.9			
			ICD 13	7	6.3			
			ICD 14	2	1.8			
			ICD 18	7	6.3			
			ICD 21	27	24.3			

Zn: Zinc, Cu: Copper, Se: Selenium, ICD: International Classification of Diseases

DISCUSSION

Zinc reference ranges do not differ by gender but do differ by age. Normal zinc values by age are as follows: 26-141 µg/dL for newborns and 6 months, 29-131 µg/dL for 6-11 months, 31-115 µg/dL for 1-4 years, 48-119 µg/dL for 4-5 years, 48-129 µg/dL for 6-9 years, 25-148 µg/dL for 10-13 years, 46-130 µg/dL for 14-17 years, 70-120 µg/dL for 18 and over. Zinc levels may increase in anemia, atherosclerosis, and coronary heart disease, while they may decrease in diabetes mellitus, cirrhosis, acrodermatitis enteropathica, nephrotic syndrome, and myocardial infarction (15). The copper reference range is 20-70 µg/dL for males and females aged ≤6 months, 90-190 µg/dL for 7 months-18 years. It is 70-140 µg/dL for males aged ≥19 years and 80-155 µg/dL for females aged ≥19 years. Copper levels increase in anemia, leukemia, lymphoma, hemochromatosis, and infection, and decrease in chronic diarrhea, Menkes disease, and Kwashiorkor (15). In our hospital laboratory, the selenium reference range is stated as 40-103 µg/L for 0-4 years, 55-134 µg/L for 4-16 years, and 63-160 µg/L for 16-110 years.

Zn is a trace element that has structural and catalytic functions for many proteins, enzymes, and transcription factors. It also has roles in cell proliferation and homeostatic processes. Zn deficiency may be involved in the etiology of atherosclerosis, nervous system diseases, and cancer (16). It has been stated that low zinc levels may be related to poor metabolic status (17). Our study was in line with previous studies (16, 17). Zn levels lower than its reference range were observed in various diseases, including ICD 4 (Endocrine, nutritional, and metabolic diseases) (N = 79, 20.3%), ICD 21 (Factors influencing health status and contact with health services) (N = 72, 18.5%), ICD 18 (Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified) (N = 58, 14.9%), and others (Table 4). Long-term use of zinc preparations causes suppression of the immune system, a decrease in high-density lipoprotein levels, anemia, and possible genitourinary complications (18). In the present study, Zn levels higher than its reference range were observed in diverse diseases, and they were as follows: ICD 4 (N = 36, 29.8%), ICD 21 (N = 19, 15.7%), and ICD 18 (N = 17, 14.0%).

In a study conducted by Marcellini et al., which included results from five European countries, it was stated that 31% of people aged 60 and over had Zn deficiency (19). The study by Yasuda and Tsutsui indicated that Zn deficiency increases with age, with 20-30% of the elderly being at risk for this condition (20). Our results were not in line with Yasuda and Tsutsui's study. In their studies, Yasuda and Tsutsi used hair samples and the device they used for analysis was inductively coupled plasma mass spectrometry. We used blood samples in our study and performed the analysis with an atomic absorption spectrometry device. For these reasons, our results may have differed. In our study, there was a statistical difference between Zn reference ranges and age intervals ($p < 0.001$), with the highest percentage within the reference values in each age group (Table 2). In their study, Hennigar and his colleagues reported that serum Zn concentrations were higher in men than in women (21). In the present study, no statistical difference was observed in gender among the age intervals of Zn ($p = 0.657$) (Table 3).

High copper levels observed in the elderly were significantly associated with the occurrence of mild cognitive impairment (22). It has been reported that changes in copper levels with age may be effective in the onset of Alzheimer's and Huntington's diseases. Impaired copper homeostasis is present in age-related macular degeneration, heart failure, cardiomyopathy, and diabetic retinopathy (23). In the present study, diagnoses were diverse, in line with previous studies (22, 23). However, in all reference range groups, ICD 18 was the highest (Table 4). No statistical difference was found between reference ranges and age intervals ($p = 0.790$) (Table 2), while

in each age group, females were observed in higher numbers (p = 0.019) (Table 3).

Se is found in the structure of selenoproteins and plays a role in antioxidant activity. Reactive oxygen species are among the factors that play a role in forming diseases associated with aging. While inflammation and DNA damage caused by reactive oxygen species are reduced with Se, it contributes to the lengthening of telomeres. Se preparations for supplementation are seen as a protective strategy for diseases associated with aging , however, they do not make a definitive contribution to the prevention of these diseases (12). Our results did not provide enough descriptive detail about Se levels in geriatric individuals. In the present study, no statistical differences were observed in reference ranges among age intervals (p = 0.700) (Table 2), or between age intervals and gender (p = 0.326) (Table 3). The diagnoses associated with Se results were as follows: ICD 21 (N = 8, 34.8%), ICD 4 (N = 7, 30.4%), and others in the below reference range group. For those within the reference range, ICD 4 (N = 43, 38.7%) and ICD 3 (N = 9, 8.1%) were prominent. Only ICD 21 (N = 1, 100%) appeared in the above reference range group (Table 4).

Strengths and Limitations

The strengths of the present study were as follows: inclusion of 5-year data from Ankara Bilkent City Hospital, one of the largest hospitals in Türkiye; inclusion of only the first result of each patient in the study; evaluation of disease diagnoses according to ICD codes; and evaluation of geriatric patients in three groups: youngest-old, middle-old, and oldest-old. On the other hand, our study had some definite limitations. Patient information on the presence of metallic implants, the use of synthetic hair dye, and the intake of vitamin supplements or other medications could not be included. Additionally, when evaluating disease diagnoses, only the preliminary diagnosis was used to assign the relevant ICD code.

CONCLUSION

Aging is an inevitable process, and this process brings aging-related diseases (12). Aging involves changes in trace element levels (5). Zn, Cu, and Se are involved in the formation of various diseases. Geriatric patients represent a significant portion of the patient population. Our study, which evaluated serum zinc, copper, and selenium levels in geriatric patients according to different age groups, ICD codes, and gender, may play a helpful role in future research.

Ethics Committee Approval: Ethics Committee approval was obtained from Ankara Bilkent City Hospital (Number: TABED 2-24-448, Date: 04/09/2024)

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Data Availability Statement: The present study's data are available from the corresponding author upon reasonable request.

Abbreviation List:

Zn: Zinc

Cu: Copper

Se: Selenium

ICD: International Classification of Diseases

ICD 1: Certain infectious and parasitic diseases

ICD 2: Neoplasms

ICD 3: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

ICD 4: Endocrine, nutritional, and metabolic diseases

ICD 5: Mental and behavioral disorders

ICD 6: Diseases of the nervous system

ICD 7: Diseases of the eye and adnexa

ICD 8: Diseases of the ear and mastoid process

ICD 9: Diseases of the circulatory system

ICD 10: Diseases of the respiratory system

ICD 11: Diseases of the digestive system

ICD 12: Diseases of the skin and subcutaneous tissue

ICD 13: Diseases of the musculoskeletal system and connective tissue

ICD 14: Diseases of the genitourinary system

ICD 15: Pregnancy, childbirth, and the puerperium

ICD 16: Certain conditions originating in the perinatal period

ICD 17: Congenital malformations, deformations, and chromosomal abnormalities

ICD 18: Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified

ICD 19: Injury, poisoning, and certain other consequences of external causes

ICD 20: External causes of morbidity and mortality

ICD 21: Factors influencing health status and contact with health services

ICD 22: Codes for special purposes

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ORIGINAL ARTICLE

EVALUATION OF DERMATOLOGY CONSULTATIONS IN GERIATRIC POPULATION IN A TERTIARY CARE UNIVERSITY HOSPITAL: A RECORD-BASED CROSS-SECTIONAL STUDY

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Abstract

Introduction: The aging population is increasing globally, with older adults experiencing distinct skin changes due to aging, comorbidities, and polypharmacy. This study aimed to identify dermatological problems in hospitalized elderly patients to guide healthcare strategies.

Materials and Method: A cross-sectional study analyzed dermatology consultations for hospitalized adults at a university hospital between 2018 and 2022. Patients were categorized as geriatric ≥ 65 years or young adult < 65 years. Data on demographics, consultation departments, and dermatological diagnoses were extracted from electronic medical records and categorized into 24 groups. Statistical analyses were performed.

Results: Of 7,430 consultations, 45.2% were for geriatric patients 55.7% women). Dermatology consultations were more frequent in geriatric patients (30.6%) than in young adults (11%). Fungal (19.6%) and bacterial (14.0%) infections were most common in geriatric patients, followed by eczematous dermatoses (10.6%) and ichthyosis (6.0%). Viral infections were significantly more frequent in young adults (13.3%). Sex differences were observed: fungal infections were more common in geriatric women (21.2%), while viral infections were more frequent in geriatric men (9.3%). Malignant and premalignant lesions (3.0%) and pruritus (4.9%) were also significantly higher in geriatric patients. Conditions such as ecchymosis and decubitus ulcers were more prevalent in elderly patients, whereas viral infections, drug eruptions, and urticaria were more frequent in young adults.

Conclusion: Dermatological conditions, particularly infections, pruritus, and ichthyosis, were more common in elderly hospitalized patients. Hospitalization provides an opportunity for comprehensive dermatological evaluation. A holistic approach is essential to address neglected dermatological problems in the growing aging population.

Keywords: Aged; Dermatology; Geriatrics; Skin Diseases.

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INTRODUCTION

The global population is aging rapidly due to declining birth and death rates (1). In Turkey, 10.2% of the population consists of individuals aged 65 and over (2), and projections indicate that it will exceed 25% by 2080 (3). Advances in healthcare have further extended life expectancy, contributing to this demographic shift.

Aging induces structural and functional changes in the skin, including reduced epidermal regeneration, decreased lipid synthesis, impaired barrier function, and increased dryness (xerosis). These changes predispose older adults to various dermatological conditions (4). Studies show that 80% of individuals over 70 years of age have at least one skin condition requiring medical attention (5).

Evaluating dermatological problems in elderly patients can be challenging in outpatient settings due to communication difficulties, physical limitations, and lack of social or financial support (6). Hospitalization provides a unique opportunity for a comprehensive dermatological assessment, as older adults often experience comorbidities and polypharmacy, increasing their risk of dermatological conditions.

This study aims to analyze dermatology consultations conducted in a tertiary care center to determine the epidemiological distribution of dermatological problems in the geriatric age group and to evaluate differences compared to other age groups. Identifying the specific needs and conditions of this population will contribute to optimizing healthcare strategies and improving patient outcomes.

MATERIALS AND METHOD

Study design

This registry-based cross-sectional study was conducted at a university hospital. According to its bulletin, the hospital provides healthcare to 14 provinces in Northeastern Anatolia, the Eastern and Central Black Sea, as well as parts of Georgia, Iran, and Azerbaijan.

Study Population

The study population consisted of all hospitalized patients aged 18 years and older who were referred to the Department of Dermatology for consultation between January 1, 2018, and December 31, 2022. To enable comprehensive analysis of the data and evaluation of rare dermatological conditions, all patients meeting the inclusion criteria and not fulfilling any of the exclusion criteria were included in the study.

Inclusion Criteria:

1. Being aged 18 years or older,
2. Having been hospitalized and referred to the Department of Dermatology for consultation between January 1, 2018, and December 31, 2022,
3. Having electronic medical records with sufficient data (clinical presentation, diagnosis, and prescribed treatment).

Exclusion Criteria:

1. Repeated consultations for the same patient and the same complaint (only the first recorded consultation was included),
2. Missing or low-quality data in the electronic medical records (e.g., missing clinical or diagnostic information),
3. Patients under 18 years of age.

During this period, 167,641 individuals ≥ 65 years of age were admitted to hospital, of whom 10,992 (6.6%) were hospitalized, while 670,592 individuals < 65 years of age were admitted, and 37,125 (5.5%) were hospitalized. Patients were divided into two groups: geriatric (≥ 65 years of age) and young adults (< 65 years of age). There were



9511 dermatology consultations for hospitalized adult patients during the period specified. After excluding 2053 duplicate consultations (21.6%) and 28 files with low data quality, 7430 patients were ultimately included in the study.

Data collection

Dermatological evaluations were performed by a rotating dermatology resident under the supervision of an attending dermatologist who determined the definitive dermatological diagnosis. Data regarding demographics (age and sex), hospitalization department, and final dermatological diagnoses were extracted from patient electronic medical records. Dermatological diagnoses were categorized into 24 groups based on common characteristics.

Ethics approval

The present study was approved by the Ethics Committee of the authors' university (February 21, 2024; B.30.2.ATA.0.01.00/253).

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Frequency and percentage were used as descriptive measures, and chi-squared analyses were used for pairwise comparisons. Differences with $p < 0.05$ were considered to be statistically significant.

RESULTS

In this study, 45.2% of consultations were performed among patients in the geriatric group, of whom more than one-half (55.7%) were women. Dermatological consultation was requested by 30.6% of geriatric patients and 11% of young adults.

Among patients ≥ 65 years of age, consultations were most frequently requested, in descending order, from endocrine diseases (10.9%), cardiology (10.3%), infectious diseases (9.3%), oncology (8.6%), and pulmonology (6.4%), while among those < 65 years of age, the order was infectious diseases (9.6%), endocrine diseases (9.5%), hematology (6.8%), oncology (5.8%), and nephrology (5.6%).

Among the young adult patients, the most common dermatological diagnoses were viral (13.3%), fungal (13.1%), and bacterial (9.6%) infections, and eczematous dermatoses (9.8%), followed by neutrophilic dermatoses (6.8%) and urticaria-angioedema (5.1%). Among geriatric patients, dermatology was consulted for fungal (19.6%) and bacterial (14.0%) infections, eczematous dermatoses (10.6%), and viral infections (7.3%), followed by ichthyosis (6.0%) and pruritus (4.9%). The distribution of dermatological diagnoses according to age group are summarized in Tables 1A and 1B. There were statistical differences between viral ($p = 0.001$), bacterial ($p = 0.001$), and fungal ($p = 0.001$) infections between the age groups (Table 1A). Viral infections were more common among young adults (13.3%), whereas bacterial (14.0%) and fungal (19.2%) infections were more common among the geriatric group. In addition, there were statistically significant differences between drug eruptions ($p = 0.040$), urticaria angioedema ($p = 0.017$), neutrophilic dermatosis ($p = 0.001$), and ecchymosis purpura ($p = 0.001$). Ecchymosis was more prevalent among geriatric patients (2.5%), whereas other diseases were more prevalent among younger patients (Table 1A).

Benign tumors (1.2% [$p = 0.046$]), malignant-premalignant lesions (3.0% [$p = 0.005$]), pruritus (4.9% [$p = 0.046$]), vascular disorders (1.9% [$p = 0.005$]), 001), decubitus ulcers (2.9% [$p = 0.001$]), ichthyosis- keratoderma (6.1% [$p = 0.001$]), pigmentation disorders (3.0% [$p = 0.005$]) were more common among geriatric patients (Table 1B). Papulosquamous diseases (2.7% [$p = 0.001$]), diseases of the oral mucosa (1.8% [$p = 0.045$]), diseases of the subcutaneous tissue (0.6% [$p= 0.001$]) and systemic rheumatological diseases (0.1%

Table 1A. Distribution of dermatological diagnoses according to age groups

Dermatological diagnoses N (%)*		Under 65 years old	65 years and older	Total	X^2	p
		N (%)*	N (%)*	N (%)*		
Viral infections	absent	3527 (86.7)	3117 (92.7)	6644 (89.4)	70.322	0.001
	present	541 (13.3)	245 (7.3)	786 (10.6)		
Bacterial infections	absent	3677(90.4)	2892(86.0)	6569(88.4)	34.282	0.001
	present	391(9.6)	470 (14.0)	861(11.6)		
Fungal infections	absent	3534(86.9)	2715(80.8)	6249(84.1)	51.532	0.001
	present	534(13.1)	647 (19.2)	1181(15.9)		
Parasitic infestations	absent	3993(98.2)	3285(97.7)	7278(98.0)	1.832	0.176
	present	75(1.8)	77(2.3)	152(2.0)		
Mycobacterial infections	absent	4056(99.7)	3358(99.9)	7414(99.8)	2.654	0.103
	present	12(0.3)	4(0.1)	16(0.2)		
Sexually transmitted diseases	absent	4057(99.7)	3351(99.7)	7408(99.7)	0.201	0.654
	present	11(0.3)	11(0.3)	22(0.3)		
Drug eruptions	absent	3864 (95.0)	3227 (96.0)	7091 (95.4)	4.221	0.040
	present	204 (5.0)	135 (4.0)	339 (4.6)		
Urticaria&angioedema	absent	3861 (94.9)	3230 (96.1)	7091 (95.4)	5.710	0.017
	present	207 (5.1)	132 (3.9)	339 (4.6)		
Neutrophilic dermatoses	absent	3791 (93.2)	3326 (98.9)	7117 (95.8)	150.216	0.001
	present	277 (6.8)	36 (1.1)	313 (4.2)		
Vasculitis	absent	4009 (98.5)	3312 (98.5)	7321 (98.5)	0.017	0.895
	present	59 (1.5)	50 (1.5)	109 (1.5)		
Ecchymosis&Purpura	absent	4017(98.7)	3278(97.5)	7295 (98.2)	15.989	0.001
	present	51 (1.3)	84 (2.5)	135 (1.8)		
Figurate Erythema	absent	4062(99.9)	3361(100.0)	7423(99.3)	2.711	0.100
	present	6(0.1)	1(0.0)	7(0.1)		
Erythema multiforme	absent	4067(100.0)	3358(99.9)	7425(99.9)	2.439	0.118
	present	1(0.0)	4(0.1)	5(0.1)		
Total (%)*		4668 (100.0)	3362 (100.0)	7430 (100.0)		

* percentage of column



Table 1B. Distribution of dermatological diagnoses according to age groups

Dermatological diagnoses N (%)*		Under 65 years old	65 years and older	Total	X^2	p
		N (%)*	N (%)*	N (%)*		
Eczematous dermatosis	absent	3668(90.2)	3006 (89.4)	6674(89.8)	1.151	0.283
	present	400(9.8)	356(10.6)	756(10.2)		
Papulosquamous diseases	absent	3957 (97.3)	3310 (98.5)	7267 (97.8)	11.984	0.001
	present	111 (2.7)	52(1.5)	163(2.2)		
Diseases of oral mucosa	absent	3995(98.2)	3321 (98.8)	7316(98.5)	4.028	0.045
	present	73(1.8)	41(1.2)	114(1.5)		
Diseases of hair	absent	4044(99.4)	3359(99.9)	7403(99.6)	12.747	0.001
	present	24(0.6)	3(0.1)	27(0.4)		
Nail disorders	absent	4054(99.7)	3339(99.6)	7403(99.6)	0.092	0.762
	present	14(0.3)	13(0.4)	27(0.4)		
Vesiculobullous diseases	absent	3985(98.0)	3245(96.5)	7230(97.3)	14.567	0.001
	present	83(2.0)	117(3.5)	200(2.7)		
Adnexal Diseases	absent	3904(96.0)	3326(98.9)	7230(97.3)	61.600	0.001
	present	164(4.0)	36(1.1)	200(2.7)		
Benign tumoral lesions	absent	4036(99.2)	3320(98.8)	7356(99.0)	3.995	0.046
	present	32(0.8)	42(1.2)	74(1.0)		
Malignant-premalignant lesions	absent	3988(98.0)	3262(97.0)	7250(97.6)	7.910	0.005
	present	80(2.0)	100(3.0)	180(2.4)		
Pruritus	absent	3908(96.1)	3196(95.1)	7104(95.6)	4.427	0.035
	present	160(3.9)	166(4.9)	326(4.4)		
Psychocutaneous disease s	absent	4043(99.4)	3349(99.6)	7392(99.5)	1.879	0.170
	present	25(0.6)	13(0.4)	38(0.5)		
Vascular disorders	absent	4029(99.0)	3298(98.1)	7327(98.6)	12.023	0.001
	present	39(1.0)	64(1.9)	103(1.4)		
Decubitus Ulcer	absent	4018(98.8)	3263(97.1)	7281(98.0)	27.568	0.001
	present	50(1.2)	99(2.9)	149(2.0)		
Diabetic Ulcer	absent	4019(98.8)	3317(98.7)	7336(98.7)	0.264	0.607
	present	49(1.2)	45(1.3)	94(1.3)		
Disorders due to physical agents	absent	4023(98.9)	3331(99.1)	7354(99.0)	0.616	0.432
	present	45(1.1)	31(0.9)	76(1.0)		
Burn	absent	4062(99.9)	3357(99.9)	7419(99.9)	0.000	0.989
	present	6(0.1)	5(0.1)	11(0.1)		

Table 1B. Continued...

