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European Journal of Geriatrics and Gerontology is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of the Academic Association of Geriatrics. It is a double peer-reviewed journal published quarterly in April, August and December electronically. The publication language of the journal is English.

Our mission is to provide practical, timely, and relevant clinical and basic science information to physicians and researchers practicing the geriatrics and gerontology worldwide. Topics of European Journal of Geriatrics and Gerontology include;

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REVIEW

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The Potential and Challenges of Creatine Supplementation for Cognition/Memory in Older Adults

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Abstract

Creatine (Cr) has been proposed as an ergogenic resource and the adhesion to its therapeutic use has gained relevance in the last 2 decades. The role of Cr in the aging process has been highlighted, with many studies aiming to understand how aging affects the depletion of Cr resources in muscle and brain, especially because Cr is a natural regulator of energy homeostasis and plays a recognized role in brain function and development, justifying the rising hypothesis that Cr supplementation can help mitigate the effects of aging. Thus, we aimed to review the role of Cr (supplemented or obtained in daily diet) and its metabolism in the aging brain, with emphasis on cognition/memory. PubMed, PsychInfo, EBSCO, Medline, BioMed central and Science Direct, constituted the searched databases. Inclusion criteria specified peer-reviewed studies investigating creatine metabolism and/or creatine supplementation, and assessing cognition, and memory in old adults, and published between January, 2000 to September, 2022. The importance of creatine in the brain's energy metabolism is well established. The relationship between the decline of cognitive function and brain creatine storage still lacks stronger evidence. Evidence is also lacking on whether creatine supplementation is beneficial in mitigating the neural effects of aging, remaining an open field of studies that brings optimistic perspectives.

Keywords: Creatine, cognition, brain, memory, aging

Introduction

Creatine is a nitrogenous compound directly linked to energy metabolism in various organs and tissues. It is proposed as an ergogenic resource for a long time; however, its therapeutic use has gained relevance and adhesion in the last two decades. Interestingly, the role of this metabolite in the aging process has been highlighted, with many studies aiming to understand how aging affects creatine resource depletion (1-4), and how creatine supplementation could mitigate this event (2,5,6). Recent studies have risen the hypothesis that creatine supplementation can help mitigate the effects of aging, supported by the fact that creatine is a natural regulator of energy homeostasis, and plays a recognized role in brain function and development (7). Thus, this mini-review shows the state of the art in the role of creatine (supplemented or obtained in daily diet) and its metabolism in the aging brain, with emphasis on cognition/memory.

Methods

The following databases were searched: PubMed, PsychInfo, EBSCO, Medline, BioMed central, and Science Direct. Inclusion criteria specified peer-reviewed studies investigating creatine metabolism and/or creatine supplementation, and assessing cognition, and memory in old adults, and published between January, 2000 to September, 2022. Each author searched for articles separately based on the descriptors "creatine supplementation", "old people", "elderly", and "aging". After removing duplicate articles and abstracts that did not meet the inclusion criteria, only common articles selected by the authors were adopted.

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Discussion

Creatine Metabolism and Energy Supply

Creatine (methyl guanidine-acetic acid) is derived and synthesized from reactions involving the amino acids arginine, glycine, and methionine in the kidneys and liver or can be ingested exogenously primarily from animal-based foods (i.e., red meat, seafood) or through dietary supplements (8-11). Ninety-five percent of creatine is found in skeletal muscle with the remaining 5% dispersed across the brain, liver, kidney, and testes (8,12). Once creatine is transported into the skeletal muscle, ~2/3 is converted to phosphocreatine (CrP) with the remainder stored as free creatine. Phosphocreatine can be rapidly catabolized via creatine kinase (CK) and acts as a metabolic intermediary of energy transfer by facilitating the rapid re-synthesis of adenosine triphosphate (ATP). The average amount of total creatine stored in the body is ~120 g (for a 70 kg human) and the rate of creatine degradation to creatinine is ~1.7% of the total body creatine pool per day (13,14). To compensate for this daily turnover, the average person requires ~2 g creatine per day, with about half of this daily requirement (1 g) synthesized endogenously and the remainder coming from dietary sources (10,12,15).

Creatine and Brain Metabolism

The brain is a metabolically active tissue, requiring ~20% of total energy consumption, despite only accounting for 2% of total body mass. Creatine content and metabolism impairments have been reported as associated with neurological and psychiatric disorders (7,16,17), rising the hypothesis that creatine intake, in the daily diet or as a supplement, could be of therapeutic value for treating neurologic/psychiatric illnesses (6,18,19).

Creatine is a natural regulator of energy homeostasis, playing a relevant role in brain bioenergetics (7), justifying the neurological disease's development and profound cognitive impairment due to the inability to synthesize or transport creatine (i.e., creatine deficiency syndrome) (6,18-20). Indeed, CK is expressed in a brain-specific isoform (BB-CK), suggesting that creatine plays a role in energy provision and homeostasis in the central nervous system (CNS) (12,20-22).

Complex cognitive tasks, hypoxia, sleep deprivation, and some neurological conditions are characterized by rapid brain metabolic activity and ATP depletion, where creatine metabolism could be essential for energy homeostasis (21-24). It is important to highlight that the brain creatine content may also decrease with age, and age-related decreases in brain creatine content could be associated with reduced brain activity or disease (22,25).

In addition, deletion of cytosolic brain-type CK in mice was shown to result in slower learning of a spatial task and diminished open-field habituation as well as increased intra- and infra-pyramidal hippocampal mossy fiber area, suggesting that the creatine-CK network is also involved in brain plasticity in addition to metabolism (26).

A growing body of literature shows that creatine supplementation can enhance brain creatine content (20,22). However, it is unclear if habitual dietary intake of creatine from food sources can be sufficient to maintain the brain's creatine stores as well and cognitive function.

Creatine and Brain Aging

The muscle creatine stores decrease with age, although it is not clear whether this reduction is due to aging or simply associated with declines in the amount of physical activity that elderly individuals engage (20). It is similarly thought that brain creatine levels may also decrease with age, and this may be due to general aging, or it may coincide with reductions in brain activity (22). Regardless of the mechanism, reductions in creatine content and its metabolites may be part of the cognitive capacity impairments, which are typically associated with aging (6). This is supported by data showing that older people with higher resting creatine concentrations tend to perform better in cognitively demanding tasks (6,21).

Aging, Obesity, and Cognition

Outside of aging, obesity may also play a role in cognition since obesity causes structural and functional cerebral microcirculation impairments, which play a crucial role in the pathogenesis of both cognitive impairment and major diseases such as Alzheimer's disease (27-29). Specifically pathophysiological consequences of cerebromicrovascular dysregulation in obesity have been associated with blood-brain barrier (BBB) disruption, neuroinflammation, exacerbation of neurodegeneration, microvascular rarefaction, and ischemic neuronal dysfunction and damage (27). These alterations are likely to have meaningful consequences on cognition. For example, overweight older women exhibit larger declines in perceptual speed over time than would be expected from normal aging (27). In fact, comparing overweight women to normal body weights ones, the observed decline in perceptual speed suggested an additional 2.4 years of aging (30). The hypothesized mechanism linking obesity and such brain alterations is related to the metabolic activity of adipose tissue, which secretes a variety of adipokines, which signal at both peripheral and central sites (27). Excessive adiposity can result in dysregulated adipokines secretion, many of them with pro-inflammatory effects, rendering the adipose tissue a major contributor to systemic inflammation (29). This low-grade inflammation, induced by circulating pro-inflammatory mediators secreted from adipocytes, is recognized as an important factor in impaired neuronal function and the pathogenesis of cognitive impairment (27).

Reduced selective attention and inhibitory function in overweight older adults affect autonomy, increasing the risk of other age-associated problems (28,29,31). Decreased ability to isolate central and flanked information can lead to postural instability and falls, while correctly discerning the surrounding environment increases autonomy. Previous studies (3,4,32-34) allow us to suggest that creatine intake in daily diet and supplementation can be an ally in maintaining the autonomy and health of old adults (33), not only due to the effects against sarcopenia but also in the maintenance of CNS activity (6,12,21).

Memory

One specific cognitive domain that appears critical in aging adults is memory. Memory is the ability to acquire, store and retrieve available information in the brain. It is also the stored information and facts, which were obtained through heard or lived experiences. The typical age-associated CNS function decline impairs the ability to store information and learn new tasks, impacting the quality of life in older adults (26,29-31,35).

Increased brain creatine content, specially CrP, has been shown to preserve the integrity and stability of the cell membrane, such as structural stability and functional maintenance, preventing cell apoptosis caused by abnormal energy metabolism (36). *In vitro*, creatine has been shown to increase oxidative phosphorylation in synaptosomes and isolated brain mitochondria (37). In rats, creatine injected into the hippocampus enhanced spatial memory and object exploration (38). In addition, cAMP-response element-binding protein (CREB) known to influence memory is upregulated 30 minutes after creatine injection (38). Recently, 4 weeks of creatine supplementation in mice enhanced isolated hippocampal mitochondria and improved memory (39). Further, creatine is important for neuronal protection (40). Future research is warranted to investigate whether creatine intake from a daily diet can alter these potential mechanisms in humans.

Neurodegenerative Diseases

Furthermore, creatine may play a role in the prevention of other neurodegenerative diseases such as Alzheimer's disease. Alzheimer's disease is associated with a reduction in brain creatine content and in a recent study using a 3xTg mouse model of Alzheimer's disease, creatine supplementation over 8-9 weeks exhibited beneficial preventative effects in females (41). It is described that the spatial memory impairments induced by beta-amyloid protein accumulation are greater in females (39,41), while Snow et al. (39,41) showed that the mitigating deleterious effects promoted by creatine supplementation are superior in females. It is important to note that the proposed underlying mechanism is not the decrease in plaque accumulation, but the greater availability of ATP/CrP, reducing the effects of neuronal apoptosis and necrosis, mainly in the hippocampus (39-41). Other proposed mechanistic effect is the down-regulation of the NF-κB inhibitor, IκB, induced by creatine (39). Notwithstanding, neuronal NF-κB regulates the expression of several genes involved in cognition and memory (39).

Creatine as a Needful Nutrient

Ostojic et al. (3) found a significant positive correlation between WAIS III Digit Symbol Substitution Test (DSS) scores and habitual dietary intake of creatine in a larger sample of older adults. Working memory for spatial locations activates the superior prefrontal cortex and posterior parietal cortex, and previous studies (6,42) showed a presence of BB-CK isoform and Cr/PCr in these brain areas, however, brain permeability to circulating creatine is limited due to the absence of creatine transporter expression in the astrocytes involved in crossing the BBB. Since the brain endogenously synthesizes creatine, it is unclear as to the importance of exogenous delivery of creatine, may differ in older adults (6,20). Thus, more specific studies on the association between daily dietary intake, biosynthesis, and creatine concentration in the CNS are needed.

Notwithstanding, the literature is conflicting on the effects of creatine supplementation on cognitive task performance in older adults (20). It is important to highlight that the difficulty in assessing brain creatine concentration is one of the main limitations of this kind of study. Despite the physiological plausibility of the proposed mechanisms for the success of creatine supplementation, added to the positive results. Some studies still show insufficient or contradictory results (15,43,44). The main challenge for the future is to measure the appropriate doses so that the results can be confirmed, increasing the strength of the evidence.

Approximately 1 g of creatine is converted to creatinine per day, suggesting that 1 g of creatine be ingested or synthesized to replenish reserves (8,10,32,33,45). It is quite common for older adults to have low protein intake, especially from meat (33), possibly due to difficulty in chewing. Older adults may need creatine supplementation beyond increasing dietary intake to help replenish reserves, regardless of whether they increase intracellular stores to improve some skill or competence.

Conclusion

The importance of creatine in the energy metabolism of the brain is already well established. The relationship between the decline of cognitive functions and creatine still lacks stronger evidence. Evidence is also lacking on whether creatine supplementation is beneficial in mitigating the neural effects of aging. Further studies should explore the scientific gaps in this field, as well as investigate the association between creatine supplementation and other interventions, such as exercise training, to minimize/ameliorate brain aging. In summary, it remains an open field of studies that brings plausible perspectives.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.M., R.P., Design: M.M., R.P., Analysis or Interpretation: M.M., R.P., Literature Search: M.M., R.P., Writing: M.M., R.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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Impact of Ethnicity on the Relationship Between Sarcopenia and Diabetes

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Abstract

Objective: Several studies have established a close relationship between sarcopenia and diabetes in aging populations, but to the best of our knowledge, no studies have analyzed if a difference in this relationship exists among different ethnic groups. The main objective of this study was to determine if there is a statistically significant difference in the relationship between sarcopenia and diabetes among different ethnic groups.

Materials and Methods: A literature search was performed via PubMed. After screening, 26 studies were included for a total of 62,070 individuals with diabetes, 39,825 individuals with sarcopenia, and 6,870 with both. A One-Way Analysis of Variance was performed on the sarcopenia-diabetes co-occurrence value for each group.

Results: Our results show that sarcopenia and diabetes appear more prevalent in Asian populations compared to other ethnic groups at a lower body mass index; however, there is no statistically significant difference in the relationship between sarcopenia and diabetes among the Asian, Hispanic, and Caucasian groups analyzed ($F=0.202$, $p=0.819$, at $\alpha<0.05$).

Conclusion: Our meta-analysis supports the previously established relationship between sarcopenia and diabetes in aged populations but does not support the hypothesis that ethnicity alone is a major determining factor for the sarcopenia-diabetes relationship.

Keywords: Sarcopenia, diabetes, metabolic syndrome, Asian

Introduction

A rapidly evolving, fast-paced, and technologically inclined global stage has given rise to an increasingly alarming incidence of chronic, metabolic diseases and associated physiological, economic, and social healthcare burdens. Diabetes is among one of the world's leading causes of morbidity, as well as mortality, and has cost the world an estimated $760 billion in 2019 (1). Depending on the definition used for diagnosis, the global prevalence of sarcopenia ranges from 10-40% of the world population (2,3). Increasing lifespan over the past centuries, coupled with a consequent increase in adults over 65 years of age, has put increasing emphasis on age-related conditions such as sarcopenia and diabetes. In the year 2020, there were 727 million individuals aged 65 years and older, representing approximately 9.3% of the world population (4). Globally, individuals 65 and older is estimated to rise from 9.3% of the world population in 2020 to 16% of the total population in 2050 (roughly 1.5 billion elderly persons) (4).

Several papers have established a reciprocal relationship between diabetes and sarcopenia, with some citing a sarcopenia prevalence two or three times higher in diabetic patients compared to healthy controls, and vice versa (2-12). Several factors have been implicated in contributing to the sarcopenia-diabetes relationship: Insulin resistance, altered metabolism, advanced age, increased adiposity, obesity, inflammation, oxidative stress, advanced glycation end-products (AGEs), mitochondrial dysfunction, vascular complications, muscular atrophy, reduced muscle quality and function, myopathies, and lifestyle (primarily exercise and diet) (Figure 1) (2-4,7,11).

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Of note, Asian populations exhibit higher rates of diabetes at lower body mass indexes (BMIs) compared to other ethnic groups (13). Given the lower initial muscle mass and higher sarcopenia prevalence in Asian populations, as well as higher rates of diabetes at lower BMIs, we hypothesize that the relationship between sarcopenia and diabetes will be stronger compared to other ethnic groups.

To the best of our knowledge, no studies have evaluated the strength of the relationship between sarcopenia and diabetes among different ethnicities. Therefore, in this study, we performed a meta-analysis to determine if a difference exists in the strength of the relationship between sarcopenia and diabetes across different ethnic groups.

Materials and Methods

Data for this meta-analysis was obtained from searching the online, international database PubMed with reference to guidelines from the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Figure 2) (14). Specific combinations of search strings for each ethnic group were developed using Boolean operators and MeSH terms to further narrow and specify search results.

Studies were screened for data on the prevalence of sarcopenia and diabetes. Studies that did not include data on participants with coexisting sarcopenia and diabetes were excluded from this study. Studies with the following characteristics were excluded: (i) not written in English, (ii) published over 10 years ago (before 2011), (iii) included individuals under 18 (child and adolescent studies), (iv) conducted on only one gender, (v) conducted on animals, and (vi) individual case studies. This meta-analysis focused on type II diabetes (T2DM); individuals with type I diabetes were not included. Individual study exclusion criteria were evaluated such that participants included in this meta-analysis were considered relatively healthy without outstanding, potentially confounding health conditions. The studies selected excluded participants with difficulties communicating, outstanding disabilities that impaired study participation, severe cognitive impairment, notable conditions that impaired adequate nutrition, serious heart, kidney, or liver disease, history of stroke, individuals with type 1 diabetes, difficulty ambulating, and incomplete information. In location-specific studies, those who were not registered residents were excluded.

Further, all studies used the Asian Working Group for Sarcopenia or European Working Group for Sarcopenia in Older People criteria for sarcopenia diagnosis; one study used the decrease in the ratio of appendicular lean mass/BMI along with handgrip strength. Diabetes diagnosis was determined via blood sample, patient self-reporting, or physician assessment during the clinic visit.

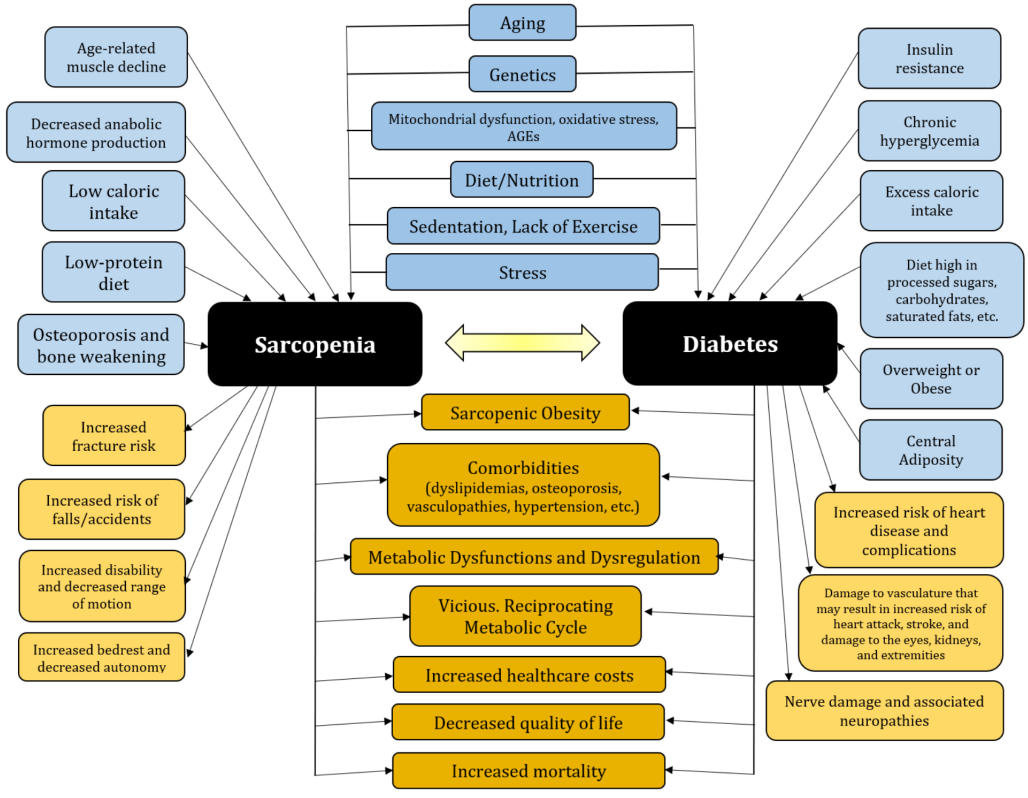

Figure 1. Graphical representation of the reciprocal relationship between sarcopenia and diabetes. The relationship between sarcopenia and diabetes may result in sarcopenic obesity, metabolic dysfunction and dysregulation, and a vicious cycle in which factors influence and are influenced by other factors in the metabolic network. Both conditions have contributed to increasing healthcare costs, decreased quality of life, and increased morbidity and mortality

JASP open-source software was used to analyze data collected from selected articles. A One-Way Analysis of Variance (ANOVA) was performed to obtain an F-statistic and p-statistic to determine significance, as well as an η^2 value to conceptualize effect size. The group means that were compared through ANOVA consisted of each group's average of the following measurement for each study, which we call the co-occurrence value:

$$\text{co-occurrence value for study x} = \frac{\text{individuals with both SC+T2DM}}{\text{total study individuals with T2DM}}$$

In this project, the co-occurrence value will serve as a numerical measure of the strength of the relationship between sarcopenia and diabetes. The co-occurrence value was calculated for each study and the co-occurrence values for all studies within the Hispanic, Caucasian, and Asian groups were averaged to produce the group mean. Moreover, the number of individuals with both sarcopenia and T2DM was divided by the total number of individuals with T2DM. Using ANOVA, the difference in means was compared within groups, as well as between groups to determine if a statistically significant difference in means exists among different ethnic groups.

For this meta-analysis, the null and alternative hypotheses were as follows:

H_0: No difference in means exists among the Hispanic, Caucasian, and Asian groups

H_a: A difference in means exists among the Hispanic, Caucasian, and Asian groups

Results were considered statistically significant at an alpha level of $p<0.05$.