Drug extravasation	absent	4063(99.9)	3345(99.5)	7408(99.7)	9.134	0.003
	present	5(0.1)	17(0.5)	22(0.3)		
Ichthyoses&Keratoderma	absent	4026(99.0)	3348(99.6)	7374(99.2)	10.833	0.001
	present	180 (4.4)	206 (6.1)	386(5.2)		
Diseases of subcutaneous adipose tissue	absent	4043(99.4)	3359(99.9)	7402(99.6)	13.530	0.001
	present	25 (0.6)	3(0.1)	28(0.4)		
Pigmentation disorders	absent	3988(98.0)	3262(97.0)	7250 (97.6)	7.910	0.005
	present	80 (2.0)	100 (3.0)	180 (2.4)		
Systemic Rheumatologic Diseases	absent	4029(99.0)	3351(99.7)	7380(99.3)	10.983	0.001
	present	39 (1.0)	11(0.3)	50 (0.7)		
Atrophies Dermal connective tissue diseases	absent	4044(99.4)	3345(99.5)	7389(99.4)	0.238	0.625
	present	24(0.6)	17(0.5)	41(0.6)		
Diseases related to metabolic and systemic diseases	absent	4056(99.7)	3353(99.7)	7409(99.7)	0.049	0.825
	present	12(0.3)	9(0.3)	21(0.3)		
Langerhans and Macrophage-associated diseases	absent	4067(100.0)	3360(99.9)	7427(100)	0.556	0.456
	present	1(0.0)	2(0.1)	3 (0.0)		
Total (%)*		4068 (100.0)	3362 (100.0)	7430 (100.0)		

*percentage of column

[p = 0.001]) were more common among young adult patients.

When geriatric patients were analyzed according to sex, there was a statistically significant difference in viral and fungal infections between males and females (p = 0.001 and p = 0.001, respectively). Males exhibited a higher rate of viral infections (9.3%) and females had a higher rate of fungal infections (21.2%) (Table 2A). As shown in Table 2B, there was a statistically significant difference between males and females with regard to oral mucosal (p = 0.038) and vesiculobullous (p = 0.003) diseases. Both diseases occurred more frequently among males than in females (1.7% and 4.6%, respectively).

DISCUSSION

There are limited data in the literature regarding dermatological problems experienced by hospitalized patients, especially those with advanced age. Age differences are rarely noted in dermatology consultations; instead, dermatological



Table 2A. Distribution of dermatological diagnoses by gender in patients aged 65 and over

Dermatological Diagnoses N (%)*		Male	Female	Total	X^2	p
		N (%)*	N (%)*	N (%)*		
Viral infections	Absent	1193(90.7)	1924(94.0)	3117(92.7)	13.571	0.001
	Present	123(9.3)	122(6.0)	245(7.3)		
Fungal infections	Absent	1103(83.8)	1612(78.8)	2715(80.8)	13.021	0.001
	Present	213(16.2)	434(21.2)	647(19.2)		
Bacterial infections	Absent	1126(85.6)	1766(86.3)	2892(86.0)	0.377	0.539
	Present	190(14.4)	280(13.7)	470(14.0)		
Parasitic infestations	Absent	1285(97.6)	2000(97.8)	3285(97.7)	0.041	0.839
	Present	31(2.4)	46(2.2)	77(2.3)		
Mycobacterial infections	Absent	1313(99.8)	2045(100.0)	3358(99.9)	2.161	0.142
	Present	3(0.2)	1(0.0)	4(0.1)		
Sexually transmitted diseases	Absent	1315(99.9)	2036(99.5)	3351(99.7)	3.014	0.083
	Present	1(0.1)	10(0.5)	11(0.3)		
Drug eruptions	Absent	1266(96.2)	1961(95.8)	3227(96.0)	0.262	0.609
	Present	50(3.8)	85(4.2)	135(4.0)		
Urticaria&angioedema	Absent	1265(96.1)	1965(96.0)	3230(96.1)	0.015	0.903
	Present	51(3.9)	81(4.0)	132(3.9)		
Neutrophilic dermatoses	Absent	1298(98.6)	2028(99.1)	3326(98.9)	1.369	0.242
	Present	18(1.4)	18(0.9)	36(1.1)		
Vasculitis	Absent	1300(98.8)	2012(98.3)	3312(98.5)	0.804	0.370
	Present	16(1.2)	34(1.7)	50(1.5)		
Ecchymosis&Purpura	Absent	1288(97.9)	1990(97.3)	3278(97.5)	1.221	0.269
	Present	28(2.1)	56(2.7)	84(2.5)		
Figurate erythema	Absent	1316(100.0)	2045(100.0)	3361(100.0)	0.001	1.00
	Present	0(0.0)	1(0.0)	1(0.0)		
Erythema multiforme	Absent	1315(99.9)	2043(99.9)	3358(99.9)	0.005	0.946
	Present	1(0.1)	3(0.1)	4(0.1)		
Total (%)*		1316 (100.0)	2046(100.0)	3362 (100.0)		

*percentage of column

Table 2B. Distribution of dermatological diagnoses by gender in patients aged 65 and over

Dermatological diagnoses N (%)*		Male N (%)*	Female N (%)*	Total N(%)*	X^2	p
Eczematous dermatoses	Absent	1188(90.3)	1818(88.9)	3006(89.4)	1.699	0.192
	Present	128(9.7)	228(11.1)	356(10.6)		
Papulosquamous diseases	Absent	1301 (98.9)	2009(98.2)	3310(98.5)	1.932	0.164
	Present	15(1.1)	37(1.8)	52(1.5)		
Diseases of oral mucosa	Absent	1293(98.3)	2028(99.1)	3321(98.8)	4.314	0.038
	Present	23(1.7)	18(0.9)	41(1.2)		
Diseases of Hair	Absent	1314(99.8)	2045(100.0)	3359(99.9)	0.149	0.700
	Present	2(0.2)	1(0.0)	3(0.1)		
Nail disorders	Absent	1309(99.5)	2040(99.7)	3349(99.6)	0.646	0.422
	Present	7(0.5)	6(0.3)	13(0.4)		
Vesiculo-bullous diseases	Absent	1255(95.4)	1990(97.3)	3245(96.5)	8.591	0.003
	Present	61(4.6)	56(2.7)	117(3.5)		
Adnexal Diseases	Absent	1297(98.6)	2029(99.2)	3326(98.9)	2.291	0.130
	Present	19(1.4)	17(0.8)	36(1.1)		
Benign tumoral lesions	Absent	1303(99.0)	2017(98.6)	3320(98.8)	0.875	0.350
	Present	13(1.0)	29(1.4)	42(1.2)		
Malignant-premalignant lesions	Absent	1285(97.6)	1977(96.6)	3262(97.0)	2.869	0.090
	Present	31(2.4)	69(3.4)	100(3.0)		
Pruritus	Absent	1239(94.1)	1957(95.7)	3196(95.1)	3.532	0.060
	Present	77(5.9)	89(4.3)	166(4.9)		
Psychocutaneous diseases	Absent	1310(99.5)	2039(99.7)	3349(99.6)	0.055	0.815
	Present	6(0.5)	7(0.3)	13(0.4)		
Vascular disorders	Absent	1291(98.1)	2007(98.1)	3298(98.1)	0.001	0.989
	Present	25(1.9)	39(1.9)	64(1.9)		
Decubitus Ulcer	Absent	1274(96.8)	1989(97.2)	3263(97.1)	0.461	0.497
	Present	42(3.2)	57(2.8)	99(2.9)		
Diabetic ulcer	Absent	1305(99.2)	2012(98.3)	3317(98.7)	3.535	0.060
	Present	11(0.8)	34(1.7)	45(1.3)		
Disorders due to physical agents	Absent	1302(98.9)	2029(99.2)	3331(99.1)	0.255	0.614
	Present	14(1.1)	17(0.8)	31(0.9)		
Burn	Absent	1312(99.7)	2045(100.0)	3357(99.9)	2.001	0.157
	Present	4(0.3)	1(0.0)	5(0.1)		
Drug extravasation	Absent	1309(99.5)	2036(99.5)	3345(99.5)	0.001	1.000
	Present	7(0.5)	10(0.5)	17(0.5)		



Table 2B. Continued...

Ichthyoses & Keratoderma	Absent					
	Present					
Subcutaneous Adipose Tissue Diseases	Absent	1314(99.8)	2045(100.0)	3359(99.9)	0.149	0.700
	Present	2(0.2)	1(0.0)	3(0.1)		
Pigmentation disorders	Absent	1285(97.6)	1977(96.6)	3262(97.0)	2.528	0.112
	Present	31(2.4)	69(3.4)	100(3.0)		
Systemic Rheumatologic Diseases	Absent	1311(99.6)	2040(99.7)	3351(99.7)	0.014	0.904
	Present	5(0.4)	6(0.3)	11(0.3)		
Atrophies Dermal connective tissue diseases	Absent	1308(99.4)	2037(99.6)	3345(99.5)	0.177	0.674
	Present	8(0.6)	9(0.4)	17(0.5)		
Diseases related to metabolic and systemic diseases	Absent	1312(99.7)	2041(99.8)	3353(99.7)	0.001	1.000
	Present	4(0.3)	5(0.2)	9(0.3)		
Langerhans and Macrophage-associated diseases	Absent	1315(99.9)	2045(100.0)	3360(99.9)	0.001	1.000
	Present	1(0.1)	1(0.0)	2(0.1)		
Total (%)*		1316 (100.0)	2046(100.0)	3362 (100.0)		

*percentage of column

problems among older patients are usually assessed during outpatient visits. As in our study, there are studies with a higher proportion of females (7) and studies with a majority of males (4,8), but the sex ratio is generally similar.

In a study from Portugal (9) that evaluated dermatology consultations in all age groups, 45.2% of requested consults were for patients > 65 years of age, while approximately 35% were for those < 65 years. In our study, dermatologists were consulted in 30.6% of inpatients ≥ 65 years of age and 11% of patients < 65 years. Previously, Nahass et al. (10) recommended skin examinations for all newly admitted patients and found skin conditions in 83 of 231 patients (35.9%), of whom 13.4% were directly related to systemic disease(s) or the reason for hospitalization. The increased likelihood of disease- and treatment-related dermatological problems in geriatric patients during hospitalization due to comorbid conditions and polypharmacy may have resulted in increased dermatology consultations in this age group. In addition, a previous population-based study reported that approximately 80% of adults > 70 years of age had ≥ 1 skin condition(s) requiring treatment or follow-up (5). Considering the difficulties that older patients experience in presenting to and being assessed in the outpatient clinic (6), it is reasonable to assume that neglected dermatological problems also occupy an important place in these consultations.

In our study, consultations for all adults were most frequently requested by internal medicine departments, similar to the findings of previous studies (11,12,13). This could be related to the longer length of stay of patients in the internal medicine wards, treatment-related diseases, or a more careful examination of all systems in these departments.

In earlier studies, infection(s), eczema, and drug eruptions were the most common dermatological

consultations in all adult age groups (9,12). According to a study by Ferreira et al. (13), dermatitis was the most frequently diagnosed condition in consultations for all age groups, followed by herpesvirus infection. Makrantonaki et al. studied hospitalized geriatric patients and found that infectious diseases (viral, bacterial, and fungal) were the most common skin problems (14). Pruritus, eczematous dermatitis, and fungal infections were the most common conditions reported in studies examining elderly patients attending outpatient clinics (8,15). In our study, the most frequently consulted conditions were infections and eczematous eruptions, followed by neutrophilic dermatoses and urticaria-angioedema in young adults, and ichthyosis and pruritus in the elderly.

Aged skin is more prone to infection due to intrinsic degenerative and metabolic changes, smoking, and exposure to ultraviolet radiation over time, among other environmental factors. In addition, comorbidities, such as stasis dermatitis, which becomes more common with advancing age, various dermatoses, diabetes, and peripheral vascular diseases, provide a gateway for microorganisms. The development of infection is facilitated in older skin (16). Opportunistic fungal infections have also been reported in healthy elderly patients without immune deficiency (17). This suggests that elderly patients, such as immunosuppressed patients, are at risk for opportunistic infections. In the present study, fungal and bacterial infections were significantly more common among the elderly (i.e., geriatric) group. In contrast, viral diseases were observed more frequently in patients < 65 years of age. In support of our data, Ferreira et al. (13) reported that herpes virus infections were among the 5 most common diagnoses in patients ≤ 55 years of age, whereas superficial mycoses and candidiasis were among the 5 most common diagnoses in those >85 years of age, in contrast with the other age groups combined. In a study by Etgü et al (15), the frequency of mycoses decreased with advancing age > 65 years. When older patients were analyzed according to sex, viral infections were more common among men and mycotic infections were more common among women (15). Similar to our study, viral infections were more common among men, and both bacterial and mycotic infections were more common among women in the study by Etgü et al. (15). In contrast, Yalçın et al. (8) found that fungal, bacterial, and viral infections were more common among male patients. In general, it is common for infectious diseases to increase with age; however, the differences between the sexes vary, although the reason for this is not clearly understood.

In our study, patients ≥ 65 years of age exhibited higher rates of ecchymosis and purpura. A study involving a geriatric patient group reported the presence of purpura in 12% of patients (18). The development of senile purpura, a common cutaneous manifestation among older patients, may be associated with dyslipidemia or medications including anticoagulants, history of dermatological disease(s), and lack of exercise (19).

Drug-related eruptions can occur in 2%–3% of hospitalized patients (20). In our hospital, it was observed in 4.6% of all age groups. We assumed that this was more common among older age groups due to polypharmacy; however, in our patient series, a higher rate of drug-related eruption was recorded in young adults. Acute urticaria is most commonly caused by medications, and infections and can occur in all age groups and sexes. Fifteen to 20% of the population will experience an acute urticaria/angioedema episode once in their lifetime. In contrast, chronic urticaria mainly affects women 20–40 years of age (21). Patients with urticaria/angioedema consulted during hospitalization had mostly drug- and infection-induced acute presentations; however, as with chronic urticaria, they were mostly young adults.

Skin cancer is the most prevalent cancer worldwide. Despite affecting individuals of all ages, its frequency increases with advancing age (22).



Approximately 30% of older adults have malignant or premalignant lesions, according to a screening study by Sinikumpu et al. (5). In a study by Ferreira et al. (13), the most prevalent diagnosis made during consultations with patients > 85 years of age was malignant skin neoplasms (17.6%). However, in our hospital, benign, premalignant, or malignant dermatological tumor lesions accounted for only 4.2% of the consultations in patients > 65 years of age. Given that cancers are more common among individuals > 65 years of age, it is imperative that hospitalized patients undergo a thorough dermatological examination. However, the fact that there were fewer consultations than expected suggests that physicians may have overlooked these asymptomatic conditions.

In addition to malignant diseases, long-term sun exposure also plays an important role in the development of pigmentation disorders. Due to damage from ultraviolet radiation, trauma, and intrinsic factors, elderly individuals are susceptible to many pigmentary disorders that do not occur in younger patient populations (19). The rate of seeking dermatological consultation for these disorders, which have a more benign prognosis, was much lower among elderly inpatients than among older patients (14). Nevertheless, it is more common among older patients.

In our study, pruritus and ichthyosis were among the most common reasons for consultation among elderly patients. While the number of diseases that can cause pruritus may increase in elderly patients, senile pruritus is also regraded as chronic pruritus of unknown origin (23). The incidence of xerosis and associated pruritus also increases as the skin barrier is compromised, and sebaceous and sweat gland activities decrease in the elderly. Fifty-four percent of patients > 65 years of age have xerosis. It has been linked to liver and autoimmune diseases, atherosclerosis of the lower limbs, and chronic renal failure (18). Ichthyosis (especially acquired ichthyosis), which is common among patients of advanced age, may also be associated with increased inflammatory, endocrinological, and neoplastic processes (24).

Vesiculobullous disease was also observed more frequently among older patients. The incidence of bullous pemphigoid, a rare autoimmune bullous disease that commonly affects the elderly, has increased in recent years. This increase is believed to be due to the aging population, the associated increase in neurological conditions, increasing use of medications that may trigger the disease, and the ability to diagnose pemphigoid variants more frequently (25). Vesiculobullous disease(s) were found more frequently among men in both our investigation and the study by Yalçın et al (8).

Among consultations for adults, connective tissue disease has been found in 2.1% (12) and psoriasis, the most common papulosquamous disease, in 4% (9). Both disease groups, however, were encountered less frequently in our study than in the literature, but were significantly less common among older patients.

The main limitation of our study was that when evaluating the consultation notes, additional diagnoses identified by the consultant during the examination that were unrelated to the reason for consultation were not included in the study. Therefore, asymptomatic and neglected dermatological problems may be much more common than previously reported. More population-based screenings are required to detect all dermatological problems in elderly patients.

In summary, elderly patients exhibited more dermatological problems than their younger counterparts when hospitalized for various medical reasons, and a dermatologist's opinion can be sought. These differences should be considered when assessing older patients. In addition, a holistic approach can diagnose neglected dermatological problems in these patient groups during their hospital stay. As the population of older adults continues to increase, there is a need to better characterize the health problems of this patient

population and increase physicians' knowledge regarding treatment and management strategies.

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ORIGINAL ARTICLE

CHARLSON COMORBIDITY INDEX IN PATIENTS DIAGNOSED WITH PERIPHERAL ARTERIAL DISEASE IN THE EMERGENCY DEPARTMENT: DETERMINATION OF SIX-MONTH MORTALITY RISK

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Abstract

Introduction: Although peripheral arterial disease is often not the primary reason for an emergency department visit, acute peripheral arterial disease is nevertheless a critical condition with a high mortality rate. We sought to evaluate the performance of the Charlson comorbidity index in predicting six-month mortality in patients diagnosed with acute peripheral arterial disease in an emergency department.

Materials and Method: This retrospective study included 197 patients (130 female, 67 male) admitted to the emergency department between January 2018 and December 2022 and diagnosed with acute peripheral arterial disease. The Charlson comorbidity index —a validated tool for assessing comorbidities— was used to evaluate the comorbidities of the patients and was compared with the six-month mortality.

Results: The median age of those who died (83 years) was significantly higher than those who did not (78 years). Age was not a statistically significant independent predictor of mortality, but cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hemiplegia, diabetes mellitus, and end-organ damage due to diabetes mellitus were. A one-unit increase in the Charlson comorbidity index score was found to increase mortality risk by 30%.

Conclusion: The Charlson comorbidity index is a reliable predictor of mortality in patients with peripheral arterial disease and can be used effectively in the emergency department setting.

Keywords: Peripheral Arterial Disease; Comorbidity; Emergency Service, Hospital; Mortality; Geriatrics.