Results

After searching and screening PubMed, 26 studies out of the initial 333 were selected for statistical analysis (Figure 2). The combinations of search terms produced a total of 333 results: Five studies for the African group; 12 studies for the Hispanic group; 89 results for the Caucasian group; and 227 studies for the Asian group. After removal of duplicates, of the 322 studies screened for eligibility, reports were excluded for the following reasons: (i) did not contain relevant data (unrelated topic, extraneous data, etc.), (ii) contained study individuals with outstanding, confounding health conditions, (iii) provided data on either sarcopenia or diabetes, but not on their co-occurrence, (iv) conducted only one gender, (v) child study or study including children (persons younger than 18 years of age), (vi) animal studies, (vii) did not include breakdown for each ethnicity, (viii) study not written in English, and (IX) case study following a single patient. After removing duplicates and conducting initial screening, 38 studies were selected for in-depth evaluation and 26 studies were selected for inclusion in the meta-analysis (6,8,15-38). Twenty-two studies had a cross-sectional design;

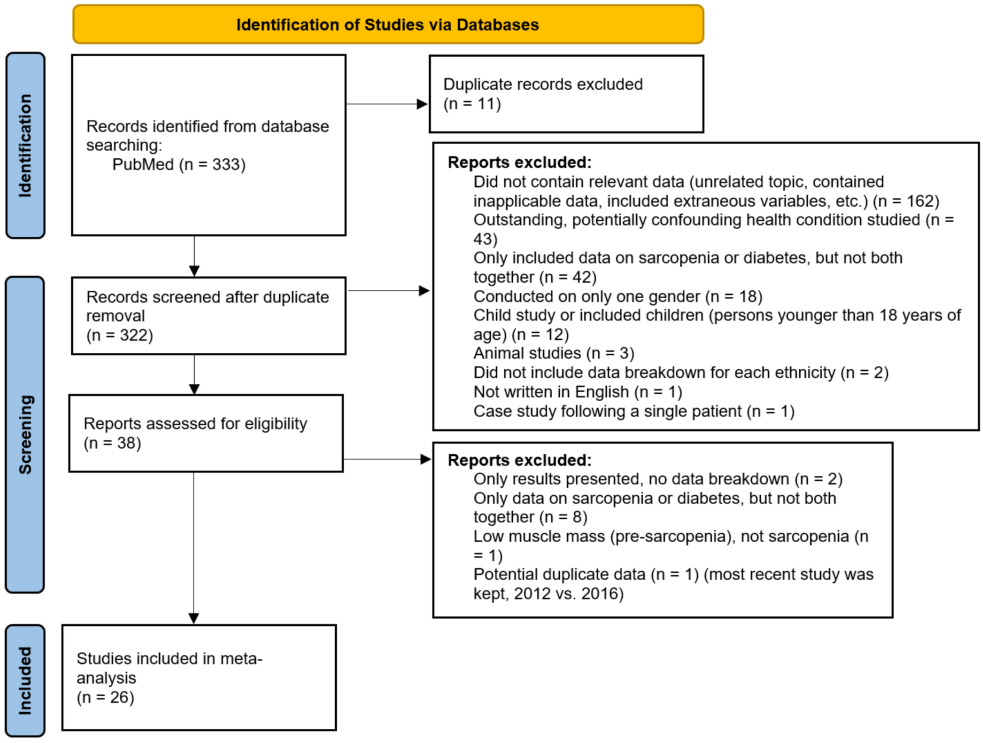

Figure 2. Preferred Reporting Items for Systematic Reviews (PRISMA) for identification of studies via databases. Chart adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. (14) Licensed under the Creative Commons Attribution License

3 studies had mixed study designs (a combination of cross-sectional and cohort); 1 study had a cohort design. There were 5 studies for the Hispanic group (6,8,18-20), 3 studies for the Caucasian group (15-17), and 18 studies for the Asian group (21-38). Due to lack of eligible study data, the African group was not able to be included in the final analysis. A scarcity of study data may be due to lack of access to medical care and documentation in these regions. Out of the 26 selected studies, 18 were chosen for the Asian group. Patients were drawn from the following countries: China (5 studies), Korea (2), Japan (7), Malaysia (1), North India (1), Singapore (1), and Thailand (1). Of the 26 selected studies, 5 were from the Hispanic group and were drawn from the following countries: Brazil (4) and Mexico (1). Furthermore, 3 of the 26 studies were included in the Caucasian group, with 1 study conducted in Australia, 1 in Italy, and 1 in the UK (encompassing England, Scotland, and Wales).

Author names, number of individuals with sarcopenia, diabetes, and both, and BMI were collected from each study (Table 1). The study population consisted of 531,023 individuals (62,070 total patients with T2DM and 39,825 total patients with sarcopenia; 6,870 patients had both sarcopenia and T2DM) with an average age of 68.27 years; 45.44% of participating individuals (241,313) were male. For all studies, the co-occurrence value (SC + T2DM/total T2DM) ranged from 7-82%. For the Asian group, the co-occurrence value ranged from 7-82%. The co-occurrence values ranged from 9-37% for the Caucasian group and 14-30% for the Hispanic group. The Asian group exhibited the greatest variation in co-occurrence values, whereas the Hispanic group displayed the least variation. Among the Asian studies, the means of the co-occurrence values for China, Korea, and Japan are as follows: 0.39, 0.27, and 0.16, respectively. The mean co-occurrence value for the studies conducted in Brazil was 0.22.

The Asian group had the highest of the group means (highest average of co-occurrence values) when the selected studies were averaged. The group means for co-occurrence value in the Caucasian, Hispanic, and Asian groups were 0.23, 0.22, and 0.27, respectively. For all studies taken together, the average for the co-occurrence value was 0.26.

ANOVA produced an F-statistic of 0.202 and a p-statistic of 0.819 with an η^2 value of 0.017. Using an alpha level of p=0.05, the p-statistic obtained is greater than the stated alpha level; therefore, the results are not statistically significant, and we fail to reject the null hypothesis. The available data therefore does not support the hypothesis that Asian groups have a stronger relationship between sarcopenia and diabetes compared to the Hispanic and Caucasian groups analyzed.

Discussion

Several published studies have established a reciprocal relationship between sarcopenia and diabetes in which the presence or onset of one influences or is influenced by, the presence or onset of the other. This meta-analysis explored if ethnicity plays a significant role in the relationship between sarcopenia and diabetes. Given the higher prevalence of sarcopenia and diabetes at lower BMIs in Asian populations, we hypothesized that this relationship would be significantly stronger in Asian groups.

The p-value obtained from ANOVA was greater than the accepted alpha level of $p<0.05$. Thus, the results do not support ethnicity as a major impacting factor in the relationship between sarcopenia and diabetes. Furthermore, based on currently available data, the Asian group did not demonstrate a stronger relationship between sarcopenia and diabetes. These findings pose additional questions for future sarcopenia and diabetes research.

A significant amount of variability was found within each study group, especially in the Asian group. A primary contributor to significant in-group variation is the inherent variability (physical, behavioral, genetic, demographic, cultural, etc.) of different study populations. The Asian group, as with Hispanic and Caucasian groups, consists of heterogenous populations of individuals from many different countries, regions, and environments. The classifications of "Hispanic", "Caucasian", and "Asian" are far from homogenous, and some individuals who fall under one category geographically may qualify for multiple categories or share more similarities with another individual from a different category compared to an individual from their own category. Data for this meta-analysis was drawn from several Asian countries (China, Japan, Korea, Malaysia, Singapore, North India, Singapore, and Thailand) with multifactorial differences that cannot be understated when examining the great degree of within-group variability obtained in this study. Further studies may explore if or how particular differences (genetic markers, diet, culture, etc.) within ethnic groups contribute to the co-occurrence of sarcopenia and diabetes. Moreover, future studies may benefit from exploring different levels and guidelines for evaluation that can more fully address the variability within ethnic groups.

Of note, a general trend observed in the study population was a general increase in sarcopenia and diabetes with age. Older study populations exhibited higher rates of sarcopenia, diabetes, and sarcopenia with diabetes. Additionally, there appeared to be an increased prevalence of sarcopenia in those populations that had diabetes. These trends further confirm previously established relationships between sarcopenia and diabetes.

Certain diseases such as diabetes, hypertension, and osteoporosis demonstrate ethnic trends in presentation, prevalence, and severity. Though this may be true when observing a certain condition by itself, analyzing multiple conditions together does not translate to statistically significant differences in the

Table 1. Study and patient characteristics from selected studies

First Author	Year	Category	Country	Study Design	# of patients	Mean Age (years)	% Men	SC Definition	T2DM Definition	Total SC	Total T2DM	SC + T2DM	(SC+T2DM)/Total T2DM percentage	Average BMI
Asian														
Xiu, Shuangling	2021	Asia	China	Cross-sectional	582	70.54	50%	AWGS, 2019 criteria	Blood samples after overnight fast (>10h), FPG	52	582	52	**8.93%**	24.33
Yuenyongchaiwat, Kornanong	2021	Asia	Thailand	Cross-sectional	330	66.85	24%	AWGS	Insulin-resistant	21	82	21	**25.61%**	**T2DM** = 26.39 **No T2DM** =25.27
Yin, Ting	2021	Asia	China	Cross-sectional	14,926	56.75	39.8%	AWGS	2010 ADA guidelines: FPG > 7.0 mmol/L	9721	744	539	**72.45%**	**Mean for all** = 24.94 **SO** = 26.54 **No SO** = 21.95
Su, Ya	2019	Asia	Japan	Cross-sectional	310	76	29%	EWGS OP2	Self-reported	25	26	6	**23%**	**Overall** =22.7 **SC** = 20.5
Kaur, Parjett	2021	Asia	North India	Cross-sectional	194	43.23	52%	EWGS OP2	Outpatient check-up; FPG and HbA1c levels measured	62	95	45	**47.37%**	**T2DM** = 28.15 **No T2DM** = 27.45
Mori, Hiroyasu	2021	Asia	Japan	Cross-sectional	1328	67.53	61.8%	AWGS 2019 criteria	Physician's diagnosis, medical chart review	102	645	76	**11.78%**	**T2DM** = 26.6 **T2DM + SC** = 21.3
Kang, Sunyoung	2021	Asia	Korea	Cross-sectional (nationwide cohort study)	2403	76	47.2%	AWGS	Self-report or current antidiabetic medication; newly diagnosed diabetes determined via ADA guidelines	284	670	88	**13.13%**	Not reported
Sazlina, Shariff-Ghazali	2020	Asia	Malaysia	Longitudinal study	506	67.6	40.0%	AWGS	FPG of ≥7.0mmol/L or ≥11.1mmol/L, respectively; or HbA1c of ≥6.3%, in accordance with Malaysian guidelines on Management of T2DM, 2015	144	506	144	**28.46%**	27.5
Sugimoto, Ken	2019	Asia	Japan	Cross-sectional	746	69.9	60.3%	AWGS	Not reported	52	746	52	**6.97%**	**SC** = 20.7 **Non-SC** = 25.0

Table 1. Continued

Li, Chun-Wei	2019	Asia	China	Interdisciplinary cross-sectional, cohort, and intervention study	102	68.65	49%	AWGS	Not reported	56	11	9	**81.82%**	**SC** = 21.44 **Non-SC** = 24.69
Okamura, Takuro	2019	Asia	Japan	Cross-sectional	391	72.4	52.4%	AWGS	Not reported	55	391	55	**14.06%**	**SC** = 21.1 **Non-SC** = 24.2
Murata, Yuko	2018	Asia	Japan	Cross-sectional	288	74.2	52.4%	AWGS	Outpatient clinic	88	288	88	**30.56%**	SC = 22.2 Non-SC = 24.2
Han, PeiPei	2017	Asia	China	Cross-sectional	711	**Non-SC** = 66.33 **SC** = 72.71	49%	AWGS	Questionnaire; combination of self-reporting and physician diagnosis	77	80	18	**22.50%**	**SC** = 22.35 **Non-SC** = 25.55
Morikawa, Yoshinobu	2021	Asia	Japan	Cross-sectional	161	65.9	48%	AWGS	Current treatment with oral hypoglycemic agents or insulin or FPG > 126 mg/dL	31	161	31	**19.25%**	**SC** = 21.1 **Non-SC** = 25.8
Sugimoto, Ken	2020	Asia	Japan	Observational longitudinal study	588	70	59%	AWGS	HbA1c, data taken from patient visits	46	588	46	**7.80%**	24.7
Chen, Fenqin	2020	Asia	China	Cross-sectional	1427	> 60	37%	AWGS, 2019 criteria	Clinic visit, questionnaire	148	1427	148	**10.37%**	Not reported
Fung, Foon Yin	2019	Asia	Singapore	Longitudinal	387	68.3	53%	EWGSOP, AWGS	Patient's electronic medical records (EMR)	106	387	106	**27.39%**	Not reported
Lim, Hee-Sook	2018	Asia	Korea	Cross-sectional	3492	68.8	53%	Not reported; data from KNHANES	Data from KNHANES	1373	340	137	**14.70%**	**SO** = 25.1 (male); 26.7 (female) **SC** = 23.4 (M); 21.0 (F) **No-SC** = 22.0 (M); 22.8 (F)

Table 1. Continued

Hispanic													
Souza, Anelza Biene Farias	2019	Hispanic	Brazil, Amazon	Cross-sectional	1078	**Non-SC** = 69 **SC** = 79 (median)	20.8%	EWGSOP	Self-reported or FPG > 126 mg/dl or HbA1c > 6.5%	101	245	35	14.29%	**SC** = 28.7 **Non-SC** = 23.5 (median)
Beretta, Mileni V.	2020	Hispanic	Brazil	Cross-sectional	610	71.35	49%	EWGSOP	Self-reported, hospital check-up	237	306	93	30.39%	Not reported
Freitas, Veronica Porto de	2018	Hispanic	Brazil	Cross-sectional	76	No average listed, all adults > 60 years	42%	EWGSOP	Self-reported, questionnaire	15	16	3	18.75%	Not reported
Trierweiler, Heloisa	2018	Hispanic	Brazil	Cross-sectional	166	**T2DM:** 65.84 **No T2DM:** 65.92	28.92%	ALM/BMI ratio and handgrip strength	Questionnaire or current use of diabetes medication	15	83	13	15.66%	**T2DM** = 28.16 **Non-T2DM** = 25.96
Manrique-Espinoza, Betty	2017	Hispanic	Mexico	Cross-sectional	543	76.1	47.30%	EWGSOP	Not reported	198	66	19	28.79%	N/A
Caucasian														
Dodds, Richard M.	2020	Caucasian	UK (England, Wales, Scotland)	Cross-sectional	499,046	**SC** = 59.9 **No SC** = 56.3	45.55%	EWGSOP2	UK Biobank data	26,671	53,442	4985	10.29%	**SC** = 28.1 **Non-SC** = 27.4
Churilov, Irina	2021	Caucasian	Australia	Cross-sectional	300	63 (median)	51.70%	EWGSOP, 2018	Prior history of T2DM; inpatient hospital visit	44	46	11	23.91%	**SC** = 21.8 **SC + T2DM** = 22.9
Landi, Francesco	2016	Caucasian	Italy	Cohort study	332	86.1	32.30%	EWGSOP	Self-report via MDS-HC form	101	97	36	37.11%	**SC** = 24.3 **Non-SC** = 26.7

AWGS—Asian Working Group for Sarcopenia; *EWGSOP*—European Working Group on Sarcopenia in Older People; *T2DM*—type II diabetes mellitus; *SC*—sarcopenia; *SO*—sarcopenic obesity

relationship between the two conditions. Moreover, in this meta-analysis, though sarcopenia and diabetes appeared more prevalent in Asian populations compared with other ethnic groups at a lower BMI, this does not necessarily translate to a stronger sarcopenia-diabetes relationship when the two conditions are analyzed together.

Worldwide, there is increased homogenization in the presentation, trends, and prevalence of comorbid metabolic diseases, a phenomenon we will call the modern-day global metabolic syndrome. This is likely a result of increasing similarities in lifestyle and diet trends, reinforced by an increasingly technological, interconnected modern landscape: More frequent and longer periods of sedentation with less frequent and shorter periods of physical activity, diets high in processed ingredients, sugar, and empty calories, and heightened, chronic feelings of anxiety, pressure, and stress. Though it is possible that genetic variations shared by similar ethnic groups may contribute to altered metabolic patterns (for instance, some increasing metabolic thrift while others decreasing it and thus predisposing some groups to certain diseases over others), these differences are superseded when considering the complex, reciprocal, and inevitable interplay of multiple co-occurring metabolic morbidities in a modern landscape.

Study Limitations

A prominent limitation in this study is the lack of data from the African, as well as Hispanic and Caucasian study groups. Out of the 5 African studies obtained from an initial keyword search, none of the studies met this study's inclusion criteria; consequently, the group had to be removed from the meta-analysis due to lack of available data. The lack of sufficient data may be due to the lack of access to adequate medical care and documentation in these regions. Moreover, some groups had more available data compared to others. Out of the 26 selected studies, 18 of these studies were from Asian countries; 5 studies were included in the Hispanic group and 3 studies were selected for the Caucasian group. Within the 18 Asian studies, 7 of these were conducted in Japan. Further research would greatly benefit from the availability of more sarcopenia and diabetes studies conducted in each of these groups.

Great variability in sample size may have contributed to non-negligible in-group variability. Sample sizes ranged from 76 participants to 499,046 (a national cross-sectional study). Given the current paucity of information, future studies are advised to draw from a larger sample size and should strive to increase the number of studies included, if or when available. Inclusion criteria should be more stringent to address limitations due to non-negligible variations that were observed in this study.

Conclusion

This meta-analysis further supports the previously established relationship between sarcopenia and diabetes. This meta-analysis has shown that, although differences in the prevalence of sarcopenia and diabetes have been demonstrated, ethnicity is not a determining factor in the strength of the sarcopenia-diabetes relationship among aged populations. Both sarcopenia and diabetes affect a substantial portion of the world population and are major contributors to increasing healthcare costs and decreased quality of life. Both sarcopenia and diabetes are becoming increasingly prevalent as populations age and undergo increased homogenization in modern lifestyle and diet transitions (which may be responsible for a phenomenon we call the modern-day global metabolic syndrome).

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Ethics

Ethics Committee Approval: Our article is a review/meta-analyses of previously published research.

Informed Consent: We did not conduct or perform any research involving patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.W., M.P., Design: R.W., M.P., Data Collection or Processing: R.W., Analysis or Interpretation: R.W., M.P., Literature Search: R.W., M.P., Writing: R.W., M.P.

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ORIGINAL RESEARCH

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Does Osteoporosis Treatment Choice Change the Prevalence or Course of COVID-19 in Older Adults?

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Abstract

Objective: This study aimed to investigate whether the prevalence or course of Coronavirus disease-2019 (COVID-19) changes according to osteoporosis treatment choice and to discuss the necessity of changing osteoporosis treatment during the pandemic especially in older adults.

Materials and Methods: We used the data of 828 subjects that we followed up with the diagnosis of osteoporosis in our outpatient clinic in the last two years. Patients were divided into four groups according to the osteoporosis treatment they received (alendronate, denosumab, teriparatide, intravenous zoledronic acid). Treatments for osteoporosis, treatment durations, and COVID-19 evaluations were obtained from electronic file records retrospectively. Symptomatology, diagnostic methods, polymerase chain reaction (PCR) results, and radiological findings of computerized tomography scans, treatments of the patients who had COVID-19 were noted.

Results: Fifty-two (6.2%) patients had been diagnosed with COVID-19. Between osteoporosis treatment groups, there were no significant differences in terms of COVID-19 prevalence, symptomatology, PCR results, radiological findings, treatments, and outcomes.

Conclusion: To the best of our knowledge, there is no clear evidence that osteoporosis treatment affects the course of COVID-19. In our study, we could not find a relationship between the actual treatments used for osteoporosis, and the prevalence or course of COVID-19. So during the COVID-19 outbreak, it is more crucial to emphasize the importance of the treatment continuity than changing modality for osteoporosis. Considering the burden of osteoporosis in the older population, the continuation of osteoporosis treatment needs to be prioritized during the COVID-19 pandemic.

Keywords: Osteoporosis, COVID-19, aged, immunosenescence

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) caused the worldwide pandemic Coronavirus disease-2019 (COVID-19) started in late 2019 and is ongoing. The virus is known to reveal a wide range of symptoms, from acute respiratory infections to severe multi-organ insufficiency resulting in death. The mortality rates are higher above the age of 80, which may be due to the presence of comorbidities and changes in immunity. Also, the course of COVID-19 can be different in older adults (1).

Osteoporosis is a public health problem characterized by reduced bone mineral density and increased fracture risk. During the COVID-19 pandemic, factors predisposing bone and muscle loss, such as inflammation, immobilization, hospitalization, and home isolation, are increased, especially in the elderly, leading to fragility and hip fractures. The one-year mortality rate due to osteoporotic hip fractures in the geriatric population was 20%, but this rate has increased to 36% with the COVID-19 pandemic (2).