INTRODUCTION

Peripheral arterial disease (PAD) is caused by the narrowing or occlusion of arteries other than the coronary and cerebral vessels, most commonly due to atherosclerosis, (1) and primarily affects leg arteries, which causes severe morbidity (2). It is estimated that more than 230 million people worldwide suffer from PAD, so changes in the prevalence of risk factors in aging populations can have large effects on the incidence and prognosis of PAD (3).

Patients with PAD often present to the emergency department (ED) with intermittent claudication, numbness, discoloration, coldness, ulcerations, or gangrene in the affected extremity.

Patients receive diagnoses through comprehensive physical examination, Doppler ultrasonography, and peripheral angiography (4-7).

The treatment and prognosis are contingent upon several variables, including the patient's age, expectations, the stage of the disease, and comorbidities present (1,8-10).

The European Society of Cardiology (ESC) emphasizes the need for more information on the epidemiology of PAD. Likewise, reliable estimates of mortality due to PAD should be kept up to date (1). Considering recent advances in PAD management, a better understanding of trends in mortality rates will add to our knowledge of the disease and contribute to increased awareness of a condition often characterized by underdiagnosis and poor adherence to medical treatment.

The Charlson comorbidity index (CCI) is a gold standard for predicting patients' long-term prognosis and survival with comorbid diseases. As the CCI score increases, the cumulative long-term survival decreases (11,12). Although the CCI is known to be a reliable index, it is helpful to conduct recent studies in different patient groups. With the new findings obtained and the tests that include these patient groups, areas that require adaptation or rearrangement of the index can be revealed. It could enable more personalized and sensitive risk assessments in clinical decision-making details and may lead to considerable progress in patient management.

Given the complex comorbidity profiles of patients with PAD, the CCI is a valuable tool for predicting long-term survival and guiding treatment decisions. Despite advances in PAD management, there remains a critical need for up-to-date epidemiological data and mortality predictions, particularly for patients presenting to ED. Addressing this gap may improve patient outcomes through more targeted interventions, and this study therefore aimed to evaluate the performance of the CCI in predicting mortality in patients diagnosed with PAD in the ED of a tertiary university hospital.

MATERIALS AND METHOD

This study was conducted retrospectively among patients who were admitted to the ED of a tertiary care hospital between January 2018 and December 2022 and diagnosed with acute PAD. Approval was obtained from the local ethics committee (Date: February 2, 2023; Decision no: 2023/36). Patients with arterial pathology other than in the extremities (e.g., aorta, carotid artery), with duplicate admissions, who later died due to COVID-19, or who later died due to trauma were excluded.

Patient data was gathered through the hospital information management system, which is a database of anamnesis information, physical examination findings, comorbidities, routine laboratory tests (e.g., hemogram, coagulation), imaging findings (e.g., Doppler USG, peripheral angiography), and reports for each patient admitted to the hospital. Historical information about patients can also be accessed. PAD diagnoses were staged using Fontaine classification into four stages: I. asymptomatic, IIa. mild claudication, IIb.

moderate to severe claudication, III. rest pain, and IV. ulceration or gangrene (13).

The CCI is scored based on pre-existing comorbidities, which are classified according to ICD-10 codes. The components of the CCI are myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), dementia, chronic obstructive pulmonary disease (COPD), rheumatic disease, peptic ulcer disease (PUD), mild liver disease, diabetes with or without chronic complications, hemiplegia or paraplegia, renal disease, any malignancy including leukemia and lymphoma (except malignant neoplasm of the skin), moderate or severe liver disease, metastatic solid tumor, and AIDS/HIV diseases. Information on patients' deaths up to 6 months after admission to the ED was obtained from the national death registry.

Statistical Analysis

Central distributions of continuous data were evaluated with histograms, Q–Q plots, and the Shapiro–Wilk test. Central dispersion and dispersion of nonparametric continuous data were assessed by medians and interquartile ranges (IQR), while categorical data were represented by number (n) and frequency (%). The Mann–Whitney U test was used to analyze nonparametric quantitative independent data, and Student's t-test was used to analyze parametric data. Pearson's χ^2 test or Fisher's exact test were used to analyze categorical independent data. Factors thought to determine survival after initial assessment and variables found to be significant in the univariate analyses were included in a multivariate logistic regression analysis. Multiple correlation was checked using correlation analysis both before and during the regression. In all analyses, the significance level was 0.05, and the analyses were performed with the R-based *Jamovi* (Version 2.3) statistical package (The Jamovi Project, 2023).

RESULTS

The participants were 197 patients (130 female, 67 male) diagnosed with PAD in the ED of a tertiary care hospital. The median age of all participants was 79 years (IQR: 69–87), of those who died during follow-up was 83 years (IQR: 72–89), and of those who survived was 78 years (IQR: 69–86) ($p = 0.038$). PAD incidence was 13% between the ages of 45 and 54 years, 24.3% between 55 and 64, 27.1% between 65 and 74, and 31.6% over 75. Nevertheless, age was not found to be a statistically significant independent predictor of mortality (OR: 1.03, 95% CI: 1.00–1.06; $p = 0.053$).

By Fontaine classification stage, none of the 29 patients with mild claudication (stage IIa) died, 14 of the 65 patients with moderate to severe claudication (stage IIb) died (7.1%), 37 of the 76 patients with rest pain (stage III) died (18.8%), and 15 of the 25 patients with ulcers or gangrene (stage IV) died (7.6%) ($p < 0.001$). Fontaine classification was found to be an independent predictor of mortality (OR: 2.85, 95% CI: 1.90–4.27; $p < 0.001$).

The predictive value of PAD symptoms was analyzed using regression analysis; pallor (OR: 4.14, 95% CI: 2.16–7.94; $p < 0.001$), pulselessness (OR: 4.85, 95% CI: 1.94–12.12; $p < 0.001$), and claudication (OR: 4.6, 95% CI: 2.05–10.34; $p < 0.001$) were found to be independent predictors of mortality. The relationships between symptoms and mortality is shown in Table 1.

The diseases that constitute the CCI were found to have a statistically significant impact on mortality: CVD (OR: 2.56, 95% CI: 1.4–4.7; $p = 0.002$), dementia (OR: 3.07, 95% CI: 1.54–6.12; $p = 0.001$), COPD (OR: 2.03, 95% CI: 1.07–3.80; $p = 0.03$), hemiplegia (OR: 2.25, 95% CI: 1.60–3.18; $p < 0.001$), diabetes mellitus (DM) (OR: 2.22, 95% CI: 1.20–4.01; $p = 0.01$), and end-organ damage due to DM (OR: 1.55, 95% CI: 1.05–2.29; $p = 0.027$). When these diseases were included in the regression analysis, they were found to be

Table 1. Comparison of Emergency Department Admission Symptoms and Mortality

Symptoms	Survivors (n= 130) n (%)	Dead (n= 67) n (%)	Total (n= 197) n (%)	p
Pain	128 (98.5)	67 (100.0)	195 (99.0)	0.787
Pallor	54 (41.5)	50 (74.6)	104 (52.8)	**<0.001**
Paresthesia	24 (18.5)	17 (25.4)	41 (20.8)	0.344
Paralysis	15 (11.5)	11 (16.4)	26 (13.2)	0.461
Pulselessness	88 (67.7)	61 (91.0)	149 (75.6)	**0.001**
Claudication	119 (91.5)	47 (70.1)	166 (84.3)	**<0.001**

Table 2. The Effect of Diseases Composing the Charlson Comorbidity Index on Mortality

Variables	Score	Survivors (n=130) n (%)	Dead (n= 67) n (%)	Total (n= 197) n (%)	p
MI	1	40 (30.8)	24 (35.8)	64 (32.5)	0.578
CHF	1	40 (30.8)	29 (43.3)	69 (35.0)	0.113
PVD	1	63 (48.5)	34 (50.7)	97 (49.2)	0.878
CVA	1	44 (33.8)	38 (56.7)	82 (41.6)	**0.003**
Dementia	1	20 (15.4)	24 (35.8)	44 (22.3)	**0.002**
COPD	1	31 (23.8)	26 (38.8)	57 (28.9)	**0.043**
CTD	1	8 (6.2)	7 (10.4)	15 (7.6)	0.428
PUD	1	72 (55.4)	33 (49.3)	105 (53.3)	0.505
DM	1	56 (43.1)	42 (62.7)	98 (49.7)	**0.014**
Hemiplegia	2	18 (13.8)	30 (44.8)	48 (24.4)	**<0.001**
CKD	2	29 (22.3)	24 (35.8)	53 (26.9)	**0.063**
DM-End organ damage	2	15 (11.5)	16 (23.9)	31 (15.7)	**0.041**
Metastatic Solid Tumor	6	5 (3.8)	5 (7.5)	10 (5.1)	0.451
Liver Disease	1	14 (10.8)	3 (4.5)	17 (8.6)	0.104
	3	4 (3.1)	0 (0.0)	4 (2.0)	
Solid Tumor	2	19 (14.6)	15 (22.4)	34 (17.3)	0.243
Leukemia	2	1 (0.8)	0 (0.0)	1 (0.5)	1.000
Lymphoma	2	2 (1.5)	0 (0.0)	2 (1.0)	0.787

MI: Myocardial Infarction, CHF: Congestive Heart Failure, PVD: Peripheral Vascular Disease, CVA: Cerebrovascular Accident, COPD: Chronic Obstructive Pulmonary Disease, CTD: Connective Tissue Disease, PUD: Peptic Ulcer Disease, DM: Diabetes Mellitus, CKD: Chronic Kidney Disease

independent predictors of mortality. The effect of the CCI diseases on mortality is shown in Table 2.

The median CCI score was 8 (IQR: 6.0–9.0) in the surviving patient group and 10 (IQR: 8.5–12.0) in the deceased patient group ($p < 0.001$). A one-unit increase in CCI increased the mortality risk by 30% (OR: 1.3, 95% CI: 1.14–1.40; $p < 0.01$).

DISCUSSION

The CCI is a reliable and highly sensitive index known to be clinically valuable and applicable to mortality predictions (11). In our study, it was successful in predicting mortality among PAD patients, with a 1-point increase in the index predicting an increase in mortality of 30%.

PAD incidence is known to increase with age, as was also found in the current study; however, Olinic et al. found age to be an independent risk factor, which we did not find. The center where the study was conducted provides healthcare services to cities that rank among the top regarding healthy longevity statistics. Factors such as region-specific lifestyle, low stress levels, and dietary characteristics are essential reasons age is not an independent risk factor for PAD.

The data on gender in the prevalence of PAD is inconsistent. In Europe, PAD has been found to be more common among males (14). Males prevalence in PAD patients was however found to be lower in a study comparing 5 EU countries and USA (47.2 vs. 59.4%) (15).

One significant predictor of mortality is intermittent claudication. According to a 2016 meta-analysis, 91% of symptomatic PAD patients complained of intermittent claudication, and the mortality rate was higher in symptomatic patients than in reference groups (16). In our study, claudication was classified as either mild or moderate to severe, according to the Fontaine stages; when these classifications were analyzed separately, hospital admission with rest pain was more common, but when we grouped all claudication into a single group, it became the most common complaint.

Beyond symptomatic indicators like claudication, underlying conditions such as diabetes and dementia also play a crucial role. Diabetes and diabetes-related end-organ damage are strongly associated with PAD, and diabetes is more severe among PAD sufferers than the general population. Diabetes also masks the classic symptoms of PAD, such as claudication and rest pain, through neuropathic effects, which causes patients to be diagnosed later, thus increasing amputation and mortality (17). Nearly half of individuals with diabetes-related foot ulcers (DFU) are affected by peripheral artery disease (PAD), often occurring alongside neuropathy. Diagnosing PAD in diabetic patients, particularly those with DFU, is complex due to altered symptom presentation and complications like neuropathy, which may obscure typical signs such as claudication and rest pain. Initial diagnosis frequently involves non-invasive bedside tests, including the ankle-brachial index (ABI) or blood pressure measurements. However, DFU patients often present with below-the-knee or foot disease, along with medial artery calcification and lower leg edema, which can impact the accuracy of these diagnostic methods. A systematic review of 8517 abstracts and 40 studies between 1980 and 2022 concluded that diabetes should be excluded in patients with PAD, even in the absence of end-organ damage, and that it increases the incidence of PAD (18). Our study yielded similar results, with higher mortality rates for PAD patients with diabetes. According to the regression analyses, both diabetes and diabetes-related end-organ damage were independent risk factors for mortality.

In a study by Taşçı et al. on dementia and PAD, the rate of PAD was found to be significantly higher among dementia patients (35.2%) and than in the control group (16.3%), which the researchers attributed to the rapid loss of function caused by



dementia, the inability of such patients to express their concerns, and their low compliance with treatment (19). According to the data in the current study, dementia is predictive of more severe PAD and is an independent risk factor for mortality, consistent with Taşçı et al., who similarly found PAD to be more severe in dementia patients, underscoring the significance of dementia as a mortality risk factor.

According to a 1-, 3-, and 6-month follow-up study of 951 patients in Japan between 2000 and 2017, patients with CVD were more likely to have PAD and to have a higher Fontaine classification; CVD was also found to decrease life expectancy among PAD patients (20). Similar results were obtained in the current study, and it was also found that CVD was an independent risk factor for mortality, increasing the risk by 2.56 times.

In a study by Liao et al. in Taiwan between 1996 and 2010, which examined 51,869 patients with COPD and a comparably sized non-COPD group, the incidence of PAD was found to be 1.23 times higher in the COPD group. COPD patients also had lower effort capacity due to insufficient lung capacity, which can result in patients recognizing symptoms such as claudication later and thus being diagnosed with PAD at a more advanced stage, increasing mortality and morbidity (21). We found similar results, with mortality roughly double among PAD patients with COPD than those without, which was thus found to be an independent mortality risk factor. These findings suggest that special attention should be paid to COPD among PAD patients because the increased mortality risk demands more aggressive management and earlier interventions.

Common examination findings of PAD patients include pain, numbness, pulselessness, pallor, loss of motor power, and claudication, which are frequently mentioned in the literature and indicate the severity of PAD. Patients often have an opportunity for early diagnosis when consulting a physician about limping for periods of less than 10 minutes, when the rate of ischemic events is around 10–15%. However, if the patient does not receive a diagnosis, ignores the symptoms, or delays treatment, ischemia can begin, with severe vascular stenosis and symptoms such as pain, numbness, pallor, pulselessness, and loss of motor power in the limbs. This can lead to amputation and increased mortality (22). In our study, claudication increased mortality by 4.6 times, pulselessness by 4.85 times, and pallor by 4.14 times. All three were found to be independent risk factors for mortality according to the regression analyses.

CONCLUSION

The Charlson Comorbidity Index (CCI) is a reliable predictor of mortality in PAD patients presenting to the ED. Conditions such as CVD, dementia, COPD, hemiplegia, and DM significantly elevate the mortality risk. However, unlike previous studies, age is not an independent risk factor, emphasizing the need for tailored comorbidity assessments.

The CCI aids in classifying patients by comorbidity burden, guiding risk management, treatment planning, and resource allocation. It supports decision-making in discharge, postoperative care, and post-hospitalization planning. Real-time integration of CCI scoring into digital health records could enhance efficiency and enable targeted care strategies. PAD-specific protocols based on CCI thresholds may improve outcomes, especially for high-risk patients.

Future research should explore interventions targeting high-risk comorbidities and examine trends in CCI scores to understand disease progression. Comparative studies with other indices may refine mortality risk prediction in PAD patients.

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The authors agree to the conditions of publication including the availability of data and materials in our manuscript.

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ORIGINAL ARTICLE

EVALUATION OF DIETARY ADVANCED GLYCATION END PRODUCTS IN OLDER ADULTS: RESULTS OF THE TÜRKİYE NUTRITION AND HEALTH SURVEY 2010–2017

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Abstract

Introduction: With aging, advanced glycation end products accumulate on nucleotides, lipids, and proteins. Reducing dietary advanced glycation end products intake is important, as advanced glycation end products are known to be associated with chronic diseases. This study was designed to determine the dietary advanced glycation end products intake of older adults in Türkiye, assess the contribution of foods to dietary advanced glycation end products intake, and evaluate the relationship between dietary advanced glycation end products content and energy and nutrient intake.

Materials and Method: Data on 24-hour dietary recalls of the older adults were obtained from the 2010 and 2017 Türkiye Nutrition and Health Survey databases, which are based on nationally representative sample.

Results: According to Türkiye Nutrition and Health Survey 2017 data, dietary advanced glycation end products intake and daily estimated dietary intake values in the older adults were 12193.73±8773.86 kilounits/day and 168.30±126.40 kilounits/(kg·day), respectively. These values were higher than those reported in the Türkiye Nutrition and Health Survey 2010 data, which were 10391.59±7310.56 kilounits/day and 148.41±110.40 kilounits/(kg·day), respectively ($p<0.001$). The food groups contributing most to advanced glycation end products intake were fats, meat/meat products, and milk and dairy products.

Conclusion: To reduce dietary advanced glycation end products intake, it is recommended that older adults decrease total fat consumption, prefer low-fat dairy products to full-fat dairy products, use moist heat cooking methods for meat/meat products, and marinate meats with ingredients like lemon juice or vinegar.

Keywords: Aged; Glycation End Products, Advanced; Nutrition Survey.

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INTRODUCTION

In recent years, the consumption of high-energy, low-nutrient ready-to-eat and processed foods has increased in Türkiye and globally. Heat treatment is a common food processing method used to enhance flavor, extend shelf life, and reduce the risk of food-borne illnesses. However, non-enzymatic biochemical reactions also occur during heat treatment. Among these reactions, the Maillard reaction occurring between the hydroxyl group of carbohydrates and the amino group of proteins at high temperatures is the most significant. Advanced glycation end products (AGEs) are formed during advanced stages of the Maillard reaction (1).

AGEs are a heterogeneous class of glycated proteins and lipoproteins that are produced endogenously in the body or ingested exogenously through food. Most endogenous AGEs are formed spontaneously and accumulate in the body throughout life. Diet, radiation, and smoking are among the exogenous causes (1, 2). AGEs are naturally present in most foods and can also form during food processing, packaging, and storage. Dry heat processing methods such as frying, grilling, and barbecuing lead to more AGEs formation compared to moist heat methods like boiling or steaming (3). The two most common types of AGEs found in foods are N-epsilon-carboxymethyllysine (CML) and N-epsilon-carboxyethyllysine (CEL). CML is the first identified and most studied (2).

Chronic diseases associated with aging are one of the most significant health problems of the 21st century. The incidence rates of non-communicable diseases, such as cardiovascular diseases, type 2 diabetes, and osteoporosis are increasing particularly in Western countries (2, 4). AGEs negatively impact health due to their known effects on proinflammatory and prooxidant pathways involved in the pathogenesis of chronic diseases (5, 6). Therefore, exposure to AGEs is crucial from a clinical perspective. The negative effects of high dietary AGEs accumulate over the years due to the glycation of proteins and their deposition in tissues (4). The most effective way to reduce AGEs formation in the body is to limit AGEs intake through diet. As a result, the number of studies focused on reducing AGEs formation has increased in recent years (7, 8). There is no study in Türkiye that has evaluated dietary AGE intake in older adults. To the best of our knowledge, this is the first study to assess dietary AGE intake in older adults using data from the 2010 and 2017 national nutrition and health surveys and to compare AGE exposure over the years.

This study was conducted to assess dietary AGEs intake in older adults in Türkiye, examine the contribution of foods to AGEs intake, and evaluate the relationship between the diet AGEs content and energy and nutrient intake.