Osteoporosis treatment regimens may cause immune system dysregulation, which may lead to reconsidering treatment options in the elderly during the COVID-19 pandemic. Bisphosphonates, specifically alendronate, one of the most commonly used agents in osteoporosis treatment, can cause monocyte/macrophage migration inhibition in addition to

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suppressing antigen presentation and inhibiting the production of a variety of bone-resorbing cytokines including tumor necrosis factor-α (TNFα), IL-1β, and IL-6 (3). Zoledronic acid can act as an immunostimulant which could increase gamma/delta (γδ) T-cell expansion or a dendritic cell modulator which possibly can change the immune regulation. As a result, the number of natural killers increases, explaining why approximately 50% of patients under zoledronic acid treatment experience an acute phase reaction (4). Furthermore, denosumab, a human monoclonal antibody with a high affinity to RANKL (receptor activator of nuclear factor K-β ligand), can act as an immune system modulator. The RANKL/RANK system takes place in lymph-node development, lymphocyte differentiation, dendritic cell survival, and T-cell activation. So denosumab treatment may modulate the immune response to viral infections (5). Teriparatide (recombinant human parathyroid hormone 1-34) is an anabolic agent for osteoporosis treatment, leading to the expansion of regulatory T-cells. It is also known that teriparatide treatment can increase peripheral hematopoietic stem cells in post-menopausal women (6).

Herein, we aimed to examine whether the prevalence or course of COVID-19 changes according to the preferred agent in the treatment of osteoporosis. Considering the effects of the agents used in the treatment of osteoporosis on the immune system, we aimed to answer the necessity of the treatment change during the pandemic, especially in older adults.

Materials and Methods

This cross-sectional study was approved by the institutional review board of Hacettepe University with the number of 2021/11-32 and was conducted in geriatric outpatient clinics of the Hacettepe University Medical Faculty Hospital, Ankara, Turkey.

A total of 828 individuals aged 65 years and older, who were admitted to geriatric outpatient clinics in the last two years (January 2019-December 2020) before the outbreak of the pandemic and receiving osteoporosis treatment were included in the study. Patients' age, gender, comorbidities, osteoporosis treatment, treatment durations, and COVID-19 evaluations were obtained from the hospital's electronic file records. Patients were divided into 4 groups according to the osteoporosis treatment they received (alendronate, denosumab, teriparatide, intravenous zoledronic acid). Symptomatology, diagnostic methods, polymerase chain reaction (PCR) findings, and radiological computed tomography (CT) scan findings of the patients who had COVID-19 were recorded. Individuals who had vitamin D deficiency, end-stage malignancy, or renal disease and take immune-suppressive treatment were excluded.

Statistics

The data collected were analyzed by using SPSS v. 23.0 (SPSS, Turkey). Categorical variables were presented as counts and percentages (n/%). Data distribution characteristics were evaluated with the Kolmogorov-Smirnov test. Abnormally distributed variables were presented as median [interquartile range (IQR)]. The chi-square test or Fisher's Exact tests were used for intergroup comparisons of categorical variables. Kruskal-Wallis test was used to compare numerical parameters with more than two categorical data. Post-hoc analysis was performed to determine the origin of the significance. Bonferroni correction was performed while calculating the p-value of the significant comparisons. A p-value of <0.05 was considered significant.

Results

A total of 828 patients were examined. One hundred fourty-one (17.1%) of the patients were male, and 687 (82.9%) were female. The median age of the sample was 78 (IQR: 10), while the median age was lower in the alendronate group ($p<0.001$). The prevalence of diabetes mellitus, dementia, and pulmonary diseases were higher in the zoledronic acid group. The prevalence of chronic kidney disease was higher in the denosumab group. Demographic features and the prevalence of comorbidities are presented in Table 1.

A total of 52 (6.2%) patients were diagnosed with COVID-19. When patients were divided into 4 groups according to their osteoporosis treatments, COVID-19 prevalences were similar. In the alendronate group, there were 8 patients diagnosed with COVID-19, in the denosumab group 14 patients, in the teriparatide group 3 patients, in the zoledronic acid group 27 patients. Fourty-six (5.5%) of the COVID-19 patients had positive PCR results, while 6 (0.7%) of the patients were negative but clinically accepted as COVID-19. CT was not performed in 14 (1.6%) patients, 11 (1.3%) of patients had no particular finding in thorax CT, while 2 (0.2%) of them had unilateral, 20 (2.4%) of them had bilateral involvement, and 5 (0.6%) of them had atypical CT findings. Also, there was no significant difference in radiological findings between groups. The patients were divided into three groups according to COVID-19 symptoms: Mild, moderate, and severe. There was no difference regarding the COVID-19 symptoms according to the osteoporosis treatment they received. Only 3 (0.3%) patients had severe symptoms. Patients were divided into five groups for COVID-19 evaluation. Most of the patients survived the disease at home. Only 1 (0.1%) patient died in the teriparatide group. There was no statistical difference between the groups regarding COVID-19 evaluation. The relationship between osteoporosis treatment and COVID-19 evaluation is shown in Table 2.

The median treatment duration for alendronate was 15 (IQR: 10) months, while it was 14 (IQR: 12) months for denosumab,

Table 1. Distribution of groups in terms of age, gender and comorbidity

		Alendronate	Denosumab	Teriparatide	Zoledronic acid	p-value
Age [median (IQR)] (year)		76 (10)	78 (10)	78 (11)	79 (10)	**p<0.001**
Sex (n) (%)	Female	167 (20.1%)	152 (18.3%)	78 (9.4%)	290 (35%)	**p<0.001**
	Male	34 (4.1%)	3 (0.3%)	4 (0.4%)	100 (12%)	
Comorbidities (n) (%)	DM	70 (8.4%)	37 (4.4%)	16 (1.9%)	101 (12.1%)	**p=0.024**
	HT	150 (18.1%)	110 (13.2%)	54 (6.5%)	267 (32.2%)	p=0.353
	HL	28 (3.3%)	21 (2.5%)	5 (0.6%)	63 (7.6%)	p=0.083
	Dementia	12 (1.4%)	37 (4.4%)	11 (1.3%)	75 (9%)	**p<0.001**
	Malignancy	8 (0.9%)	17 (2%)	4 (0.4%)	25 (3%)	p=0.069
	CKD	1 (0.1%)	26 (3.1%)	-	4 (0.4%)	**p<0.001**
	Pulmonary diseases	20 (2.4%)	2 (0.2%)	7 (0.8%)	51 (6.1%)	**p<0.001**
	CAD	33 (3.9%)	16 (1.9%)	10 (1.2%)	63 (7.6%)	p=0.248
	Rheumatologic diseaese	6 (0.7%)	10 (1.2%)	5 (0.6%)	17 (2%)	p=0.412

DM: Diabetes mellitus, HT: Hypertension, HL: Hiperlipidemia, CKD: Chronic kidney disease, CAD: Coronary artery disease, IQR: Interquartile range

Table 2. The relationship between osteoporosis treatment and COVID-19 evaluation

		Alendronate	Denosumab	Teriparatide	Zoledronic acid	Total
COVID-19 symptomatology [n (%)]	Not have disease Mild symptoms Moderate symptoms Severe symptoms	193 (23.3%) 6 (0.7%) 0 2 (0.2%)	141 (17%) 9 (1%) 5 (0.6%) 0	79 (9.5%) 1 (0.1%) 1 (0.1%) 1 (0.1%)	363 (43.8%) 20 (2.4%) 7 (0.8%) 0	776 (93.6%) 36 (4.2%) 13 (1.5%) 3 (0.3%)
p-value		0.701	0.639	0.165	0.432	
COVID-19 treatment [n (%)]	No treatment Home treatment Hospitalized NIV ICU Death	193 (23.3%) 6 (0.7%) 0 0 2 (0.2%) 0	141 (17%) 10 (1.2%) 4 (0.4%) 0 0 0	79 (9.5%) 1 (0.1%) 1 (0.1%) 0 0 1 (0.1%)	363 (43.8%) 19 (2.2%) 7 (0.8%) 1 (0.1%) 0 0	776 (93.6%) 36 (4.2%) 12 (1.3%) 1 (0.1%) 2 (0.2%) 1 (0.1%)
p-value		0.701	0.835	0.165	0.853	
PCR findings [n (%)]	Not evaluate Positive Negative	193 (23.3%) 8 (0.9%) 0	141 (17%) 12 (1.4%) 2 (0.2%)	79 (9.5%) 3 (0.3%) 0	363 (43.8%) 23 (2.7%) 4 (0.4%)	776 (93.6%) 46 (5.3%) 6 (0.6%)
p-value		0.267	0.707	0.519	0.442	
Radiological signs [n (%)]	Not have radiology Not have pathologic signs Unilateral pathologic signs Bilateral pathologic signs Atypical signs	5 (0.6%) 2 (0.2%) 0 1 (0.1%) 0	3 (0.3%) 3 (0.3%) 1 (0.1%) 4 (0.4%) 3 (0.3%)	1 (0.1%) 1 (0.1%) 0 1 (0.1%) 0	5 (0.6%) 5 (0.6%) 1 (0.1%) 14 (1.6%) 2 (0.2%)	14 (1.6%) 11 (1.2%) 2 (0.2%) 20 (2.2%) 5 (0.5%)
p-value		0.092	0.322	0.971	0.313	
COVID-19 diagnosis [n (%)]	Diagnosed Not diagnosed	8 (0.9%) 193 (23.3%)	14 (1.6%) 141 (17%)	3 (0.3%) 79 (9.5%)	27 (3.2%) 363 (43.8%)	52 (6.4%) 776 (93.6%)
p-value		0.205	0.250	0.383	0.476	

COVID-19: Coronavirus disease-2019, NIV: Non-invasive ventilation, ICU: Intensive care unit, PCR: Polymerase chain reaction

15 (IQR: 7.25) months for teriparatide, and 17 (IQR: 11) months for zoledronic acid. In the zoledronic acid group, a significant difference was found between treatment durations and COVID-19 evaluation, as shown in Table 3 (p=0.024).

Discussion

The COVID-19 outbreak caused impairment in both the treatment and follow-up of many chronic diseases, especially in geriatric population. Physicians may consider treatment modification of chronic diseases such as osteoporosis since COVID-19 has various effects on the immune system. There are a few studies focusing on COVID-19 outcomes who were receiving anti-osteoporosis drugs. In this study, we considered the older population.