MATERIALS AND METHOD

Study design

The study utilized data from the 'Türkiye Nutrition and Health Survey (TNHS)' conducted nationally in Türkiye in 2010 and 2017. TNHS 2010 and TNHS 2017 are comprehensive nutrition and health surveys conducted by the Ministry of Health of the Republic of Türkiye (T.C.), with sample sizes that represent the national population (9, 10). A total of 1374 individuals aged 65 years or over in the TNHS 2010 database and 1913 in the TNHS 2017 database were included in the study. Older adults with low (<500 kcal/day) or excessive (>5000 kcal/day) energy intake were excluded. Official permission for the use of the data was obtained from the T.C. Ministry of Health, and ethics committee approval (GO 21/344) was obtained from Hacettepe University Noninterventional Clinical Research.

Dietary intake and anthropometric measurement

In the TNHS 2010 and TNHS 2017 studies, individual food consumption records of older adults were

obtained using 24-hour dietary recalls (9, 10). The program Nutrition Information System (BeBIS) 8.1 was used to calculate the daily energy and nutrient intake. Anthropometric measurements of the older adults were taken by trained personnel following measurement techniques (9, 10) and evaluated by sex (11). Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2), and the World Health Organization (WHO) classification was used to assess its compliance with the standard (11). A waist-to-hip ratio greater than 0.90 in men and 0.85 in women was considered a high risk for metabolic complications, while a waist-to-height ratio greater than 0.5 was considered the cut-off point for cardiovascular and metabolic risk (12).

Determination of dietary advanced glycation end products

The AGEs content of the diet was calculated based on the food consumption amounts in the 24-hour dietary recalls in the TNHS 2010 and 2017 databases. The CML database, prepared by Uribarri et al. (13), was used for the calculation. For foods not included in the database, the CML value of the food most similar in terms of content, preparation, and cooking methods was used. The dietary AGEs intake of the older adults was evaluated according to energy intake and divided into tertiles. Estimated dietary intake (EDI), which expresses the estimated daily AGEs exposure, was calculated by dividing the daily AGEs intake of the older adults by their body weight (14).

Statistical analysis

The data were analyzed with the SPSS 23.0 package program. Categorical data are presented as numbers (n) and percentages (%), while quantitative data are expressed as means ($\bar{x}$) and standard deviations (SD). The mean dietary AGEs intake was adjusted for daily energy intake using the residuals method. For comparisons between two independent groups, the Mann-Whitney U test was used for continuous variables, while the linear trend Chi-square test was applied for categorical variables. For comparisons of more than two independent groups, the Kruskal-Wallis test was applied. Bonferroni correction was performed post hoc when the difference between groups was statistically significant. Correlation between variables were evaluated by Spearman's correlation. Values of $p<0.05$ were considered statistically significant.

RESULTS

Table 1 presents the general characteristics of the older adults according to dietary AGEs tertiles. No significant difference was found in age or sex distribution across dietary AGEs tertiles ($p>0.05$). In the TNHS 2010 study, the percentage of older adults with chronic diseases was higher in the T3 tertile ($p=0.034$). Although similar results were observed in the TNHS 2017 study, no significant difference was found ($p=0.082$). The differences in BMI, waist-hip ratio, and waist-height ratio averages between dietary AGEs tertiles were not significant ($p>0.05$). In the TNHS 2017 study, the percentage of older adults in the high-risk group according to waist-hip ratio and waist-height ratio classifications was higher in the T3 tertile compared to the T1 tertile ($p=0.048$, $p=0.047$, respectively).

The dietary AGEs intake and EDI averages of the older adults by year are shown in Figure 1. In the TNHS 2017 study, the dietary AGEs intake and daily EDI values of the older adults were 12193.73±8773.86 kU/day and 168.30±126.40 kU/(kg·day), respectively. These values were found to be higher than those in the TNHS 2010 study, which were 10391.59±7310.56 kU/day and 148.41±110.40 kU/(kg·day), respectively ($p<0.001$).

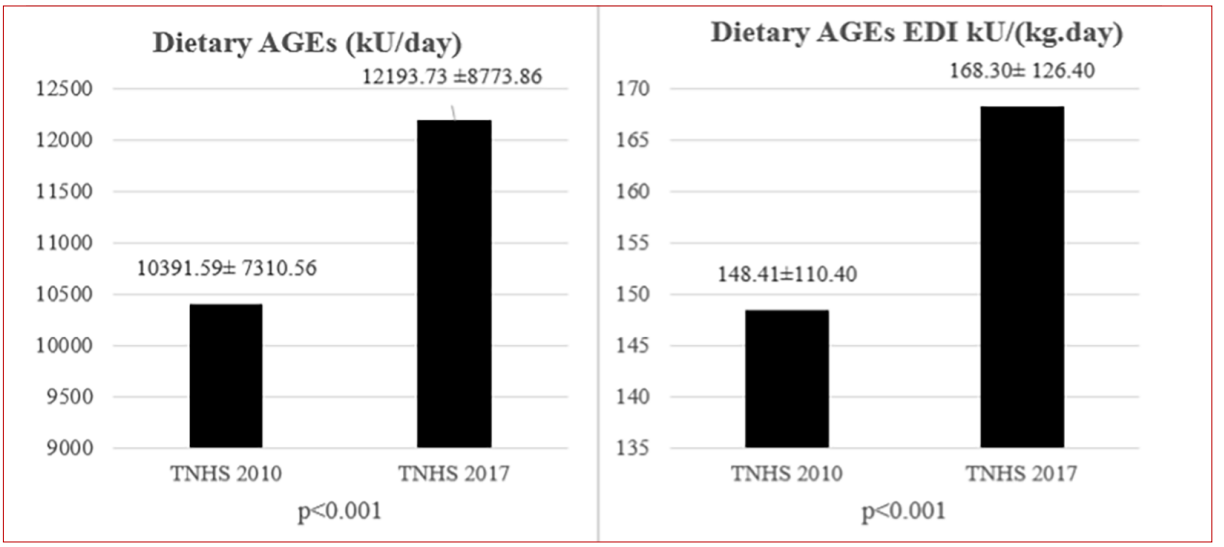
The contribution of foods to dietary AGEs intake is shown in Figure 2. In the TNHS 2010 and TNHS 2017 studies, the food groups that contributed

Table 1. General characteristics of older adults according to dietary AGEs tertiles.

	Dietary AGEs tertiles (KU/day)									
	TNHS 2010					TNHS 2017				
	n	T_1	T_2	T_3	p_1	n	T_1	T_2	T_3	P_2
Cut-off	1374	≤6365.38	6365.38-11659.71	≥11659.72		1913	≤8506.28	8506.29-12955.40	≥12955.41	
Characteristics N (%)										
Age (year) §	1374	73.8±6.27	73.8±6.08	72.7±6.07	0.985	1913	73.7±6.94	72.9±6.50	73.1±6.28	0.120
Sex	1374					1913				
Male		170 (37.1)	175 (38.2)	176 (38.4)	0.909		248 (38.9)	284 (44.5)	270 (42.3)	0.126
Female		288 (62.9)	283 (61.8)	282 (61.6)			389 (61.1)	354 (55.5)	368 (57.7)	
Chronic disease	1290					1891				
Yes		321 (73.5)	331 (77.2)	343 (80.9)	0.034		530 (83.9)	531 (84.3)	553 (87.9)	0.082
No		116 (26.5)	98 (22.8)	81 (19.1)			102 (16.1)	99 (15.7)	76 (12.1)	
Anthropometric measurements										
BMI (kg/m2) §	1235	28.95±5.67	29.28±5.65	29.19±5.40	0.660	1759	30.5±6.3	30.4±6.2	29.7±5.5	0.660
BMI classification	1233					1759				
Underweight		5 (1.2)	9 (2.2)	5 (1.2)	0.405		20 (3.4)	17 (2.8)	9 (1.6)	0.347
Normal		99 (23.6)	73 (18.0)	80 (19.7)			102 (17.5)	86 (14.4)	90 (15.5)	
Overweight		154 (36.7)	154 (37.9)	149 (36.6)			189 (32.5)	201 (33.6)	198 (34.2)	
Obese		162 (38.6)	170 (41.9)	173 (42.5)			271 (46.6)	294 (49.2)	282 (48.7)	
Waist-height ratio §	1238	0.62±0.10	0.63±0.09	0.62±0.08	0.394	1735	0.65±0.10	0.65±0.09	0.65±0.09	0.394
Waist-height ratio classification	1276					1735				
Normal		40 (9.5)	33 (8.1)	29 (7.1)	0.349		29 (5.1)	19 (3.2)	14 (2.4)	**0.048**
High risk		382 (90.5)	374 (91.9)	380 (92.9)			542 (94.9)	511 (96.8)	588 (97.6)	
Waist-hip ratio §	1292	0.92±0.10	0.92±0.09	0.92±0.08	0.190	1735	0.94±0.08	0.95±0.08	0.94±0.09	0.190
Waist-hip ratio classification	1292					1735				
Normal		117 (27.0)	116 (27.6)	101 (23.9)	0.926		107 (18.7)	81 (13.7)	85 (14.9)	**0.047**
High risk		317 (73.0)	304 (72.4)	321 (76.1)			464 (81.3)	511 (86.3)	487 (85.1)	

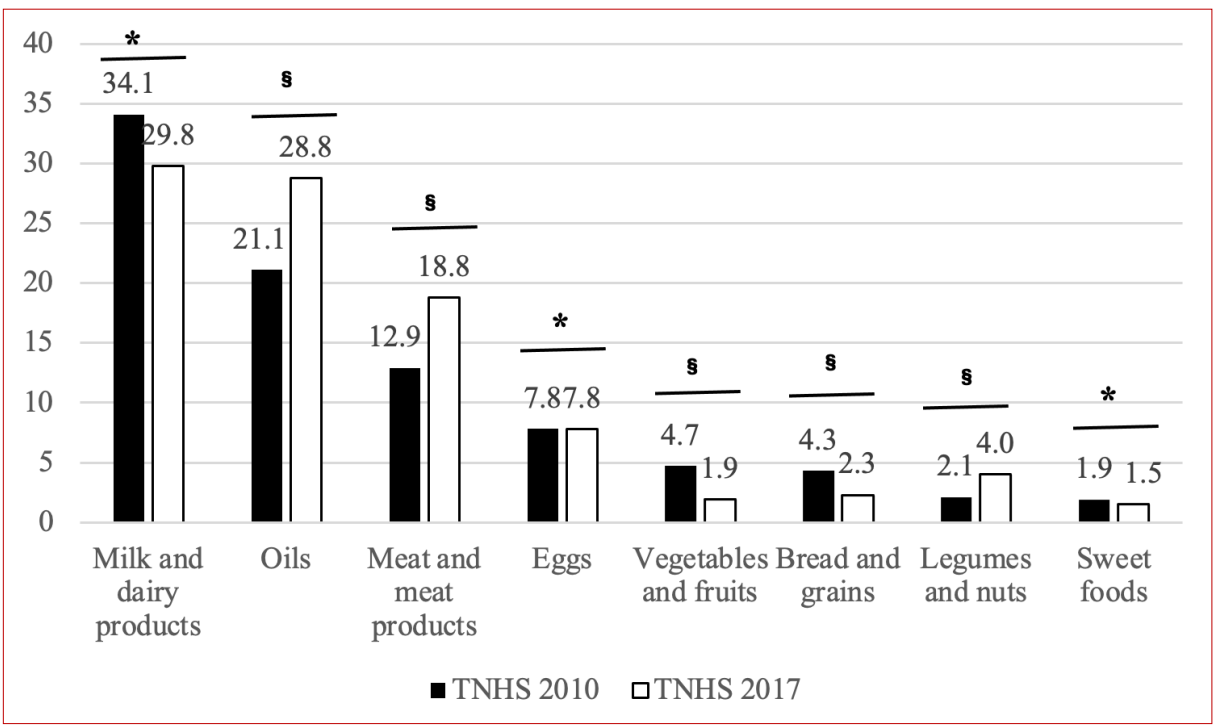
§ Values are means ± SD. Dietary AGEs adjusted for energy intake by using the residual method before calculating tertiles p values calculated with the Kruskal-Wallis test (continuous variables) or linear trend Chi-square test (categorical variables).(p_1:TNHS 2010, p2:TNHS 2017). Abbreviations: TNHS:Türkiye Nutrition and Health Survey, T:Tertile (T_1 the lowest and T_3 the highest), BMI: Body mass index

Figure 1. Dietary AGEs intake and EDI values according to TNHS 2010 and TNHS 2017.



Dietary AGEs adjusted for energy intake by using the residual method. (AGEs: Advanced glycation end products, EDI: Estimated dietary intake, TNHS: Türkiye Nutrition and Health Survey). Values are means ± SD. p -values calculated with Mann Whitney U test.

Figure 2. Contribution of food sources on dietary AGEs (%)



(TNHS: Türkiye Nutrition and Health Survey). p -values calculated with Mann Whitney U test.

§ p<0.001, * p>0.05

Table 2. Daily energy and nutrient intakes of older adults according to dietary AGEs tertiles.

	Dietary AGE tertiles (KU/day)							
	TNSH 2010 (n=1374)				TNSH 2017 (n=1913)			
	T1 (n=458)	T2 (n=458)	T3 (n=458)	P1	T1 (n=637)	T2 (n=638)	T3 (n=638)	P2
Energy (kcal)	1525.93±668.68	1456.75±549.34	1890.01±647.69	0.190	1520.27±611.28^{a}	1627.45±635.06^{bc}	1608.18±619.18^{b}	**0.001**
Protein (%)	13.26±3.47^{a}	13.39±3.87^{a}	14.39±3.81^{c}	**<0.001**	13.94±3.57^{a}	14.83±3.89^{b}	15.34±4.00^{c}	**<0.001**
Carbohydrate (%)	60.82±9.02^{a}	52.45±8.81^{b}	44.83±9.92^{c}	**<0.001**	57.45±10.33^{a}	50.66±9.73^{b}	47.80±11.04^{c}	**<0.001**
Fiber (g)	22.29±11.90^{a}	19.59±10.21^{b}	16.55±9.59^{c}	**<0.001**	21.29±10.82^{a}	22.04±11.37^{a}	20.53±10.51^{b}	**0.027**
Total Fat (%)	25.88±9.18^{a}	34.60±9.09^{b}	40.20±9.88^{c}	**<0.001**	28.42±9.58^{a}	34.43±8.90^{b}	36.70±10.09^{c}	**<0.001**
Saturated fat (%)	6.99±3.38^{a}	11.18±3.36^{b}	15.37±5.3^{c}	**<0.001**	8.83±3.97^{a}	11.41±3.46^{b}	13.50±4.73^{c}	**<0.001**
Cholesterol (mg)	97.62±108.50^{a}	167.08±147.20^{b}	215.65±152.70^{c}	**<0.001**	145.08±133.47^{a}	203.10±155.42^{b}	227.92±164.09^{c}	**<0.001**
Vitamin B6 (mg)	1.30±0.68	1. 24±.0.59	1.18±0.58	0.050	1.01±0.57^{a}	1.08±0.48^{b}	1.31±0.68^{b}	**<0.001**
Vitamin B12 (mg)	1.51±1.75^{a}	2.37±4.14^{b}	3.06±5.51^{c}	**<0.001**	2.33±2.59^{a}	4.05±10.43^{b}	5.07±12.72^{c}	**<0.001**
Folic acid (µg)	329.09 ±173.67	317.41±145.64	292.16±143.60	0.092	289.99±159.15^{a}	310.09±150.60^{b}	358.61±195.12^{b}	**<0.001**
Calcium (mg)	549.53±297.21^{a}	567.31±282.82^{a}	581.22±318.99^{b}	**<0.001**	666.39±325.72^{a}	710.44±302.19^{b}	741.56±338.49^{b}	**<0.001**
Iron (mg)	10.22±5.34^{a}	9.54±4.54^{a}	9.05±4.53^{c}	**0.006**	8.30±4.22^{a}	9.46±4.65^{b}	9.21±4.93^{b}	**<0.001**
Zinc (mg)	7.72±3.45	7.71±3.62	7.92±3.58	0.484	6.89±3.41^{a}	8.30±3.85^{b}	8.47±4.38^{b}	**<0.001**

Values are means ± SD. Dietary AGEs adjusted for energy intake by using the residual method before calculating tertiles . p_1 and p_2 values calculated with Kruskal-Wallis test . (p_1:TNHS 2010, p_2:TNHS 2017). Bonferroni correction was performed as post hoc. Abbreviations: TNHS: Türkiye Nutrition and Health Survey, T:Tertile (T_1 the lowest and T_3 the highest)

Table 3. Correlation between food sources and dietary AGEs.

	Dietary AGEs (kU/day)			
	TNHS 2010 (n=1374)		TNHS 2017 (n=1913)	
Food sources	r	p_1	r	p_2
Milk and dairy products	0.584	**<0.001**	0.611	**<0.001**
Meat and meat products	0.474	**<0.001**	0.475	**<0.001**
Eggs	0.217	**<0.001**	0.212	**<0.001**
Legumes and nuts	0.119	**<0.001**	0.110	**0.018**
Bread and grains	0.067	**0.014**	0.014	0.535
Vegetables and fruits	0.144	**<0.001**	0.190	**<0.001**
Oils	0.401	**<0.001**	0.408	**<0.001**
Sweet foods	0.156	**<0.001**	0.132	**<0.001**

p values calculated with Spearman correlation. (p_1:TNHS 2010, p_2:TNHS 2017). Abbreviations: TNHS:Türkiye Nutrition and Health Survey

most to dietary AGEs intake were meat and meat products, oils, and milk/dairy products. In terms of food consumption, the contribution of oils, meat/meat products, legumes and seeds to dietary AGEs intake increased over the years, while the contribution of vegetables and fruits decreased ($p<0.001$). The contribution of milk/dairy products and sweet foods to dietary AGEs intake did not change ($p>0.05$).Table 2 presents the daily energy and nutrient intakes of the older adults according to dietary AGE intake tertiles. According to TNHS 2017 and 2010 data, daily energy intake was higher in the T3 tertile than in the T1 tertile ($p=0.001$, $p>0.05$, respectively). In both studies, the intakes of protein (%), fat (%), saturated fat (%), cholesterol, vitamin B6 (TNHS 2017), vitamin B12, folic acid (TNHS 2017), calcium, iron, and zinc (TNHS 2017) were higher in the T3 tertile ($p<0.05$), while carbohydrate (%) and fiber intakes were lower ($p<0.001$).

The relationship between the amount of food consumed by the older adults and dietary AGEs intake is presented in Table 3. A moderate ($r=0.584$) and a high ($r=0.611$) significant relationship were found between dietary AGEs intake and milk/dairy products consumption in the TNHS 2010 and TNHS 2017 studies, respectively ($p<0.001$). In both studies, a moderate relationship was found between dietary AGEs intake and meat/meat product consumption ($r=0.474$, $r=0.475$, respectively; $p<0.001$), and fat consumption ($r=0.401$, $r=0.408$, respectively; $p<0.001$). A weak relationship was found with egg consumption ($r=0.217$, $r=0.212$, respectively; $p<0.001$). A low level of relationship was found between the consumption of legumes and seeds, bread and cereals (TNHS 2010), vegetables and fruits, and sugary foods and dietary AGEs intake ($p<0.05$). In the TNHS 2017 study, no association was found between the consumption of bread and cereals and dietary AGEs intake ($p>0.05$).