During the early stages of SARS-CoV-2 infection, lymphopenia, neutrophil count increase, depletion of both CD4+ and CD8+ T-cells, reducing T-cell receptor repertoires occurs as the virus enters the cell. Tissue-resident dendritic cells (DC), especially in the respiratory tract, get infected. Infection of DC causes a massive immune reaction response in COVID-19. An acute increase of serum levels of inflammatory mediators, such as IL-6, C-reactive protein, interferon-γ (IFN-γ), IFN-γ induced protein 10 (IP-10, or CXCL-10), TNF-α, IL-1β, IL-8, monocyte chemotactic protein (MCP)-1 (CCL2 chemokine ligand 2), and MCP-3 can be seen during the course known as the cytokine storm (7). Also, IFN- γ release from infected cells causes expansion of gamma/delta (γδ) T-cells. γδ T-cell expansion is associated with higher anti-SARS-CoV IgG titers. Toll-like receptors (TLR) play a crucial role in recognizing the strategic parts of the viruses by the antigen-presenting cells. In older individuals, both the TLR expression and downstream signaling are impaired, higher levels of proinflammatory cytokines IL-6, IFN-γ, and TNF-α, and lower T-cell counts (CD8+ and CD4+ T lymphocytes) are seen in the peripheral blood named as inflammaging, and due to immunosenescence, decreasing number of circulating competent B-cells, increasing terminally differentiated and senescent memory CD27 B-cells can be seen. They are the reasons for the severe course of COVID-19 in older population (8,9).

When the relationship of zoledronic acid with the immune system is examined, it was seen that it might inhibit the prenylation of small GTPases, which can cause endosomal exocytosis blockage in the DC. Thus it may lead to a T-cell expansion and increased natural killer cell activity (4,10,11). Some studies showed a decrease in serum levels of IL-2, IL-7, IL-12, and IL-15 following zoledronic acid treatment. These cytokines are responsible for T-cell activation, differentiation, and proliferation. As a result, T-cell reduction was observed in the bone marrow. In rat model studies, changes in the proportion of CD3+ T-cells and ϒδ T-cells in peripheral blood have been shown after zoledronic acid treatment (12). It was shown that preexisting use of zoledronic acid was associated with a reduced incidence of COVID-19 compared to oral bisphosphonate or denosumab regardless of treatment duration. The authors attributed this result to the protective effect of zoledronic acid on DC. And they emphasized that this protective effect prevents the progression of COVID-19 because it causes immune stimulation of T-cell expansion and enhanced activity of natural killer cells (13). In our study, the duration of zoledronic acid use was longer in patients who did not have COVID-19, thus, the protective effect of zoledronic acid treatment against COVID-19 can be mentioned.

Another bisphosphonate used in the treatment of osteoporosis is alendronate. It can cause increased neutrophil counts by reducing serum TNFα, IL-1β, and IL-6 and can inhibit monocyte-macrophage migration and suppress antigen presentation. Alendronate was found beneficial for patients with chronic idiopathic neutropenia associated with osteopenia-osteoporosis (14). In our study, we did not find a difference in the course of COVID-19 between individuals that were under bisphosphonates treatment and other treatment regimens.

Denosumab, a human monoclonal antibody, inhibits the RANKL. RANKL inhibition can lead to decreased activity of pro-inflammatory cytokines. Osteoprotegerin (OPG) is a receptor for RANKL and OPG/RANKL/RANK systems and was demonstrated in lymphoid tissue. It has a role in the development of T and B lymphocytes. In addition, denosumab is known to increase serious adverse events of infections, mainly of the ear, nose, throat, and gastrointestinal origin (5). Kyrgidis et al. (15) showed that denosumab administration could increase peripheral blood monocyte CD14 + in female patients, which is one of the causes of immunity changes with denosumab treatment (15). Although there are initial suspicions against denosumab

Table 3. The relationship between treatment durations and COVID-19 evaluation

	Alendronate Treatment duration (month)	Denosumab Treatment duration (month)	Teriparatide Treatment duration (month)	Zoledronic acid Treatment duration (month)
COVID-19 diagnosis (+)	15 (9.75)	14 (12)	15 (8)	17 (11)
COVID-19 diagnosis (-)	14.5 (12.25)	14 (10.25)	14 (-)	20 (13)
p-value	0.948	0.872	0.770	**0.024**

COVID-19: Coronavirus disease-2019

therapy, in the short report by Formenti et al. (16), it was reported that denosumab treatment did not pose any risk factors for COVID-19. Also, Atmaca et al. (17) showed that using anti-osteoporotic drugs in women did not alter the course of COVID-19 or the risk of mortality, and authors mentioned that anti-osteoporosis drugs are safe during the COVID-19 era. In the study in which the relationship of zoledronic acid with reduced risk of COVID-19 was shown, the same effect was shown with denosumab (13). In our research, most of the denosumab using patients suffered from mild COVID-19, and there was no significant difference with other therapies in the prevelance of COVID-19.

Teriparatide, a parathormon (PTH) analog, causes an increase in the number of regulatory T-cells in human peripheral blood (18). PTH receptor presence was previously shown in human mononuclear cells (19). Also, in rat model studies, teriparatide treatment was proven to cause YΔ T-cells to increase in the peripheral blood (12). In addition, exogenous PTH administration was shown to cause an increase in the numbers of circulating lymphocytes and neutrophils in rat models (20). However, the exact effect on the immune system in the chronic use of teriparatide is unknown. In our research, three of the patients that received teriparatide had suffered from COVID-19, one of them died, and the deceased patient had a previously diagnosed pulmonary disease. There was no increased risk compared to other treatments.

Study Limitations

We should also mention the limitations of the study; the retrospective design and the relatively low number of patients with COVID-19 can be defined as the limitations. In addition, other drugs, comorbidities, socio-economic status and social backgrounds of participants should be considered. Random selection of participants may have hindered significant results. Further studies with more specific groups are needed.

Conclusion

To the best of our knowledge, there is no clear evidence that osteoporosis treatment affects the course of COVID-19. Our study could not find a relationship between the current treatments used for osteoporosis and the prevalence or course of COVID-19. Therefore, during the COVID-19 outbreak, it is crucial to emphasize the importance of treatment continuity than changing the treatment modality for bone metabolism. Considering the burden of osteoporosis in older adults, the management of osteoporosis needs to be prioritized during the COVID-19 pandemic.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the institutional review board of Hacettepe University with the number of 2021/11-32 and was conducted in geriatric outpatient clinics of the Hacettepe University Medical Faculty Hospital, Ankara, Turkey.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H., Concept: M.H., M.G.H., Design: M.H., M.G.H., Data Collection or Processing: A.O.B., Z.Ş., Analysis or Interpretation: A.O.B., Ç.Ç., B.B.D., M.C., M.G.H., Literature Search: Z.Ş., Ç.Ç., Writing: M.H., B.B.D., M.C., M.G.H.

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ORIGINAL RESEARCH

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The Relationship of Sarcopenia with Geriatric Syndromes and Folate

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Abstract

Objective: Folates are essential for healthy cell division, growth and function. With the discovery that folate provides the proliferation and differentiation of muscle cells, the relationship between folate and sarcopenia has attracted the curiosity of researchers. Geriatric syndromes may have a common pathogenesis, as they are considered clinical conditions with common risk factors. Our aim in this study was to investigate the relationship of sarcopenia with geriatric syndromes and serum folate level.

Materials and Methods: The study population consisted of 287 patients (202 female) who were admitted to our geriatrics outpatient clinic for the first time and underwent a comprehensive geriatric assessment (CGA) during the one year between January 2018 and January 2019. Demographic information, chronic diseases, drugs used by the participants and their current chronic diseases, CGA results and laboratory findings of patients were recorded. Diagnosis of sarcopenia was made under the guidance of the European working group on sarcopenia in older people 2.

Results: Eighty-eight (31%) of the 287 patients were sarcopenic. While age, number of drugs, the frequency of chronic kidney disease and malnutrition were statistically significantly higher in patients with sarcopenia, mini-mental state examination score and serum folate levels were significantly lower (p=0.001, p<0.001, p=0.040, p<0.001, p=0.001, p=0.028; respectively). The result of univariate logistic regression analysis showed that sarcopenia was independently associated with folate [odds ratio: 0.926 (95%) confidence interval: 0.864-0.993, p=0.031]. Serum folate level in patients with malnutrition was also significantly lower (7.12±4.39, p=0.008).

Conclusion: Since sarcopenia is associated with malnutrition, they should be evaluated together. As we found that serum folate levels were lower in patients with both sarcopenia and malnutrition, we recommend that risky groups be supported with folate-rich foods or folic acid supplementation.

Keywords: Sarcopenia, folate, folic acid, malnutrition, geriatric syndrome

Introduction

Geriatric syndromes are clinical conditions and symptoms with common risk factors that mostly occur in the elderly with atypical symptoms and cannot be fully explained by the definition of "disease" (1). Geriatric syndromes, such as malnutrition, cognitive impairment, depression, sarcopenia and polypharmacy causes increased mortality, morbidity and health care costs (2).

Sarcopenia is a medical condition that increases in frequency with aging and was defined in the European working group on sarcopenia in older people 2 (EWGSOP2) as a decrease in both muscle strength and muscle mass. It may occur due to secondary reasons or may occur due to aging on its own (3). Decreased appetite and inadequate food intake that occur with aging can cause malnutrition and subsequently sarcopenia (4). Sarcopenia is accepted as one of the pathophysiological causes of frailty and may cause adverse outcomes such as the increased risk of falling, dependency, disability, poor quality of life and death (5). EWGSOP2 recommends screening for sarcopenia with the 5-item SARC-F questionnaire, which has been translated and validated into many different languages (6). Since the pathophysiology, diagnosis and treatment methods are still not clear, studies on sarcopenia are going on. The concept of sarcopenia still contains

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uncertainties. Sarcopenia, which is considered a geriatric syndrome by some, is placed in a separate class by others. Geriatric syndromes may have a common pathogenesis, as they are considered clinical conditions with common risk factors. If the relationship between sarcopenia and other geriatric syndromes can be found, common pathophysiological pathways can be revealed and existing uncertainties can be clarified.

Folate is one of the water-soluble vitamins that are necessary for life. Folate, also known as vitamin B9 and folacin, has a critical role in the metabolism of nucleic acid precursors and several amino acids. Folate cannot be synthesized in humans and is present in many foods such as green leafy vegetables, fruits, beans, eggs, meat, and dairy products. The synthetic form, which is better absorbed, is folic acid (7). Folate is necessary for cell division, growth and function. It is vital for the musculoskeletal system as well as for all tissue and organ systems. Studies in the literature have shown that folic acid has an important role in myogenesis and promotes skeletal muscle development through the protein kinase B (Akt) signaling pathway (8). Folate deficiency is common, especially in the elderly and the most common causes of folate deficiency are decreased intake, decreased absorption, increased demand, congenital disorders and certain medications (9). With the discovery of the important effects of folate on the musculoskeletal system, the relationship between sarcopenia and folate has been a subject of interest. Our aim in this study was to investigate the association of sarcopenia with chronic diseases, geriatric syndromes and folate.