DISCUSSION

As life expectancy increases worldwide, the prevalence of chronic diseases in later life has also

risen (15). It is well-established that environmental factors and lifestyle habits, alongside the genetic structure of older adults, play a significant role in the development of these diseases (16). Among lifestyle habits, dietary factors hold particular importance. Numerous studies have highlighted a strong association between the adoption of healthy eating patterns (e.g., Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet) and the prevention or development of chronic diseases (17, 18). However, it is believed that factors closely associated with consumed foods, such as acrylamide intake (19) and AGEs intake (6), are related to aging and the development of chronic diseases. This study assessed the dietary AGEs intake of the older adults, evaluated the contributions of different food sources to AGEs intake, and investigated its association with various parameters. This study is the first to evaluate dietary AGEs intake in the older adults using data from the 2010 and 2017 national nutrition and health surveys conducted in Türkiye. As aging progresses, AGE accumulation in the body increases, while AGEs excretion decreases. Consequently, exogenous AGEs become the primary source of AGEs in the body (6). In the TNHS 2010 and TNHS 2017 studies, no significant differences were observed in sex, age, and anthropometric measurements across dietary AGEs intake tertiles ($p>0.05$). According to TNHS 2010 data, the percentage of older adults with chronic diseases was lower in the T3 tertile ($p=0.034$), whereas no significant difference was observed in the TNHS 2017 study ($p=0.082$) (Table 1). This may be attributed to older adults adopting healthier diets as a response to the increased prevalence of chronic diseases with aging (20, 21). With aging, the metabolism of dietary AGEs absorption and excretion changes, leading to an increase in the accumulation of AGEs in tissues. Therefore, assessing dietary AGEs intake and developing nutritional recommendations to reduce intake are essential for protecting the health of older adults (6).

Obesity is defined as abnormal and excessive fat accumulation, and according to the WHO, the waist-hip ratio reflects the distribution of body fat. An increase in the waist-hip ratio elevates the risk of chronic diseases, such as type 2 diabetes and cardiovascular diseases, as well as obesity-related morbidities (11). In this study, the mean waist-height ratio values of older adults according to dietary AGEs tertiles were found to be above 0.5 in all tertiles. In the TNHS 2017 study, the proportion of older adults at risk for metabolic diseases, as determined by waist-hip and waist-height ratio classifications, was significantly higher in the T3 tertile ($p<0.001$) (Table 2). During the aging process, the reduction in total energy expenditure, resulting from decreases in both basal metabolic rate and physical activity, affects nutrition and overall health, leading to an increase in body fat mass and a decrease in muscle mass (16). Therefore, interpreting the relationship between dietary AGEs intake and anthropometric measurements in the older adults can be challenging.

The dietary AGEs intake and daily EDI values in the older adults were found to be higher in the TBSA 2017 compared to the TBSA 2010 ($p<0.001$) (Figure 1). This indicates that the dietary AGEs intake among the older adults increased over the seven-year period. In a study conducted by Almajwal et al. (6), dietary AGEs intake in the older adults was reported to be 13121±6785.1 kU/day in male and 14712±6122.8 kU/day in female. Urribarri et al. (14) classified dietary AGEs intake exceeding 15000 kU/day as high AGEs intake. The average dietary AGE intake among older adults in Türkiye is lower compared to findings from other studies. In Türkiye, the Mediterranean diet is the traditional dietary pattern that is, rich in vegetables, fruits, legumes, whole grains, and oilseeds, and low in red meat, processed meat and refined sugar (22). For this reason, the Mediterranean diet, which is also widely followed in Türkiye, contains low amounts of AGEs (3). According to the NOVA classification,

processed and ultra-processed foods are the primary sources of AGEs (3, 14). Limited access to processed foods among the older adults can also contribute to their low dietary AGEs intake (7). However, considering the negative effects of AGEs on health, the increasing dietary AGEs intake and exposure in Türkiye over the years is a concerning trend.

Dietary AGEs are known to be high in processed foods and meat products, particularly those with high protein and fat content (3, 14). According to national data, the contribution of oils, meat/meat products, legumes, and oilseeds to dietary AGEs intake in the older adults has increased over the years ($p<0.001$), while the contribution of milk/dairy products and sweet foods has remained unchanged ($p>0.05$) (Figure 2). Additionally, diets high in AGEs are characterized by higher levels of saturated fat and cholesterol, which are associated with the consumption of meat/meat products, as well as milk/dairy products (5). In the study, energy, protein (%), fat (%), saturated fat (%), and cholesterol intake were higher in the high T3 tertile (Table 2). However, in the TNHS 2010 study, no significant difference in energy intake was observed between dietary AGEs tertiles. The results of studies examining the relationship between dietary AGEs content and energy intake are quite heterogeneous (20, 23). This variability is likely due to the differing energy contributions of the nutrients that contribute to dietary AGEs intake. In fact, the TNHS 2010 study showed that the contribution of meat/meat products, as well as fats, to dietary AGE intake was lower compared to the TNHS 2017 study (Figure 2). In the T3 tertile, carbohydrates (%) was lower, in contrast to the higher protein and fat (%) ($p<0.001$) (Table 2). The AGEs contents of a diet rich in protein and fat may differ from those of a diet rich in carbohydrates, even if the energy intake is the same (24). Similar results have been reported in other studies, which attribute this to the high water and antioxidant content of complex carbohydrates and fiber-rich foods (5, 23). However, in the T1 tertile, protein (%), carbohydrates (%), fat (%), and fiber intake align with the nutritional recommendations for the older adults (Table 2). When consumed with adequate liquid, the fiber from legumes, whole grains, vegetables, and fruits can help prevent common age-related conditions such as constipation and diverticulosis. Additionally, high-fiber diets play a key role in the prevention and management of diabetes, cardiovascular diseases, and obesity (16). Since meat/meat products, which are high in dietary AGEs, are also rich in vitamin B6, vitamin B12, iron, and zinc, and milk/dairy products are sources of vitamin B12 and calcium, the intake of these nutrients was found to be higher in the T3 tertile compared to the T1 tertile in our study (Table 2). Due to decreased energy requirements and changes in nutrient absorption in the older adults, it is important to prioritize foods that are low in energy but rich in micronutrients (16). However, to avoid increasing AGEs intake, cooking methods that minimize AGEs formation should be preferred. Moist heat cooking methods are effective alternatives to dry heat cooking methods, as they reduce AGEs formation in foods (1). In Turkish cuisine, the use of local spices, herbs, and plants is quite common. The frequent use of spices and herbs in food preparation not only enhances flavor but also reduces the formation of AGEs due to their antioxidant properties (7). One study reported that spices, such as cloves, allspice, cinnamon, tarragon, rosemary, ginger, black pepper, and bay leaf, possess antiglycation properties. The results of the study highlight the potential of natural plant extracts and spices as a strategy to reduce AGE formation in foods (25). Additionally, for older adults, adding spices to low-salt or salt-free meals enhances the flavor and makes them easier to eat (22).

A moderate significant relationship was found between milk/dairy product consumption and

dietary AGEs intake in the TNHS 2010 study, and a strong significant relationship was found in the TNHS 2017 study ($p<0.001$). In both studies, there was a moderate relationship between meat/meat product consumption, fat consumption, and dietary AGEs intake, and a weak relationship with egg consumption ($p<0.001$) (Table 3). To reduce dietary AGEs intake, it is recommended to limit the consumption of fatty meats, full-fat milk/dairy products, and processed foods. Additionally, cooking methods should involve short cooking times at low temperatures and moist heat, such as boiling and steaming, and meats should be marinated (3, 13). To reduce dietary AGE intake, attention should be paid to the variety of vegetables and fruits in the diet, as well as the use of herbal products such as spices with high antioxidant content (7, 25). These recommendations are in line with general healthy eating guidelines and it is suggested that an individual's preference for healthy food groups and the consumption of foods prepared using healthy cooking methods will positively contribute to reducing the AGE load in the body (1, 3). Dietary guidelines should include sample menus of traditional Turkish recipes with low-AGE content for all age groups. Due to the high prevalence of chronic diseases in older adults, it is recommended to develop personalized dietary guidelines (22).

This study has limitations. As a cross-sectional study, it is not suitable for establishing a cause-and-effect relationship. The database used to calculate dietary AGEs intake consists of 549 foods and, is commonly employed in studies. However, this database does not include AGEs values for foods specific to each culture. As a result, analogy was used to determine the AGEs content of some foods. The study also has several strengths. The use of TNHS 2010 and 2017 data, which represent a national sample of Türkiye, is one of its strengths. Additionally, this is the first study to evaluate dietary AGEs intake in the older adults on a national scale. Given the rising prevalence of chronic diseases associated with aging, reducing dietary AGEs intake is crucial for maintaining health. This study evaluated the dietary AGEs intake among the older adults in Türkiye and the contribution of various nutrients to AGEs intake. The findings may contribute to the development of dietary recommendations aimed at reducing AGEs intake in older adults.

CONCLUSIONS

This study is the first in Türkiye to calculate dietary AGEs intake using the National Nutrition and Health Survey database of the older adults. Dietary AGEs intake and exposure were found to be higher in the TNHS 2017 study compared to the TNHS 2010 study. The food groups that contribute the most to dietary AGEs intake were meat/meat products, fats, and milk/dairy products. The results show a correlation between dietary AGEs intake and the consumption of meat/meat products, milk/dairy products, fats, and eggs. Given the increase in dietary AGEs intake and exposure over the years in Türkiye, nutritional recommendations and dietary models should be developed to reduce dietary AGEs intake. Additionally, laboratory studies are needed to determine the AGEs content of foods in Türkiye.

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ORIGINAL ARTICLE

INVESTIGATION OF AGE-RELATED CHANGES IN THE MUSICAL PERCEPTUAL SKILLS OF MUSICIAN AND NON-MUSICIAN ADULTS

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Abstract

Introduction: Our study examined age-related changes in the musical perception skills of musicians and non-musicians.

Materials and Method: This study included two groups. The first group consisted of 40 individuals, including 20 musicians aged 45-64 and 20 musicians aged 65-85. The second group also consisted of 40 individuals, including 20 non-musicians aged 45-64 and 20 non-musicians aged 65-85. Together, both groups comprised 80 adults. Participants' musical perception skills were evaluated using the Musical Perception Test.

Results: The results showed that musicians had higher scores than non-musicians on the Musical Perception Test total score and all music subtests ($p<0.05$). In addition, when age-related changes were examined, musicians between the ages of 45-64 had significantly higher scores than musicians between the ages of 65-85 on multiple instrument recognition, total instrument score, pitch discrimination, total pitch, and total Musical Perception Test scores ($p<0.05$). Similarly, non-musicians aged 45-64 had significantly higher scores than non-musicians aged 65-85 in rhythm recognition, single instrument recognition, total instrument score, musicality, melody recognition, melody recognition in noise, total melody score, and total Musical Perception Test score ($p<0.05$). In the 45-64 age group, there was a significant difference between musicians and non-musicians on all sub-scores except that for rhythm recognition ($p<0.05$). In the 65-85 age group, there was a significant difference between musicians and non-musicians on all scores except pitch recognition, pitch discrimination, and the total pitch score ($p<0.05$).

Conclusion: The results suggest that music education preserves auditory and musical perception skills despite advancing age.

Keywords: Aging; Music; Perception.

INTRODUCTION

Auditory stimuli at various sound levels have features such as rhythm, pitch, melody, and timbre. Musical perception, which varies among individuals, (1) is the process of distinguishing these sound features to identify and make sense of them. Research indicates that music education, in particular, has positive effects on musical perception. Music education improves auditory processing abilities; thus, musicians can better understand speech in noisy environments than non-musicians. Studies have shown that music education leads to greater neuroplasticity in the auditory pathway, which extends from the brainstem to the cortex, and this neuroplasticity improves auditory abilities. (2)

Age-related hearing decline in hearing ability is a ubiquitous part of aging, and it often impacts speech comprehension, especially in noisy environments. While these effects are partly due to changes in the cochlea, they also involve challenges beyond measurable hearing loss. Several studies have observed that central auditory processing skills, as opposed to simple peripheral mechanisms, play a critical role in the management of hearing ability later in life (3).

Recent research has shown that music training in young adults positively alters neural mechanisms and produces long-lasting improvements in auditory abilities and non-auditory tasks involving cognitive control (4). These results suggest that music training can counteract the age-related changes in auditory cognition commonly observed in older adults (5).

Previous studies have shown the positive effects of music training on auditory processing and neuroplasticity. However, the long-term protective role of these effects on age-related changes in musical perception has not been adequately investigated. This study aims to contribute to the literature by objectively evaluating the effect of music education on auditory cognitive changes due to aging with MPT test.

However, with this study examined age-related changes in the musical perception skills of musicians and non-musicians. The participants' performance was measured using the Musical Perception Test (MPT), which we used to determine the level of protection offered by music education in musical perception skills despite advancing age.

MATERIALS AND METHOD

Permission to conduct the study was obtained from the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee on 08.06.2023 with Decision No: 502. This study was conducted at the Istanbul Aydın University Audiology Laboratory between June and August 2023.

Two groups were included in this study. The first group consists of 40 musicians: 20 between the ages of 45-64 and 20 between the ages of 65-85. The 2nd group included 40 non-musicians, 20 between the ages of 45-64 and 20 between the ages of 65-85. Participants were included in the study by voluntary application method; the selection process was carried out through standard forms in order to minimise self-selection bias. The musicians included in the study had at least one year of professional music education. This training was given by the choir conductor in the form of a structured programme with active participation 2-3 days a week for at least 1 year. All of the musicians are actively performing professionally in the choir. The non-musicians did not play any instruments or receive any music education. Both groups included individuals with at least a high-school education level. Participants in both groups were administered the MOCA test and those with a score of 21 and above were included in the study. For both groups, it was ensured that the participants had a moderate socioeconomic level. Individuals with a history of psychological or neurological disorders and those who could not cooperate in the test were excluded.

Method

Participants who agreed to participate in the study signed an Informed Voluntary Consent Form. Afterward, the researcher verbally asked the questions in the Data Recording Form and filled in the answers. Next, Pure Tone Audiometry evaluations were performed. The Montreal Cognitive Assessment Test (MoCA) was then administered to the participants for cognitive assessment. Participants who scored in the normal range on the MoCA were administered the MPT in a quiet room, using an ASUS-branded computer with the test CD inserted and Supraaural professional headphones with a Sennheiser HD 400 Hi-Fi system.

Data Collection Tools

The Data Recording Form, MoCA test, Pure Tone Audiometry test, and MPT were performed on the participants who voluntarily agreed to participate in the study and met the study criteria.

Data Recording Form

The Data Recording Form, which examined the participants' interests and experiences related to music along with sociodemographic information, was completed before the evaluation. This data form included 25 open- and closed-ended questions. Questions 1-10 asked about age, sex, education, occupation, marital status, socioeconomic status, hearing loss, illness/disability, and medication status, and questions 11-25 collected information about the participants' professional music education, duration and type of music education, playing an instrument, level of interest in music, frequency of listening to music, and their preferred music genre.

Audiological Evaluation

The Pure-Tone Audiometry test was performed with a Maico MA 42 portable audiometer to verify the hearing of the individuals participating in the study. TDH-39 headphones were used to determine the airway thresholds of each ear at octave frequencies of 250-8000 Hz. A Radioear B71 brand vibrator was used to determine bone conduction thresholds of each ear at octave frequencies of 500-4000 Hz. The Pure Sound Average (SSO) was calculated by averaging the thresholds at 500-1000-2000-4000 Hz. Participants with a pure tone average (SSO) of 25 dB or less were considered to have normal hearing thresholds.

Montreal Cognitive Assessment (MoCA)

The MoCA was developed as a rapid screening test for mild cognitive impairment. The test assesses various cognitive functions, including attention and concentration, executive function, memory, language, visual structuring skills, abstract thought, calculation, and orientation. The application of the MoCA required approximately 10 min to complete. The maximum total score obtained on this test was 30. Accordingly, a score of 21 points and above was considered normal. (6)

Musical Perception Test (MPT)

The MAT, originally named the MPT, was developed by Marinda Uys and Catherine van Dijk (7). The necessary permissions were obtained through a protocol between the University of Pretoria and Hacettepe University, and the translation, adaptation, and validity-reliability studies of the test into Turkish were completed by Prof. Dr. A. Sanem Şahlı and Prof. Dr. Erol Belgin in 2016 (8). The adaptation and normalization results of the test were published in 2019 in an international journal using the SCI-expanded index. The MPT is the first and only valid musical perception test in Turkey that can objectively evaluate different music components. The rationale for the selection of the test is its comprehensive subtest structure and the fact that it is supported by previous validity and



reliability studies. To use the test, the researcher must have an MPT Application Certificate. The MPT consists of four domains and 11 subtests on a test CD with 14 audio files, including subtest contents, introductory and closing speeches, Musical Perception Assessment Answer Sheet, and Answer Key. The Answer Key was prepared such that the examiner could evaluate the answer sheet.

Statistical Methods Used in the Data Analysis

Data obtained from both musicians and non-musicians were analyzed using SPSS 25.0. The percentage distributions of both the demographic and music-related characteristics were calculated separately for the two groups. The compatibility of the MPT and MoCA scale scores with a normal distribution was investigated using the Kolmogorov-Smirnov test. The Mann–Whitney U test was used to compare the scores by sex and age groups separately for the musicians and non-musicians. A significance level of α=0.05 was used in all statistical tests. To compare the MPT scores for demographic characteristics, an independent sample t-test was used for independent two-category comparisons, whereas a one-way analysis of variance (ANOVA) was applied for comparisons with three or more categories. In groups where differences were detected, the source of the difference was determined using Bonferroni's multiple comparison test.

RESULTS

The results showed that musicians had higher scores than non-musicians on the total MPT and all music subtests ($p<0.05$) (Table 1).

Table 1: Comparison of the total and subtest scores on the Musical Perception Test (MPT) between musicians and non-musicians

In addition, when age-related changes were examined, musicians between the ages of 45-64 scored significantly higher than musicians between the ages of 65-85 on multiple instrument

Table 1. Comparison of Musical Perception Test (MPT) total score and subtests total scores of musician and non-musician group

Scores	Group	N	$\bar{x}$	SD	z	P[1]
Total Rhythm Score	Musician	40	33.400	3.5717	-5.730	0.000**
	Non-musician	40	26.900	4.3721		
Total Timbre Score	Musician	40	21.420	6.0672	-5.737	0.000**
	Non-musician	40	13.370	3.3713		
Total Pitch Score	Musician	40	14.300	2.71935	-4.262	0.000**
	Non-musician	40	11.800	2.01533		
Total Melody Score	Musician	40	35.970	1.8183	-6.142	0.000**
	Non-musician	40	30.450	4.1931		
Total MPT Score	Musician	40	105.050	11.52244	-6.739	0.000**
	Non-musician	40	82.400	10.53395		

**p<0.05 *p<0.05 1:Mann Whitney U test $\bar{x}$:Mean SD:Standard Deviation

Figure 1. Comparison of Musical Perception Test (MPT) total score and subtests total scores of musician and non-musician group

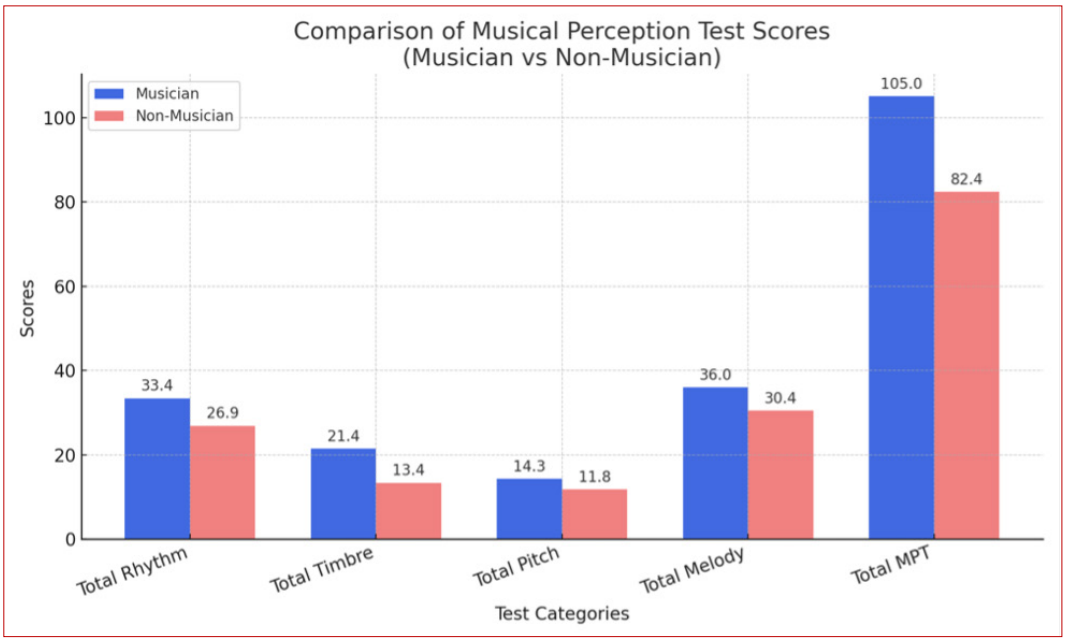


Table 2. Comparison of musical perception total scores according to age group in musician group

Scores	Group	N	$\bar{x}$	SD	z	P[1]
Total Rhythm Score	**45-64**	20	34.35	3.3289	-1.645	0.100
	65-85	20	32.45	3.6342		
Total Timbre Score	**45-64**	20	24.60	5.6138	-3.391	0.001**
	65-85	20	18.25	4.7779		
Total Pitch Score	**45-64**	20	15.50	2.1884	-2.579	0.010**
	65-85	20	13.10	2.7125		
Total Melody Score	**45-64**	20	36.20	1.7947	-0.508	0.611
	65-85	20	35.75	1.8602		
Total MPT Score	**45-64**	20	110.6	11.013	-2.924	0.003**
	65-85	20	99.45	9.2308		

**p<0.05 *p<0.05 1:Mann Whitney U test $\bar{x}$:Mean SD:Standard Deviation

recognition, total instrument, pitch discrimination, total pitch, and total MPT (p<0.05) (Table 2).

Table 2: Comparison of Musical Perception Test (MPT) total scores by age group in musicians

Among non-musicians, individuals aged 45-64 had significantly higher scores than non-musicians aged 65-85 for rhythm recognition, single instrument recognition, total instrument

score, musicality, melody recognition, melody recognition in noise, total melody score, and total MPT ($p<0.05$) (Table 3).

Table 3: Comparison of Musical Perception Test (MPT) total scores by age group in non-musicians

In the 45-64 age group, there was a significant difference between musicians and non-musicians on all scores except for rhythm recognition ($p<0.05$). Similarly, in the 65-85 age group, there was a significant difference between musicians

Figure 2. Comparison of musical perception total scores according to age group in musician group

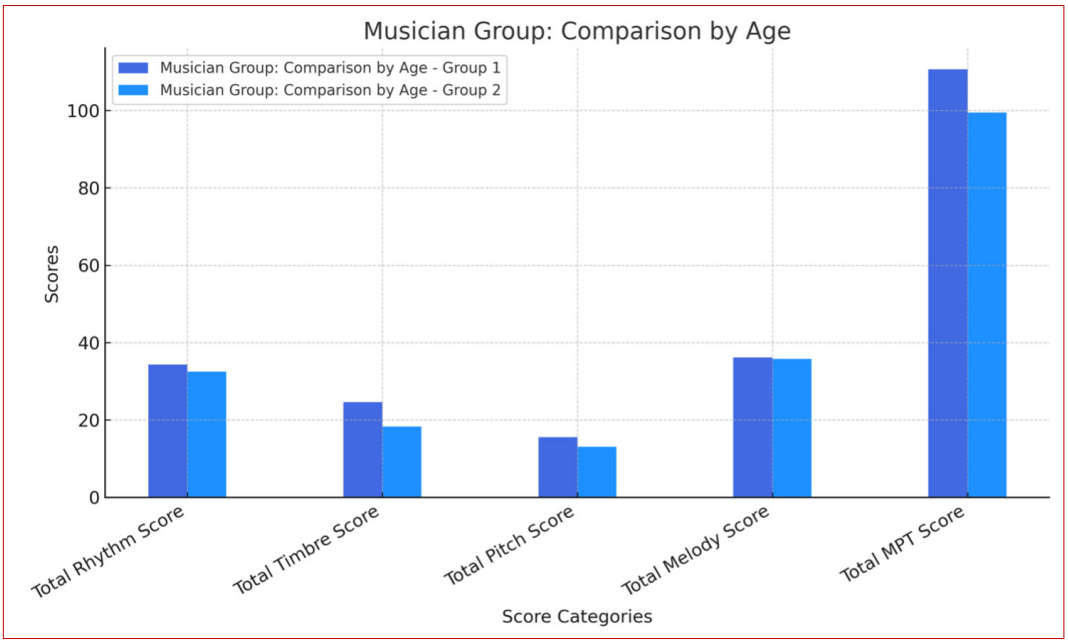
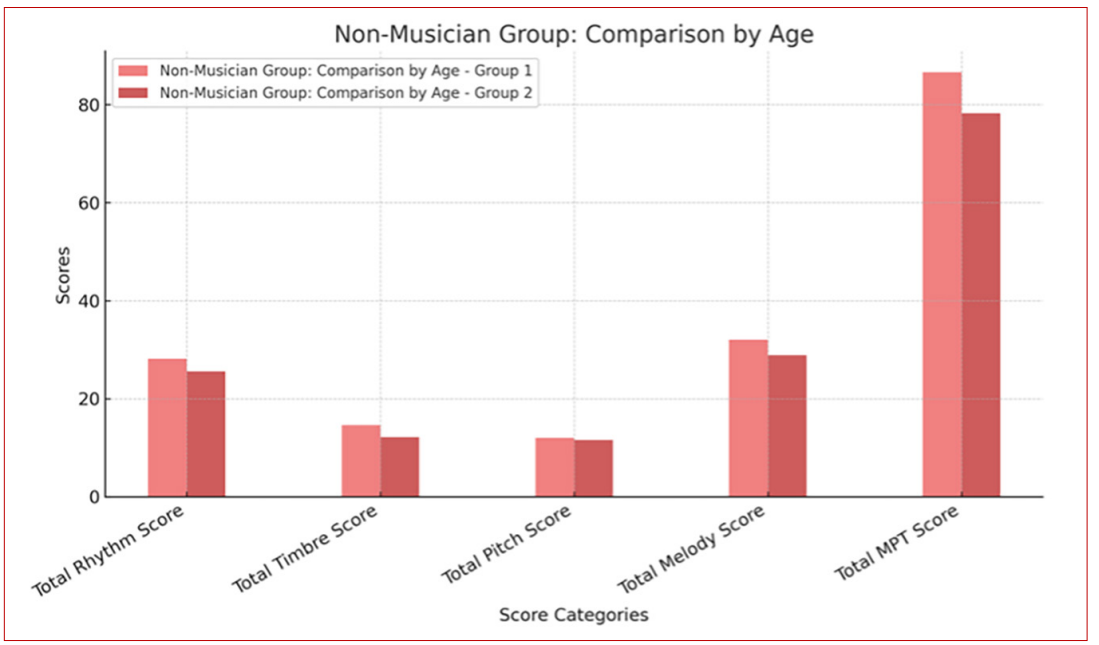


Table 3. Comparison of musical perception total scores by age group in non-musician group

Scores	Group	N	$\bar{X}$	SD	Z	P[1]
Total Rhythm Score	**45-64**	20	28.200	4.3115	-1.887	0.059
	65-85	20	25.600	4.1345		
Total Timbre Score	**45-64**	20	14.600	3.5894	-1.999	0.046*
	65-85	20	12.150	2.7003		
Total Pitch Score	**45-64**	20	12.000	1.9735	-0.691	0.490
	65-85	20	11.600	2.0875		
Total Melody Score	**45-64**	20	32.050	4.2485	-2.634	0.008**
	65-85	20	28.850	3.5581		
Total MPT Score	**45-64**	20	86.600	9.8054	-2.329	0.020*
	65-85	20	78.200	9.7203		

**p<0.05 *p<0.05 1:Mann Whitney U test $\bar{X}$:Mean SD:Standard Deviation

Figure 3. Comparison of musical perception total scores by age group in non-musician group



and non-musicians in all scores except those for pitch recognition, pitch discrimination, and total pitch ($p<0.05$). Although there were no significant differences in the pitch subtest and total pitch scores, musicians showed a significantly higher mean total MPT score than non-musicians across the education levels ($p<0.05$).

DISCUSSION

A musician's suprathreshold sound processing ability declines with age, just as it does for a non-musician. However, lifetime studies indicate that musicians have better auditory performance than non-musicians on a variety of psychoacoustic tasks because musicians exhibit higher levels of performance in frequency or temporal dimensions and speech understanding in noise (4). Previous studies have also shown that long-term music training and experience can cause neuroplastic, structural, and functional changes. Moreover, the effects of music education not only increase musical abilities but also improve various cognitive functions. Recent studies have highlighted the advantages of music training on cognitive functions, including speech perception (9), pitch perception (10), working memory (11), and attention in both auditory and visual modalities (12).

The effects of music education have been studied in detail due to its positive impact on perceptual and cognitive skills. Research has shown that music training improves performance, particularly in auditory tasks. For example, musicians have demonstrated a greater ability than non-musicians to detect silent gaps between sustained sounds, discriminate the duration of auditory events, and detect errors in synchronized rhythms (13,14). Musicians also outperformed non-musicians in their ability to understand speech in noisy environments, especially when presented with simultaneous auditory stimuli from different spatial locations. Intensive music training develops complex auditory skills related to music, such as speech, language, emotion recognition, and other auditory processing tasks. Studies have suggested



that good performance in these skills is a result of training rather than a genetic predisposition. (15) In addition to changes in perceptual performance, music training leads to changes in neuroplasticity. Neuroimaging techniques used in cross-sectional studies have revealed that music training is associated with neuroplastic changes in the auditory brainstem responses, auditory cortex, motor cortex, visuospatial brain regions, and high-level brain regions associated with working memory and executive functions (2).

In a validity and reliability study conducted by Şahlı et al. on 100 normal hearing individuals aged 18-40 years, the levels of education and interest in music significantly affected the MPT test results (8). In our study, it was found that there was a statistically significant difference between the mean levels of interest in music and frequency of listening to music according to the groups ($p<0.05$). The level of interest in music and the frequency of listening to music were higher in the musician group and there was a statistically significant difference in the MPT total score of the musician group compared to the non-musician group ($p<0.05$).

When the total musical perception scores of the participants were analysed according to their educational level, a statistically significant difference was observed in the MPT total score as the educational level increased ($p<0.05$). It is thought that with the increase in education level, general culture and cognitive skills such as learning and intelligence are positively affected and this increases the total test scores of musical perception. Our findings are consistent with those of previous studies and suggest a decrease in the MPT total score with advancing age. Testing across different age groups shows that aging affects the peripheral and central auditory systems, which is believed to affect both auditory perception and musical skills. However, the effect was less pronounced among musicians than non-musicians. Based on the results from controlling for musical perception skills between groups, it was hypothesized that being a lifelong musician may positively impact the auditory processing of the central auditory mechanisms.

Grassi et al. evaluated the auditory and visual memory of 40 individuals, including 20 musicians ($65 \leq$ age ≤ 84 years) and 20 non-musicians ($65 \leq$ age ≤ 84 years). The results of the auditory tasks revealed similar performances between musicians and non-musicians in pure-tone audiometry. In contrast, musicians performed better than non-musicians in terms of auditory processing abilities and frequency and duration discrimination skills. Regarding cognitive abilities, musicians performed better than non-musicians in complex working memory and visuospatial tasks, while the two groups did not differ in short-term memory measurements (16). Cohen et al. evaluated auditory and visual memory and demonstrated that musicians had superior auditory memory compared to non-musicians in terms of both musical and non-musical sounds (17). Consistent with the literature, our study showed a significant difference in the total MPT and subtest scores between musicians and non-musicians in the 65-85 age range.

Habibi et al. recorded the behavioral and event-related brain potential responses of musicians and non-musicians to rhythm differences between unusual melody pairs based on Western classical rules. Musicians detected rhythm deviations significantly better than non-musicians (18). In our study, the rhythm total score and subdomain scores of musicians were significantly higher than those of non-musicians.

Dubsky et al. examined whether 10 weeks of choral training using the QuickSIN (Speech-In-Noise) and the FDL (frequency difference limens) test could improve auditory processing and noisy speech perception in older adults. The results showed that choral singing may be used as an effective intervention to reduce age-related losses in auditory-perceptual abilities in as few as 10 weeks. More importantly, the intervention improved

older adults' ability to perceive speech in noisy environments (19). In another study, Parbery-Clark et al. investigated the effects of music training on noisy speech performance. Musicians exhibited better frequency discrimination and working memory than non-musicians and also outperformed non-musicians on both the QuickSIN and HINT (20). In our study, no significant differences were found in musicians by age group on the melody recognition subtest in noise, whereas a significant difference on the subtest was found in non-musicians by age group. The present findings show that music education can preserve auditory and musical perceptions despite advancing age. Finally, we believe that the ability to understand speech in the presence of noise, which deteriorates with age, can be preserved through music education.

The use of a cross-sectional design in this study limits the establishment of a causal relationship between the results. In addition, factors such as sample size and age group distribution may affect the generalisability of the findings. The fact that the participants' music education backgrounds were not differentiated in detail makes it difficult to consider additional variables that may affect the performance differences between the groups. In the future, it is recommended that similar research be conducted with longitudinal studies and larger sample groups.

The findings suggest that music education can preserve auditory and musical perception despite advancing age. These results may guide the development of music-based therapeutic approaches that can be integrated into interventions aimed at preserving cognitive and auditory functions in older adults. For example, the implementation of regular music education or music therapy programmes can be considered as effective interventions in supporting speech comprehension, working memory and other cognitive functions in noisy environments. In the future, the design and implementation of intervention studies will make important contributions to the literature in this field.

CONCLUSION

Studies show that music education can preserve auditory and musical perception despite advancing age. These findings reveal the potential benefits of integrating music-based interventions into auditory rehabilitation programmes for older adults. The ability to understand speech, especially in noisy environments, is one of the main challenges that older adults face in social communication and activities of daily living. Difficulties in speech comprehension in noise can lead to social isolation, communication disorders and a decrease in overall quality of life in older adults. Preservation of auditory processing and cognitive abilities supported by music education may help to reduce such difficulties.

The results of our study show that music education preserves auditory and musical perception skills despite advancing age.

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Declarations: Conflict of Interest: The authors declare no financial or nonfinancial conflicts of interest.

Ethical Approval: This study was approved by Istanbul Medipol University (ethical code E-10840098-772.02-3622). All the procedures were performed in accordance with the 2013 version of the 1964 Helsinki Declaration.

Previous Presentations: This study was presented at the IVth Otology and Audiology Congress (Online) held on 20-21 May 2023.

Author Contributions: Opinions: Ayse Sanem Şahlı and Cihan Aslan. Design: Cihan Aslan, Ayse Sanem Şahlı. Audit: Ayse Sanem Şahlı, Uğur Embiye Özgür. Data Collection and/or Processing: Cihan Aslan. Analysis and/or Comment: Ayse Sanem Şahlı, Uğur Embiye Özgür. Writing the first draft: Cihan Aslan. Writing, revising, and editing: Ayse Sanem Şahlı and Cihan Aslan. Approval of the final draft: All authors.



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ORIGINAL ARTICLE

BALANCE DISORDERS ASSOCIATED WITH ALZHEIMER'S DISEASE

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Abstract

Objective: The risk of falling dramatically increases in Alzheimer's disease. This study utilized static and dynamic balance tests to determine the stage of Alzheimer's disease at which balance impairment and fall risk become more pronounced.

Materials and Method: A total of 198 patients between 60 and 85 years of age were categorized into normal, mild cognitive impairment, mild dementia, moderate dementia, and advanced dementia based on the standardized Mini-Mental State Examination scores and the Reisberg Global Deterioration Scale. Static tests comprised the Romberg and Single-Leg Stance tests, and the 10-Step Tandem Gait Test was used as the dynamic test.

Results: Patients who failed the single-leg and Romberg tests had significantly lower Mini-Mental State Examination scores ($p<0.001$) and higher Reisberg Global Deterioration Scale scores ($p<0.001$). Similarly, failure in the 10-step tandem test correlated with lower Mini-Mental State Examination scores ($p<0.001$) and higher Reisberg Global Deterioration Scale scores ($p<0.001$). ROC analysis revealed a significant increase in the single-leg and tandem test failure rates when Mini-Mental State Examination scores dropped below 18.5, while positive Romberg results were significantly below 15.5. For Reisberg Global Deterioration Scale, failure rates rose above scores of 3.5 for the single-leg and tandem tests and above 4.5 for the Romberg test.

Conclusion: In patients with Alzheimer's disease, balance disorders begin in the early stages and increasing their risk of falls compared to the normal elderly population. Early environmental modifications are critical to prevent falls and injuries.

Keywords: Alzheimer Disease; Neuropsychological Tests; Accidental Falls.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the brain, characterized by a gradual loss in neurons' structure and function, ultimately leading to their death. It is the most common type of dementia in older adults, accounting for approximately 60-80% of all dementia patients (1). As a significant cause of dementia, Alzheimer's disease affects approximately 35 million people worldwide. The disease is most common in people over 65 years of age; however, approximately 5% of cases are classified as early-onset, developing in patients over 40 years of age (2). Its pathophysiology is marked by the accumulation of extracellular β-amyloid (B), the build-up of intracellular hyperphosphorylated tau (pTau), loss of neurons, and inflammation (3). The initial indication of the condition is typically a decline in recent memory. Early symptoms can encompass feelings of depression, anxiety, a tendency to socially isolation, and disruptions in sleep patterns. These symptoms are often distinguished from other neurodegenerative disorders by their early predominance of memory-related complaints and less frequent occurrence of motor dysfunction in the initial stages. As the disease advances, cognitive abilities further decline, resulting in significant memory impairment, neuropsychiatric issues such as hallucinations and delusions, and various behavioral challenges in the later stages. In addition, some patients may experience varying degrees of visual-spatial, language, executive, and motor dysfunctions (4).

AD is now recognized as a spectrum disease with the advent of clinical and biological tools, such as imaging techniques (PET and MRI scans) and biomarker analysis (amyloid-beta and tau levels in cerebrospinal fluid). The US National Institute on Aging-Alzheimer's Association (NIA-AA) group considered AD in 3 different spectra. The first is the preclinical stage, where there is no cognitive impairment, but biomarkers of Alzheimer's disease are detected. Stage 2 is mild cognitive impairment (MCI). This stage is characterized by evidence of impairment in memory or other cognitive domains, as well as biomarkers of AD on standard assessment. The final stage is dementia due to AD (5).

Falling is the foremost cause of trauma-related injuries, disabilities, and deaths in older adults. About 30% of older adults living in the community experience one or multiple falls each year. The consequences of falls range from fractures to severe morbidity (6). The incidence of falls in individuals with Alzheimer's disease is 60-80% higher than in elderly individuals with normal cognitive function . Injury after a fall is shown to be more common in patients with AD. The increased risk of falls among older adults with dementia and cognitive impairment can be linked to difficulties in navigating obstacles, balance issues, and problems with spatial awareness and vision. Effective fall prevention strategies are essential in reducing falls and their associated adverse consequences as well as the associated personal, societal, health, and economic costs (7). In this study, we utilized static and dynamic balance tests to determine the stage of AD at which the loss of balance first became pronounced and the risk of falls significantly increased.