Materials and Methods

Study Population

Our study is a retrospective cross-sectional study. The study population consisted of 287 patients (202 female) who were admitted to our geriatrics outpatient clinic for the first time and underwent CGA during the one-year between January 2018 and January 2019. Demographic information, drugs used by the participants and their current chronic diseases, CGA results and laboratory findings of patients were recorded. The data of the patients were obtained from the patient files.

Ethics

Ethical approval was obtained from the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (date: 09.09.2020-number: 117344).

Comprehensive Geriatric Assessment

The number of drugs used by the patients was recorded. Nutritional status was evaluated with mini-nutritional assessment (MNA) long form and patients with a score of less than 23.5 of 30 points were considered risky for malnutrition (10). The group named "with malnutrition" in the study corresponded to being at risk of malnutrition. Functional levels of the patients were evaluated with the Katz basic activities of daily living scale and the Lawton & Brody instrumental activities of daily living scale (11,12). Mini-mental state examination (MMSE) scale was used to determine cognitive impairment (13). The possibility of depression was evaluated with the short form of the geriatric depression scale (GDS) (14). Urinary incontinence was defined as any involuntary urinary incontinence complaint within the last one year (15).

Laboratory Findings

Folate, total protein, albumin, hemoglobin and creatinine values of the patients at admission were recorded from the patient files. The blood taken for the biochemical parameters we examined in our study was taken into a gel tube in the morning after 8 hours of fasting and analyzed by ELISA method ng/mL for folate, g/dL for total protein, g/dL for albumin, mg/dL for creatinine, pg/mL for vitamin B12, ng/dL for vitamin D and g/dL for hemoglobin were used as units.

Diagnosis of Sarcopenia

In clinical practice, handgrip and bioelectrical impedance analysis (BIA) measurements are made for all patients who admit to our geriatrics outpatient clinic for the first time. The diagnosis of sarcopenia was made under the guidance of EWGSOP2 and patients with low muscle strength and muscle mass were included in the sarcopenia group (3). Skeletal muscle strength was evaluated with a hand dynamometer (Takei® TKK 5401 model, Takei Scientific Instruments Co., Tokyo, Japan). Both of the hands were measured 3 times with a 1-minute rest period and the greatest value was recorded. Cut-off value for the handgrip test was considered as 27 kg for men and 16 kg for women. A BIA device (Tanita Body Composition Analyzer® TBF-300 model, Tanita Co., Tokyo, Japan) was used to evaluate skeletal muscle mass. Skeletal muscle mass index (SMMI) was calculated with SMM/height^2 (kg/m^2) formula. As specified in EWGSOP2, SMMI cut-off value was considered as 7.0 kg/m^2 for men and 5.5 kg/m^2 for women.

Only the data of the patients who were able to cooperate with the tests and who completed the BIA and hand grip measurement were included in the study. Patients under 65 years of age, with a history of trauma and infection in the last month, with a diagnosis of any terminal disease or malignancy were not included in the study in order to exclude acute events as they may reduce the reliability of the tests. Since steroid use can lead to myopathy, it was among the exclusion criteria. Patients with stage 3, 4 or end-stage chronic kidney disease and receiving a folic acid replacement were excluded from the study because it could affect serum folate levels, also patients with joint amputation were not included because it would affect the result of BIA.

Statistics

Demographic information, comprehensive geriatric assessment results and chronic diseases were summarized with descriptive statistics. Categorical variables were expressed as numbers and percentages. Normally distributed continuous variables were presented as mean ± standard deviation, and skewed distributed continuous variables were presented as median and interquartile ranges. The chi-square test was used for comparing categorical variables. The Student's t-test was used for normally distributed continuous variables and Mann-Whitney U test was used for continuous variables that did not show normal distribution. The relationship between sarcopenia and folic acid was analyzed with the univariate logistic regression (LR) method. The Spearman correlation coefficient was used to assess the correlation between folate, muscle strength, muscle mass and MNA. The Spearman correlation coefficient was interpreted according to r level as follows: <0.19 (very weak), 0.2-0.39 (weak), 0.4-0.59 (moderate), 0.6-0.79 (strong), and >0.8 (very strong). P-value less than 0.05 was considered as statistically significant. SPSS-22 statistical program was used for the statistical analysis.

Results

Eighty-eight (31%) of the 287 patients were sarcopenic. 67% of patients with sarcopenia and 72% of patients without sarcopenia were female (p=0.410). Age, a number of drugs, number of chronic diseases, the frequency of chronic kidney disease, atrial fibrillation and malnutrition were statistically significantly higher (p=0.001, p<0.001, p<0.001, p=0.040, p=0.18, p<0.001; respectively), MNA and MMSE score was significantly lower in patients with sarcopenia (p<0.001, p=0.001; respectively). While serum folate level was 7.01±4.63 in patients with sarcopenia, it was 8.34±4.25 in patients without sarcopenia, and this difference was statistically significant (p=0.028). Demographic data, chronic diseases, geriatric assessment scores and laboratory findings of patients with/without sarcopenia are given in Table 1.

As a result of univariate LR analysis, a significant association was found between sarcopenia and folate [odds ratio (OR) 0.926 (95%) confidence interval 0.864-0.993, p=0.031]. Correlation analysis showed a very weak correlation between folate and muscle strength (p=0.005, r=0.175), and a significantly weak correlation between folate and muscle mass and MNA (p<0.001, r=0.285; p<0.001, r=0.256, respectively).

Serum folate level (7.12±4.39) in patients with malnutrition was statistically significantly lower than in patients without malnutrition (8.57±4.29) (p=0.008) (Table 2).

Discussion

Our study revealed the relationship between sarcopenia and folate, pointing to the trial of folate replacement in the prevention or treatment of sarcopenia, which is still uncertain in many respects. In our study, besides the relationship between sarcopenia and folate, the relationship between sarcopenia and other geriatric syndromes was also investigated. While there are many studies in the literature investigating the relationship between sarcopenia and only one geriatric syndrome, we wanted to plan a more comprehensive study examining several geriatric syndromes that we frequently encounter in clinical practice.

There are many studies in the literature showing that folic acid has an important role in myogenesis, especially in the proliferation and differentiation of muscle cells (16). Hwang et al. (17) examined the effects of folic acid on myogenesis with a cell study and found that folic acid induces the differentiation of myoblasts to multinucleated myotubes by activating the Akt signaling pathway. In another study by again Hwang et al. (17), it was emphasized that folate has an important role in both myoblast proliferation and differentiation and revealed that in folate deficiency, the cell cycle was interrupted, the number and length of myotubes were reduced and the differentiation phase was strongly affected due to genotoxic stress, so they concluded that folic acid is necessary for normal skeletal muscle development.

Revealing the positive effects of folate on muscle cells has brought a new perspective to sarcopenia. The relationship between sarcopenia and folate has been the focus of attention of many researchers and many studies have been published on this subject. In a cross-sectional study including 56 primary care patients (>65 years old) with diabetes mellitus folate levels were found to be significantly correlated with grip and leg strength (18). When we examined more recent studies examining the relationship between sarcopenia and sarcopenia-related nutrients, including folate, low serum folate level or folate intake was found to be associated with sarcopenia or its components, again in line with our study. In Yeung et al.'s (19) study higher folate intake was associated with both higher muscle mass and muscle strength. Greater intake of folate was correlated with improved functional outcome measurements in Behrouzi et al.'s (20) study. In a study conducted with 432 hospitalized patients (44 with sarcopenia), it was observed that red cell folate was significantly lower in patients with sarcopenia at admission (during acute illness) and at 6 weeks (recovery period) compared to the group without sarcopenia (21). In another study conducted with 1.606 community-dwelling older adult dietary pattern with high folate content (rich in fish, soybean products, potatoes, most vegetables, mushrooms, seaweeds, and fruits) has been clearly shown to be inversely associated with sarcopenia (22). Likewise in our study, serum folate level was significantly lower in the sarcopenia group (p=0.028). There was also a significant relationship between folate and hand grip strength and muscle mass, which are components of sarcopenia. On the contrary, in a Taiwan study involving 731 adults aged 65 and over, serum levels of vitamin D, vitamin B_{12} and folic acid,

Table 1. Demographic data, chronic diseases, comprehensive geriatric assessment scores and laboratory findings of patients with/without sarcopenia

	Total (n=287)	With sarcopenia (n=88)	Without sarcopenia (n=199)	p
Gender (female/male)	202/85	59 (67%)	143 (72%)	0.410
Age*	76.78±7.78	79.04±7.51	75.87±7.78	**0.001**
Number of drugs*	6.41±3.80	7.64±4.03	5.90±3.59	**<0.001**
Number of chronic diseases*	2.42±1.47	3.20±1.50	2.09±1.34	**<0.001**
Hypertension	210 (73%)	61 (69%)	149 (75%)	0.327
Diabetes mellitus	121 (42%)	44 (50%)	77 (39%)	0.074
Osteoporosis	81 (28%)	26 (30%)	55 (28%)	0.741
Chronic obstructive pulmonary disease	26 (9%)	10 (11%)	16 (8%)	0.366
Chronic kidney disease	17 (6%)	9 (10%)	8 (4%)	**0.040**
Cerebrovascular disease	32 (11%)	13 (15%)	19 (9%)	0.195
Ischemic heart disease	25 (8%)	6 (7%)	19 (9%)	0.450
Chronic heart failure	22 (7%)	7 (8%)	15(7%)	0.903
Atrial fibrillation	33 (11%)	16 (18%)	17 (8%)	**0.018**
Malnutrition	126 (44%)	63 (71%)	63 (31%)	**<0.001**
Urinary incontinence	44 (15%)	17 (19%)	27 (13%)	0.212
BADLs**	0 (0-2)	0 (0-2.5)	0 (0-2)	0.284
IADLs**	14 (10-17)	14 (10-17)	13 (9-16)	0.704
MNA*	20.69±5.93	22.03±7.80	27.5±6.41	**<0.001**
MMSE*	24.68±5.07	22.8±5.9	25.4±4.4	**0.001**
GDS**	4 (2-8)	5 (2-9)	4 (1-7)	0.127
Handgrip*	20.03±9.89	13.29±5.32	23.11±10.06	**0.001**
Muscle mass*	6.11±0.71	5.87±0.84	6.23±0.66	**0.016**
Folate (ng/mL)*	7.92±4.38	7.01±4.63	8.34±4.25	**0.028**
Vitamin B12 (pg/mL)*	436.6±198.4	457.4±220.3	430.5±189.9	0.601
Vitamin D (ng/dL)**	18.75 (6.08-29)	19 (8-29)	17 (4.8-29)	0.522
Total protein (g/dL)*	6.96±0.58	6.99±0.50	6.94±0.62	0.562
Albumin (g/dL)*	4.22±0.44	4.23±0.37	4.21±0.46	0.761
Hemoglobin (g/dL)*	12.16±2.25	11.96±1.54	12.56±1.57	**0.003**
Creatinine (mg/dL)*	0.93±0.36	0.93±0.35	0.94±0.35	0.872