MATERIALS AND METHOD

This study included patients aged 60-85 with mild cognitive impairment and AD, as well as healthy volunteers. The participants were recruited from a neurology outpatient clinic between December 2023 and November 2024. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. An authorized institution granted ethics committee approval with protocol number 18/12/2023-352, and informed consent was obtained from all participants.

In the patient and control groups, the Standardised Mini-Mental test (MMSE) and Reisberg

Global Deterioration Scale (RGDS) were evaluated by an experienced neurologist and clinical psychologist. MMSE scores were considered normal between 24 and 30, mild between 20 and 23, moderate between 10 and 19, and advanced dementia between 0-9 (8). RGDS stage 1 was considered as control group without cognitive impairment, RGDS stage 2 as cognitive loss due to normal aging, RGDS stage 3 as mild cognitive impairment (MCI), RGDS stage 4 as mild dementia, RGDS stage 5 as moderate dementia, and RGDS stage 6-7 as advanced dementia (9).

Two different neurologists assessed balance tests in both the patient and control groups at separate times, and any discrepancies in results led to a third evaluation. Participants underwent two static tests and one dynamic test to assess the balance and fall risk. The static tests included the single-leg stance and the Romberg test. Participants raised their dominant leg and bent the other leg at a 90-degree angle for the single-leg stance test, maintaining balance without external support. This test was conducted with the eyes open. Patients who failed to maintain their balance for 5 seconds during the test were deemed at risk for falling (10).

In the Romberg test, the patient was instructed to assume an upright position with the feet positioned at shoulder width and the arms held at the sides in a stationary position. All participants were instructed to wear flat footwear during the test. The subject was not provided with any assistance and was asked to maintain an upright stance with their eyes open and then closed. Measures were taken to prevent falling during the test. A positive Romberg sign indicated an abnormal deviation, or a step taken by an individual while standing with eyes open or closed for 10 seconds. A negative score indicated minimal or no deviation from the standing position (11).

The 10-step tandem gait test, performed as the dynamic assessment, is widely recognized for evaluating balance and coordination, particularly in populations at risk of falls (12). In this test, participants were asked to stand with their feet together and walk ten steps in a straight line, ensuring that the toe of one foot touched the heel of the other. The number of steps taken before the first misstep was noted. After completing the initial 10-step tandem gait test, the patient was instructed to turn around and repeat the test along the same line, with the steps counted similarly.

The higher score from the two attempts was considered in the evaluation. Participants were categorized into five subgroups based on the number of consecutive steps taken during the test: grade 0 (unable to walk), grade 1 (3 steps or fewer), grade 2 (fewer than 10 steps), grade 3 (10 steps but unstable, swaying side to side), and grade 4 (10 steps, normal). Patients who scored between grades 0 and 3 were considered to have failed. The dementia stages of the participants were determined using the MMSE and RGDS, and the results of the dynamic and static tests were compared.

The study excluded several patient groups including patients with a history of stroke and demyelinating diseases. Patients with central nervous system tumors or hydrocephalus observed on brain imaging were also excluded. In addition, patients with traumatic or inflammatory spinal cord conditions, any form of peripheral neuropathy (including diabetic, inflammatory, hereditary), and diabetes mellitus regardless of having diabetic polyneuropathy confirmed by standardized tests were also excluded. Furthermore, the study did not include patients with degenerative or inflammatory joint diseases that hindered walking and patients with severe visual impairment from any cause.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package software. Categorical data were presented as frequency and percentage, and continuous data were described as mean and



standard deviation. The normality of the numerical variables was evaluated according to the skewness and kurtosis coefficients. Skewness measures the asymmetry of the data distribution, while kurtosis indicates the sharpness or flatness of the distribution compared to a normal distribution. The variables followed a normal distribution, as the coefficients were within the range of ±2. As a result, parametric statistical methods were used in the study. In addition, a receiver operating characteristic (ROC) curve analysis was performed to determine whether a specific numerical variable could effectively differentiate between various diagnostic categories. For comparisons between groups, the "Independent Sample T-test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 198 patients were included in the study. The MMSE and RGDS tests were administered to all participants. The mean age was 75.16 ± 4.78 years, with 48% (n=95) female. This distribution closely reflected the general demographics of Alzheimer's disease, where prevalence tended to increase with age, and women were disproportionately affected due to their longer life expectancy. The mean MMSE score was 18.53 ± 5.61, while the average RGDS score was 3.52 ± 1.69.

According to the MMSE results, 5.6% (n=11) of the patients were classified as having advanced dementia, 50.5% (n=100) as having moderate dementia, 24.7% (n=49) as having mild dementia, and 19.2% (n=38) as having normal cognitive function. The RGDS results showed that 17.2% (n=34) of the patients were classified as having advanced dementia, 15.7% (n=31) as having moderate dementia, 16.2% (n=32) as having mild dementia, 19.2% (n=38) as having mild cognitive impairment, 16.7% (n=33) as having age-related cognitive impairment, and 15.2% (n=15) as being in the normal range.

Among the study participants, 54.5% (n=108) were unable to complete the single-leg test, 19.2% (n=38) failed the Romberg test, and 48% (n=95) could not complete the tandem test. These differences in failure rates may reflect the varying physical and cognitive demands of each

Table 1. Demographic Characteristics of Patients

(n=198)	Mean±SD
Age	75.16±4.78
MMSE	18.53±5.61
RGDS	3.52±1.69
	n(%)
Gender	
Woman	95(48.0)
Man	103(52.0)
MMSE	
Severe Dementia	11(5.6)
Moderate Dementia	100(50.5)
Mild Dementia	49(24.7)
Normal	38(19.2)
RGDS	
Normal	30(15.2)
Age-related cognitive impairment	33(16.7)
Mild Cognitive Impairment	38(19.2)
Mild Dementia	32(16.2)
Moderate Dementia	31(15.7)
Severe Dementia	34(17.2)
Single Leg	
Successful	90(45.5)
Failed	108(54.5)
Romberg	
Positive	38(19.2)
Negative	160(80.8)
Tandem	
Successful	103(52.0)
Failed	95(48.0)

SD: Standard Deviation, MMSE: Standardised Mini-Mental Test, RGDS: Reisberg Global Deterioration Scale

Table 2. Relationship of test results according to MMSE and RGDS

	MMSE			RGDS		
	Mean±SD	**t**	**p**	**Mean±SD**	**t**	**p**
Single Leg						
Successful	22.11±4.63	10.074	**<0.001**	2.43±1.36	-0.210	**<0.001**
Failed	15.55±4.51			4.43±1.38		
Romberg						
Positive	13.00±3.63	-9.535	**<0.001**	5.13±1.07	-9.326	**<0.001**
Negative	19.84±5.19			3.14±1.58		
Tandem						
Successful	21.66±4.62	10.029	**<0.001**	2.58±1.38	-9.963	**<0.001**
Failed	15.14±4.52			4.54±1.37		

SD: Standard Deviation, MMSE: Standardised Mini-Mental Test, RGDS: Reisberg Global Deterioration Scale, t: Independent Sample T-Test *: p<0.05

test. For example, the single-leg test focused on lower body strength and balance, while the Romberg test relied more on sensory input, such as proprioception and vision. The dynamic tandem test required coordination and spatial awareness, which may explain its intermediate failure rate (Table 1).

The MMSE and RGDS scores were analyzed using the Independent Sample T-Test to compare the means between two independent groups and determine statistically significant differences. The results showed that MMSE scores were significantly lower (22.11±4.63 vs. 15.55±4.51; t=10.074, p=0.000), whereas RGDS scores were significantly higher (2.43±1.36 vs. 4.43±1.38; t=-0.210, p=0.000). In addition, MMSE scores were also significantly lower (t=-9.535, p=0.000), and RGDS scores were significantly higher (t=-9.326, p=0.000). MMSE values were notably lower in patients who failed the Tandem Test (t=10.029, p=0.000), while RGDS scores were significantly higher (t=-9.963, p=0.000). These significant differences suggested that individuals with lower MMSE scores and higher RGDS scores had greater impairments in cognitive and functional domains, which may have impacted their inability to complete balance-related tasks successfully (Table 2).

A ROC analysis was performed to determine the best cut-off points for MMSE and RGDS values. This method is particularly suitable for evaluating the diagnostic ability of numerical variables, as it provides sensitivity and specificity values at various thresholds, enabling the identification of the optimal cut-off points. A notable rise in failure rates was observed in patients with MMSE scores below 18.5 for the single-leg and tandem Tests (sensitivity: 75.0%, specificity: 83.3%). These sensitivity and specificity values suggested that the tests were relatively reliable for identifying individuals at risk of balance issues, with a good balance between detecting true positives and minimizing false positives. A statistically significant positive rate was also identified in patients with MMSE scores below 15.5 for the Romberg Test (sensitivity: 80.0%, specificity: 81.6%). These cut-off points may guide clinicians in identifying patients at higher risk of falls, enabling early interventions such as balance training, physical therapy, or home safety modifications to mitigate these risks. For the single leg and tandem tests, a significant increase in failure rates was noted in patients with RGDS scores above 3.5 (sensitivity: 75.9%, specificity: 83.3%; sensitivity: 74.7%, specificity: 74.8%, respectively). Compared to MMSE cut-off values, which had similar pattern with scores below 18.5, the RGDS scores provided an additional perspective by focusing more on

global deterioration, complementing the cognitive emphasis of MMSE. Furthermore, a statistically significant positive rate was found in patients with RGDS scores above 4.5 (sensitivity: 78.8%, specificity: 81.6%) for the Romberg test. (Table 3, Figure 1, Figure 2).

Tablo-3. ROC Cut-Off Point for diagnosis in test results related to MMSE and RGDS Scores

Score	Test	Cut-Off Point	Sensitivity-Selectivity
MMSE	Single Leg	18.5	75.0%-83.3%
	Romberg	15.5	80.0%-81.6%
	Tandem	18.5	73.7%-74.8%
RGDS	Single Leg	3.5	75.9%-83.3%
	Romberg	4.5	78.8%-81.6%
	Tandem	3.5	74.7%-74.8%

ROC: Receiver Operating Characteristic, MMSE: Standardised Mini-Mental Test, RGDS: Reisberg Global Deterioration Scale

Figure 1. OC: Receiver Operating Characteristic, MMSE: Standardised Mini-Mental Test

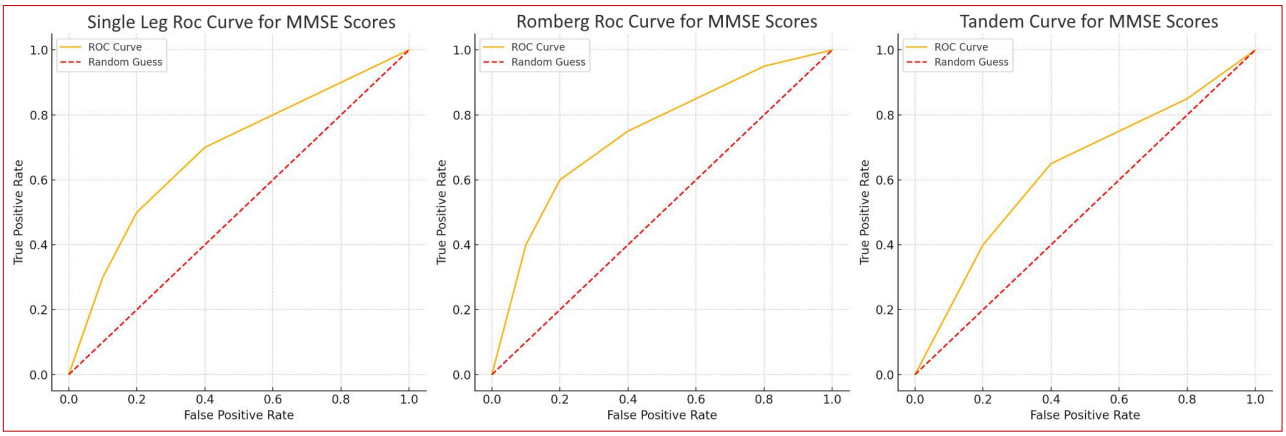
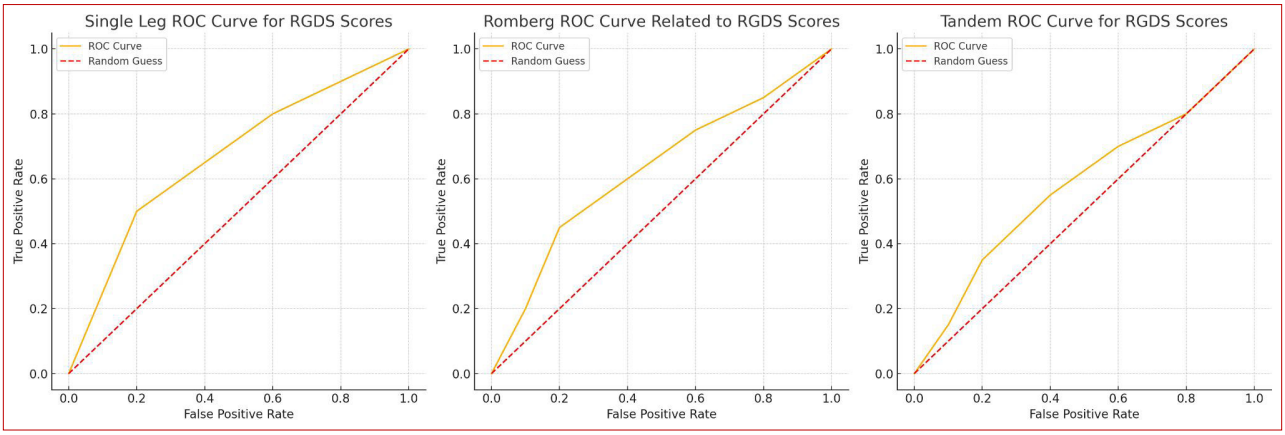


Figure 2. ROC: Receiver Operating Characteristic, RGDS: Reisberg Global Deterioration Scale



DISCUSSION

Looking at our findings, the decline in dynamic and static balance tests becomes pronounced at moderate dementia levels as measured by the MMSE and at mild cognitive impairment levels according to the RGDS. As the condition advances, deficits in balance tests become increasingly evident. We observed that the onset of deterioration in these balance tests occurred at similar stages of dementia. Some studies suggested that the severity of dementia assessed by the MMSE could differ from that evaluated using the RGDS. The MMSE assesses various cognitive functions, including short- and long-term memory, language skills, and orientation to time and place (13). However, it has been shown that MMSE scores are generally normal in patients with mild cognitive impairment at the initial stage of dementia (14). In our study, we hypothesize that the difference in balance tests at different stages of dementia determined according to various scales may be due to this reason.

Previous studies have found different results when using clinic-based and laboratory-based tests to investigate postural stability in AD. The most common clinic-based static balance tests are the tandem gait, Romberg, and single-leg stance tests (15). The tandem gait test and the functional reach test can be used in the clinic for dynamic balance (16). Functional performance tests also measure dynamic and static balance together. Among these tests, studies have assessed balance and coordination in AD using the Up and Go Test, the Berg Balance Scale, and the Parametric Rating Scale for Balance and Limb Coordination (17). The most popular tests in studies investigating balance loss in AD include the Computerized Dynamic Posturography Platform (EquiTest), the Force Platform, Stabilometry, and the NeuroCom Balance Master (18). The common feature of these studies is that static, dynamic, and functional tests deteriorate in early AD. Our study concluded that both dynamic and static tests revealed deteriorations in the early stages, similar to previous studies. Unlike other studies, instead of measuring the longest time patients could maintain balance in clinical tests, we classified patients according to their ability to complete the test within a certain time. This enabled us to assess patients' balance more quickly in an outpatient setting. In addition, unlike previous studies, we included a similar number of patients at similar ages at each stage from RGDS stage 1 to stage 6. We found that the deterioration in balance tests increased linearly.

Developing effective prevention strategies requires recognizing the multifaceted nature of falls among older adults. Understanding the underlying mechanisms of falls enables more accurate clinical assessments and analyses of the associated risks. The most common causes of falls are loss of balance and dizziness, followed by falling down stairs or steps (19). Multiple factors contribute to falls in AD, including cognitive, physical, sensory, psychological, medication-related, and environmental factors (20).

As cognitive impairment worsens, the likelihood of falls increases. Challenges such as impaired judgment, memory issues, difficulties with executive functions, attention deficits, and the inability to perform dual tasks can hinder a person's ability to navigate obstacles. This diminishes decision-making skills and heightens the risk of falling (21).

Impairments in cognitive processes affect functional mobility (gait and balance) and muscle strength through disruptions in motor planning, control, attention, and sensory integration. They may also affect motor function by disrupting neural networks fundamental to the planning and execution of various motor behaviors. Sensory deficits are also associated with gait and balance problems and an increased risk of falling. In particular, visual attention, perception, and peripheral sensory loss impairments are typical in AD (22).

In individuals with AD, psychological factors such as depression, anxiety, delirium, and sleep



disorders can lead to falls by reducing alertness. Side effects of medications prescribed to individuals with AD, including antidepressants, antipsychotics, and cholinesterase inhibitors, such as dizziness, imbalance, and weakness, may further increase the risk of falls (23).

More than 70% of falls in people with Alzheimer's disease occur at home, with approximately 10% occurring on stairs. Carrying heavy or bulky objects, slippery floors, and insufficient lighting are reported to be the most common environmental hazards associated with falls (24). Patterns on the floor or walls can also pose a potential danger by distorting or enhancing visual perception. Another significant risk factor is using poorly fitting or slippery footwear (25).

Our study had some limitations. Only clinic-based tests were used to assess patients' balance. Incorporating laboratory-based tests with clinic-based tests could enhance sensitivity. A second limitation was that we did not monitor changes in balance tests in individuals without cognitive impairment as they potentially developed dementia over time. As a result, we could not determine whether participants without dementia would face an increased risk of developing dementia in the future with impaired balance tests, based on MMSE and RGDS scores. Further studies with extended follow-up periods and multiple visits are needed to explore this potential association.

CONCLUSION

Balance impairment in AD begins in the early stages of the disease. Compared to the normal elderly population, individuals with AD face a significantly higher risk of falls due to impaired balance. Early intervention to address environmental factors is crucial, particularly in preventing potential falls and associated injuries.

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ORIGINAL ARTICLE

COMPARISON OF RANDOM SACCADE TEST AND CLINICAL SACCADOMETRY TEST RESULTS OF HEALTHY ELDERLY AND YOUNG INDIVIDUALS

Abstract

Introduction: The effects of aging on oculomotor functions and higher-level cognitive processes are increasingly being investigated, and saccadic eye movements are considered an important tool to evaluate these changes related to aging. The aim of our study is to compare the random saccade and clinical saccadometry test parameters of healthy young and elderly participants.

Materials and Method: The study included two healthy adult groups, Group I (Young adults (18–30 years)) and Group II (Elderly adults (65–80 years)). Participants were administered random saccade test and prosaccade and antisaccade tests with the newly developed clinical saccadometry protocol, respectively.

Results: A total of 71 participants were included in the study, 37 in group I and 34 in group II. Random saccade latency in group I was determined to be significantly earlier compared to group II ($p<0.05$). Prosaccade and antisaccade latencies in group I were found to be earlier, while prosaccade and antisaccade directional error rates in group I was lower compared to group II ($p<0.05$). There was no significant difference between the groups in terms of velocity and accuracy parameters.

Conclusion: Our results suggest that age-related changes affect certain oculomotor functions, while some parameters remain stable in healthy aging. These findings enhance our understanding of oculomotor aging; however, further research is needed to assess their clinical relevance. Additionally, saccadometry may help elucidate cognitive and neural mechanisms in aging and serve as a potential tool for differential diagnosis.

Keywords: Saccade; Aging; Eye Movements; Cognition.

INTRODUCTION

Saccades are rapid conjugated eye movements that enable fast focusing of environmental targets on the fovea (1). They are evaluated using the parameters of latency, velocity, and accuracy. Latency is the duration of time from the appearance of the target to the onset of the saccades, which is between 170-350 ms in healthy subjects (2, 3). Velocity refers to the maximum speed achieved during eye movement and can range from 50° to 700°/second in adults. Average values above 230°/second are considered normal. Accuracy indicates how accurately and appropriately the eye moves toward the target. Scores above 70-80% gain are considered normal (3).

Measurement of saccadic eye movements can be useful as a biomarker, especially in the diagnosis and follow-up of neurodegenerative disorders. Thus, saccadic tests are valuable in facilitating the diagnosis. Saccadic tasks include prosaccade (PS), which aims to focus rapidly on the visual stimulus, antisaccade (AS) which is the movement that is in the opposite direction from the stimulus and involves more complex tasks such as memory-guided saccade, i.e., the movement towards the position of a subject that is no longer present (4). The function of AS pertains to the inhibition of a dominant visual-motor response, and it is a well-proven executive function test for aging and neurodegeneration (5).

Premotor circuits in the cerebellar reticular formation, frontal cortex, visual cortex, thalamus, basal ganglia, lateral geniculate ganglia, superior colliculus, and brain stem take part in the creation of AS and PS. That is the basis for the supposition that neurological dysfunction or degeneration may alter saccade performance (6). It has been proposed in the literature that AS test is useful in the evaluation of neurodegenerative disorders, especially Parkinson's disease and dementia (7, 8).

Saccadometry is a sophisticated ocular motor test that enables the functional evaluation of various brain regions and circuits that are active in the creation of rapid, appropriate, and task-specific saccadic eye movements. Saccadometry consists of PS and AS tests that provide useful information in locating the lesion and include the parameters of latency, velocity, accuracy, and directional error. These measurements that are utilized in the evaluation of saccadic and antisaccadic systems may also provide data pertaining to concussion, traumatic brain injury, neurodegenerative diseases, movement disorders, depression, attention deficit disorders, and other neurological disorders (9). Although there exist different saccadometry protocols for these patient groups in the literature (10-12), there is only one study that proposes a test that has been adapted for a clinical environment, and is simplified, time efficient, and tested on a healthy population (6). Demian et al. analyzed the saccadic alterations due to aging in 5 different age groups from a population of patients aged 18-69 years. They created a practical protocol by standardizing tests that utilize Video-Oculography (VOG) devices and that enable clinicians to use their standard equipment. Their protocol allows the evaluation to be completed in a period as short as minutes. In contrast to previous studies, the application of PS and AS tasks in different blocks and by turns prevents loss of attention and learning effect (6).

We did not encounter any study in the literature that included subjects from a wider age range, and which analyzed the results from both random saccade and the aforementioned new saccadometry protocol.

Although saccadometry has been explored as a potential biomarker in the diagnosis and monitoring of neurodegenerative disorders, this study aims to establish normative saccadic parameters in healthy individuals, providing a foundation for future research involving clinical populations. In this regard, we aimed to compare the random saccade and clinical saccadometry results between healthy

young adults (age range 18-30 years) and healthy elderly adults (65-80 years).

MATERIALS AND METHOD

Ethics committee approval

Ethical approval for this study was obtained from a local ethics committee for non-interventional clinical research (approval number: 1677). Informed consent forms were taken from every participant. This research was conducted in compliance with the principles of the Helsinki Declaration.

Study Design and Participants

This research was designed as a cross-sectional study. The study was conducted in two locations: the Audiology Unit of the Department of Otorhinolaryngology at Ege University Medical Faculty Hospital and the Otorhinolaryngology Clinic at Ankara Etlik City Hospital.

The research was carried out between August 2024 and November 2024. The study included the relatives of patients visiting the clinics at both centers, university and hospital staff, intern university students, and patients who met the inclusion criteria and presented various ailments at the outpatient clinic.

The study population was divided into two distinct age groups to evaluate age-related differences in saccadic eye movement parameters: Group I – Young Adults (aged between 18 and 30 years) and Group II – Elderly Adults (aged between 65 and 80 years).

The inclusion criteria were as follows: being in the age range of 18-30 or 65-80 years, being able to understand Turkish both in writing and verbally, understanding the test instructions and completing the tests, scoring at least 24 points on the Mini Mental State Examination (MMSE) for cognitive screening, and achieving a score of 0 on the Dizziness Handicap Inventory (DHI).

The exclusion criteria were as follows: Having a neuro-otological problem, having been diagnosed with vestibular diseases, having been diagnosed with psychiatric and/or neurological diseases, having advanced visual impairment and cognitive problems, regular medication use, and having a cognitive problem.

MMSE and DHI were administered to all participants on the same day before random saccade and saccadometry tests.

The projected sample size was derived based on the saccadometry test score, utilizing the paired Student's t-test with 80% power, an α value of 0.05, and a "large" Cohen's d effect size. Consequently, it was considered necessary to include at least 26 participants in each group. The groups consisted of 80 participants, including 40 individuals from each group. Three individuals from the group I and six people from the group II were excluded from the research due to their inability to adjust to the test. The study was concluded with a total of 71 participants.

Data Collection Tools

In this study, participants underwent a random saccade test and saccadometry test using the Micromedical VisualEyes™ 525 VNG device (Interacoustics A/S, Middelfart, Denmark). The participants wore videonystagmography (VNG) goggles to record eye movements.

They were seated on a fixed stretcher, 1 meter away from the stimulus monitor/TV screen where they could observe the light movements, and the height was adjustable. They were instructed to sit upright and wear VNG goggles to record their eye movements. After the prerequisites were met, the calibration stage was initiated. For VNG calibration, the participants were instructed to look straight ahead and keep their heads still, following targets moving on the horizontal and vertical axes only with their eyes. After the calibration phase, the random

saccade test and the saccadometry test were administered, respectively. All tests in the study were administered to the participants by the same doctor audiologists (G.K. and G.S.U.). The doctor audiologists administered all tests on the same day.

Random Saccade Test

The participants were instructed to follow a randomly illuminated target on the horizontal plane within the 5-30° range without head movement, and the test was concluded after a total of 30 jumps (15 to the right and 15 to the left). Eye movements were evaluated based on the parameters of latency, velocity, and accuracy.

Saccadometry Test

Each participant was administered the PS and AS tests, respectively. During these tests, the TV screen background was black, and the central target that was continuously lit in the center and the stimulus targets were chosen in red. During the PS test phase, the participants quickly moved their gaze from the central target to the stimulus target and swiftly returned to the central target upon the disappearance of the stimulus. In the AS test, the participants looked in equal and opposing directions from the stimulus target and quickly returned their gaze to the central target when the stimulus target disappeared. Each stimulus target was presented at a jump size of 10 degrees to the right or left of the center target on the screen following a random delay. The tests were performed on the horizontal plane at a 10° angle, and a total of 60 jumps were recorded (30 to the right and 30 to the left). The recording duration was determined at 151 ms for each test (6).

In the saccadometry test, the measurement parameters of velocity, latency, and directional error (DE) rate were evaluated. Velocity was measured in degrees/second, latency in milliseconds, and accuracy in percentages. In the PS test, the DE ratio is formed by the participant looking away from the stimulus, while in the AS test, it is formed by looking toward the stimulus (6). The averages of the right and left values in the test were included in the analysis.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS software version 25.0. The normal distribution of the data was assessed with the Kolmogorov-Smirnov test. Parametric tests were used as parameters showed a normal distribution. Numerical data were presented using descriptive statistics. Comparison of numeric variables between groups was made using an independent samples t-test, and categorical variables were compared using a Chi-square test. A p-value lower than 0.05 was accepted as statistically significant.

RESULTS

A total of 71 participants were included in the study, 37 in group I and 34 in group II. The mean age of Group I was 23.7 ± 3.21 years, while the mean age of Group II was 71.58 ± 4.3 years. When the Group I and Group II groups were compared in terms of gender distribution, no significant difference was determined (p=0.718) (Table 1).

Table 1. Demographic features of the groups

	Group I (18-30 Years)	Group II (65-80 Years)	p
Age (years) Mean± SD	23.7 ± 3.21	71.58 ± 4.3	-
Gender (F/M)	19/18	16/18	0.718*

*Chi square test



The groups were then compared in terms of random saccade parameters. Latency was found to be significantly different, with Group 1 showing a shorter latency than Group II ($p<0.05$). Velocity and accuracy did not differ significantly between the two groups ($p=0.125$ and $p=0.370$, respectively) (Table 2).

Prosaccade and antisaccade parameters between groups differed significantly. When PS and AS parameters were evaluated, both PS and AS latency values were significantly shorter and both PS and AS error rates were significantly lower in the young group ($p<0.05$). Velocity and accuracy values did not differ significantly between the groups ($p=0.319$ and $p=0.392$ for PS and $p=0.589$ and $p=0.594$ for AS, respectively) (Table 3).

No significant difference was found between males and females in any parameters ((age ($p=0,707$); RS latency, velocity, accuracy ($p=0,606$, $p=0,699$, $p=0,251$, respectively); PS latency, velocity, accuracy ($p=0,679$, $p=0,963$, $p=0,992$, respectively); and AS latency, velocity, accuracy ($p=0,089$, $p=0,358$, $p=0,554$, respectively)).

Table 2. Comparison of random saccade parameters between the groups

	Group I (18-30 Years) (n:37)		Group II (65-80 Years) (n:34)		p
	(Mean±SD)	Range (Min-Max)	(Mean±SD)	Range (Min-Max)	
Latency (ms)	176.02±36.47	**125-238**	206.29±30.65	**157-248**	**0.000***
Velocity (°/s)	349.00±22.25	**269-377**	357.73±25.17	**306-420**	0.125
Accuracy (%)	95.24±4.7	**75-102**	96.17±3.86	**85-102**	0.370

SD: standard deviation, Significant at level:*: $p<0.05$

Table 3. Comparison of Prosaccade and Antisaccade parameters between the groups

	Group I (18-30 Years) (n:37)		Group II (65-80 Years) (n:34)		p
	(Mean±SD)	Range (Min-Max)	(Mean±SD)	Range (Min-Max)	
PS-Latency (ms)	226.89±45.83	160-349	270.79±60.24	182-457	**0.001**
PS-Velocity (°/s)	268.21±25.76	184-313	275.58±35.67	178-342	0.319
PS-Accuracy (%)	96.16±6.46	71-110	97.97±10.84	73-126	0.392
PS-Directional Error (%)	0.78±1.4	0-6	3.23±3.74	0-15	**0.000**
AS-Latency (ms)	325.56±49.33	242-424	383.73±80.10	181-508	**0.000**
AS-Velocity (°/s)	244.05±40.71	166-346	249.94±50.50	154-365	0.589
AS-Accuracy (%)	99.43±22.92	63-161	103.41±38.32	40-246	0.594
AS-Directional Error (%)	12.18±9.76	2-32	37.23±23.20	2-84	**0.000**

PS: Prosaccade, AS: Antisaccade, SD: standard deviation, Significant at level:*: $p<0.05$

DISCUSSION

In the study, the standard saccade latency, velocity, and accuracy along with PS and AS latency, velocity, accuracy, and DE parameter results of the saccadometry test were compared between healthy young and elderly adults. There is a study in the literature that compared the results between healthy participants aged between 18-69 years grouped according to age decades using the newly developed time-efficient saccadometry protocol (6). However, no study was encountered in the literature in which test results of both the random saccade and the new clinical saccadometry protocol were evaluated by taking a wider age range, especially in the elderly group. In this sense, the present study is unique in the literature.

Saccadic eye movements have been examined as biomarkers in Parkinson's and Huntington's Diseases, and it has been demonstrated that saccade latency is prolonged, velocity diminishes, and accuracy decreases with aging (13, 14). Abel et al. found that saccades were significantly slower in elderly individuals compared to young ones (15), and Munoz et al. demonstrated that age-related increases in the saccadic reaction period varied between 100-150 ms (12).

It has been reported that as a result of slowing in reflexes, receding in visual perception and motor performance, and decrease in fast movements along with aging, saccade functions can be affected due to prolonged reaction periods and latency (12, 16, 17). Yilmaz et al. found the saccade latency as 183.71±37.16 ms in the group aged between 65-82 years, while this value was determined as 124.25±22.58 ms in the group aged between 18-45 years (17).

Irving et al. reported that the saccade latency reached adult levels after age 14 and it was prolonged to 264 ms at age 80, following a course of increase after age 50 (18). Gedik et al. found significantly longer saccade latency in the group aged between 50-70 years compared to other age groups (19). Although the saccade latency period varied in studies, similar results were obtained, and a significant prolonging was observed in the latency period along with aging. In our study, similar to the literature, the saccade latency was found to be statistically significantly longer in the 65-80 age group (206.29±30.65) compared to the 18-30 age group (176.02±36.47), and the younger group showed a better performance. Tobener et al. concluded that the saccade latency differed with aging and that reaction times were prolonged, especially in childhood and old age periods, and they argued that these prolongations might have stemmed from age-related changes in cerebellar functions (20). Irving et al. stated that loss of cortical gray matter and decrease in neuronal density along with age could lead to prolongation in latencies (18).

In the literature, there is no consensus on whether saccadic velocity and accuracy change depending on age. Abel et al. could not determine a significant correlation between age and saccadic velocity (15). Gedik et al. determined that saccadic velocity and accuracy measurements did not differ between pediatric, young adult, and 50-70 age groups. They proposed that as the neural mechanisms responsible for saccadic accuracy mature at early ages, accuracy may not be affected by age (19). Spooner et al. found lower saccadic velocity in elderly individuals 65 years old and above compared to the younger group (21). In the study by Irving et al., saccadic velocity and accuracy especially in large saccades decreased along with age, and the researchers associated this situation with age-related neurological changes in the brain stem and cortical functions and the decrease in the mechanical efficiency of eye muscles (18). Similar to our study, Hopf et al. found no effect of age on saccade velocity and accuracy. They suggested that both parameters are resistant to the effects of normal aging and remain constant throughout life



(1). Moreover, this inconsistency in the literature may reflect methodological differences, age ranges of the sample groups, and individual characteristics.

In our study, AS and PS velocity and accuracy values did not differ between groups. Similar results were obtained in the study by Mack et al (22). They suggested that the basic function of the saccadic system, directing the eyes towards the next fixation target, is preserved throughout life and that this does not change saccade accuracy with age. They also stated that the reason why saccade velocity does not change is because the burst neurons in the saccade generator in the brainstem are resistant to aging.

PS and AS latencies of the younger group were found to be earlier compared to the elderly group in the saccadometry test in our study. In addition, intragroup AS latencies of both groups were prolonged compared to PS latencies. In studies conducted in the literature, while AS and PS performances decreased with aging, the values obtained varied (6, 12, 23). In their study, Demian et al. reported that the differences obtained in studies may have resulted from the number of repetitions in the saccadic movements, sampling differences, movement degrees for the saccadic movements, and the instructions given during tests (6).

Especially the brain makes a greater effort in AS formation compared to PS formation, and in the AS formation stage, procedures such as covertly orienting attention to the visual stimulus, inhibiting the prosaccade, and rematching the coordinates of the stimulus with the new position in the counter visual area should be performed (24). Connolly et al. examined the brain function during AS and PS tasks through functional magnetic resonance imaging (fMRI) and determined that the AS test activated especially the parietal and frontal regions more compared to the PS test and that during AS, the brain activated regions related to covert orienting, response inhibition, and coordinate transformation more. Therefore, it is believed that the earlier achievement of the PS latency compared to the AS latency may have resulted from the fact that executive functions and inhibition processes in the AS task require a higher cognitive burden (24). Thus, Demian et al. emphasized that it is important to use both tests together and that the cognitively more demanding AS and automatic PS reflected the integrity of the executive function (6).

In our study, PS and AS DE rates were found to be significantly lower in the younger group compared to the elderly group. On the other hand, the AS DE rate was found to be higher compared to the PS DE rate in both groups, and AS velocity was lower compared to PS velocity. It has been proposed that the decrease in AS performance can be associated with functional and structural changes in fields such as frontal eye fields (FEF), supplementary eye fields (SEF), dorsolateral prefrontal cortex (DLPFC), and superior colliculus (SC) (9). Mirsky et al. compared accurate AS response percentages in healthy elderly participants with neuropsychological test performance and gray matter volume measured through MRI. Even when the demographic variables such as age, gender, and education were controlled, they found that accurate AS response percentages were associated with executive functions. They determined that the accurate AS performance was associated with the gray matter volume of inhibitory control networks in the frontal lobe (specifically the right Supplementary Eye Field [SEF] and left Inferior Frontal Junction [IFJ]) (25). Structural differences in these regions have been considered important biological markers that may reflect deterioration in AS performance in normal aging or neurodegenerative processes (25). Wilcockson et al. found that with the AS task paradigm, the error rate increased in patients with mild cognitive impairment compared to normal people. They emphasized that mild cognitive disorders could be overlooked with traditional cognitive evaluations, and therefore eye tracking paradigms such as AS task could detect these disorders that may cause dementia in the

future and provide support as an early diagnostic marker (26). Even though our study focused healthy older participants, the results regarding saccadic performance could be the starting point for further studies into the potential of saccadometry as a precursor to cognitive decline. However, based on the available data, no definitive conclusions about cognitive disorders can be made.

In our study, no significant difference was found in AS and PS parameters in terms of genders. In their study, Demian et al. obtained similar results except for gender and velocity. They found that females had higher DE rates and longer latency in the AS test (6). Mack et al. found AS reaction time to be shorter in men than in women. They found no significant difference between the genders in terms of accuracy and error rates (22). Bonnet et al., similar to our study, found no difference between the genders (27). Inconsistencies in the literature regarding gender differences may be due to factors such as methodological differences and task design, sample size, and participant demographics. Mack et al. underlined the need of reporting the gender distribution in studies on eye movements even if the outcomes in the literature can differ. This makes it possible to compare the results of different studies in a more precise and thorough manner (22).

LIMITATIONS

In our study, participants up to the age of 80 years were included in the elderly group. However, since individuals of more advanced age were not evaluated, differences between sub-age groups within the elderly population could not be thoroughly examined. Future studies that will include older participants may more comprehensively elucidate the impact of aging not only on oculomotor functions but also on cognitive functions. In our study, a total of 60 jumps (151 ms) were performed for each PS and AS test. Increasing the number of jumps may result in more errors in the elderly group, especially in the directional error rate (DE) parameter. In future studies, it would be useful to evaluate the effect of increasing the number of jumps on saccadic parameters in a larger sample group. Finally, in our study, cognitive functions were evaluated with MMSE scores, but education levels were not compared. It is recommended that the effect of education level on saccadic parameters be evaluated in future studies. Moreover, more comprehensive neuropsychological evaluations were not included, which could be a focus of future research.

CONCLUSION

There is no study in the literature that comprehensively evaluates the results obtained with both the classical random saccade test and the new clinical saccadicometry protocol, especially in the elderly group, covering a wide age range (65-80 years). In this context, our study may contribute to the literature not only by deeply examining the effects of aging on the oculomotor system but also by revealing the clinical validity and potential application areas of the new saccadometry protocol in older age groups.

Our results suggest that age-related changes affect certain oculomotor functions, but some parameters remain consistent across healthy aging populations. Although our results contribute to normative data on saccadic performance in aging, they do not directly assess cognitive decline and neurodegenerative problems. Although our study focused on healthy individuals, our results may guide future research, including studies on neurodegenerative diseases, to evaluate the potential clinical value of oculomotor parameters.

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