BADLs: Basic activities of daily living, IADLs: Instrumental activities of daily living, MMSE: Mini mental state examination, GDS: Geriatric depression scale, Data are shown as *mean ± standard deviation (SD) or **median (interquartile intervals), significant p-values are bolded

Table 2. Laboratory findings of patients with/without malnutrition

	With malnutrition (n=126)	Without malnutrition (n=161)	p
Folate (ng/mL)	7.12±4.39	8.57±4.29	**0.008**
Total protein (g/dL)	6.98±0.58	6.94±0.59	0.525
Albumin (gr/dL)	4.20±0.46	4.24±0.41	0.465
Hemoglobin (g/dL)	12.08±1.85	12.23±2.51	0.594
Creatinine (mg/dL)	0.94±0.39	0.92±0.33	0.510

Data are shown as *mean ± standard deviation (SD), significant p-values are bolded

biochemical markers of nutritional status, were not significantly associated with sarcopenia (23). In our study, although a significant relationship was found between sarcopenia and folate, the OR for folate was found to be 0.926, that is, a value close to 1. For this reason, it would be appropriate to conduct studies with a larger number of patients in order to put forward this relationship more concretely.

The second mechanism in sarcopenia that occurs in folate deficiency can be considered as hyperhomocysteinemia due to folate deficiency. Since folate is involved in one-carbon metabolism as a precursor of cofactors, its deficiency causes increased homocysteine levels in plasma. Studies have shown that hyperhomocysteinemia causes many diseases, such as cardiovascular and neurodegenerative diseases, stroke and cancer by triggering oxidative stress and inflammation (24,25). Skeletal muscle weakness has also been implicated as one of the consequences of hyperhomocysteinemia. In the study of Veeranki et al. (26) on mice, it was shown that hyperhomocysteinemia causes skeletal muscle weakness by causing mitochondrial dysfunction. Swart et al. (27) found an association between high plasma homocysteine levels and reduced muscle strength and physical performance in older women. Homocysteine levels of the patients were not measured in our study, but folate deficiency induced hyperhomocysteinemia may be one of the contributors to sarcopenia in our study patients.

Malnutrition is a clinical condition defined as an imbalance in nutrient and/or energy intake and its frequency increases with aging (28). Malnutrition is found in the pathophysiology of sarcopenia and causes adverse outcomes similar to sarcopenia. Malnutrition and sarcopenia are in such a close relationship with each other that the clinical presentation that emerged in their association has begun to be called malnutrition-sarcopenia syndrome (29). In a 4-year follow-up study of 336 patients, it was shown that the risk of developing sarcopenia/severe sarcopenia is approximately fourfold higher in malnutrition and the researchers emphasized that malnutrition can be a strong predictor of the onset of sarcopenia (30). We also found a significant relationship between malnutrition and sarcopenia ($p<0.001$).

Researchers looking for an answer to the question of whether folate could be an indicator of malnutrition found different results in their studies. While Kozman et al. (31) reported that serum folate of less than 7.0 ng/mL indicates malnutrition, Soysal et al. (32) emphasized that folate levels are not associated with nutritional status. In our study, serum folate levels were found to be significantly lower in malnourished patients (7.12 ± 4.39, $p=0.008$).

Sarcopenia is common in patients with chronic kidney disease and many different mechanisms are implicated in sarcopenia in renal failure. These are chronic inflammation, metabolic acidosis, stimulation of the ubiquitin-proteasome system and hormones such as parathyroid hormone, glucocorticoid and angiotensin II (33,34). The uremic environment in chronic renal failure also disrupts the balance between skeletal muscle regeneration and catabolism (35). In a study including patients with chronic kidney disease stages 3-5 (not on renal replacement therapy), loss of appendicular skeletal muscle mass was found to be significantly related to the decline in glomerular filtration rate (36). Since folate metabolism may be affected in renal failure, we only included patients with stage 1 and 2 chronic kidney disease in our study. Despite the small sample size and only early-stage chronic kidney disease patients were included, the significant association we found between sarcopenia and chronic kidney disease is remarkable.

Studies have frequently revealed the association between sarcopenia and cognitive impairment. In a systematic review and meta-analysis in which Peng et al. (37) examined 15 studies, sarcopenia was found to be associated with an increased risk of cognitive impairment, thus they emphasized the importance of early diagnosis of sarcopenia to prevent cognitive impairment. Also in a cross-sectional study of 619 patients, the frequency of cognitive impairment was found to be significantly higher in patients with both possible and definitive sarcopenia (38). Likewise in our study MMSE score was statistically significantly lower in patients with sarcopenia. In the present study, sarcopenia was found to be associated with the number of medications. Likewise, in a study involving 1.502 participants from the Berlin aging study II, polypharmacy (use of 5 or more drugs daily) was found to be associated with sarcopenia (39). Researchers of a systematic review also found an association between sarcopenia and polypharmacy and the number of drugs in community-dwelling older adults, but not in hospitalized patients or nursing home residents (40). Studies have shown that the frequency of atrial fibrillation is increased in sarcopenic individuals, and the presence of sarcopenia increases 1-year mortality in atrial fibrillation. In our study, the frequency of atrial fibrillation was higher in sarcopenic individuals in line with the literature (41,42).

Diabetes mellitus can cause sarcopenia by accelerating the loss of muscle mass and strength and increasing the levels of inflammatory cytokines (43). In our study, the presence of diabetes mellitus was not found to be associated with sarcopenia ($p=0.074$). This may be due to the fact that the duration of diabetes mellitus and hemoglobin A1c levels of the patients we included in the study were not examined. The relationship between depression and sarcopenia has also been examined many times in the literature, and it has been concluded that sarcopenia is more common in depressive individuals due to physical inactivity and deterioration in oral intake, seen in depression. When viewed backward, sarcopenia may also cause depression by causing physical decline (44). We also found a

higher GDS score, which indicates the possibility of depression, in sarcopenic individuals, but we could not detect a significant difference between the two groups (p=0.127). This may be because the GDS indicates the possibility of depression and that clinical evaluation is essential for the diagnosis of depression. The relationship between sarcopenia and hypertension is still an issue that has not been clarified. While there are studies that found a relationship between sarcopenia and hypertension, there are also studies that did not find a relationship between them (45,46). When studies on this subject were examined, it was noticed that hypertension was associated with sarcopenic obesity rather than sarcopenia (47). In our study, the frequency of hypertension was not found to be increased in sarcopenic individuals, which is consistent with many studies (p=0.327). Although we expect sarcopenic patients to be affected in their daily and instrumental living activities, we did not find a significant difference between patients with and without sarcopenia in our study. This may be attributed to the fact that the study participants were clinically stable patients without advanced comorbidities.

Our study is important because we investigated the relationship of sarcopenia with several chronic diseases and geriatric syndromes. We showed that the frequency of malnutrition is increased in sarcopenic patients, and that serum folate levels are lower in both malnourished and sarcopenic individuals. This brought to mind the idea of folate supplementation in individuals at risk for malnutrition and sarcopenia.

Study Limitations

This study has some limitations. First, this study had a retrospective cross-sectional design, so it is not possible to determine causal relationships. And second, the fragility associated with sarcopenia was not among the geriatric syndromes evaluated in our study. This was because the study was retrospective and the fragility status was not recorded in the patients' files.

Conclusion

Since sarcopenia is associated with malnutrition, these two conditions should be evaluated together and when one of them is detected, the patient should be screened for the other. As we found that folate levels were lower in patients with both sarcopenia and malnutrition in our study, we recommend that risky groups be supported with folate-rich foods or folic acid supplementation.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (date: 09.09.2020-number: 117344).

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

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.B.K., Concept: H.Y., Design: B.B.K., Data Collection or Processing: B.B.K., Analysis or Interpretation: H.Y., Literature Search: H.Y., B.B.K., Writing: H.Y.

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ORIGINAL RESEARCH

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The Fear of Falls in the Older People Living in Nursing Home and the Factors Associated with Falls

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Abstract

Objective: This descriptive and correlational study was conducted to determine the prevalence of falls, fear of falling, and risk factors for falling in older adults living in nursing homes.

Materials and Methods: The population of the study was composed of older adults living in a nursing home located in the Central Anatolian Region. No sampling calculation was made in the study. All the older adults living in the institution were intended to be reached. The data of the study were collected using introductory information form, fall behavioral scale for older people, standardized mini-mental state examination (MMSE), timed up and go test (TUG), and Tinetti Balance and Gait Assessment (TBGA).

Results: The average age of the older adults included in the study was 77.5±8.8 and 44.2% of them were female. It was determined that the participants fell 1.9±1.08 times on average and 75.2% had the fear of falls. The changes in MMSE score accounted for 16.9% of the fear of falls and the number of falls in older adults ($F=11.001$; $p<0.001$; $R2=0.169$) and the changes in TBGA accounted for 15.8% of the fear of falls and the number of falls of the older adults ($F=10.166$; $p<0.001$; $R2=0.158$).

Conclusion: It was determined that the fear of falls and the number of falls were high in the older adults living in the institution. It was concluded that TUG, TBGA and MMSE were significant determinants in explaining the correlation between the fear of falls and the number of falls.

Keywords: Aging, older age, nursing home, falls, fear of falls

Introduction

It has been stated that according to the foresight of the World Health Organization approximately 1.2 million people will be at the age of 60 and over in 2025 and 80% of the elderly population to reach 2 million in 2050 would live in developing countries (1). It is estimated that the rate of the elderly population aged 65 and over, which was 8.8% in 2019, would reach 17.6% in 2050 in Turkey. Due to the traditional/cultural structure, elderly individuals in Turkey can live with their families or stay in nursing homes affiliated to the Republic of Turkey Ministry of Family and Social Services (ASHB), where the elderly with low income levels are cared for free of charge. Approximately 13,000 elderly individuals stay in nursing homes affiliated with ASHB (2). The increase in the elderly population brings some physical, psychological and social problems together with the ageing process.

Falls are the leading cause of injuries and death that is commonly seen in older people (3). It has been determined that one-third of the older adults the age of 65 and over experience falls at least once a year. It was determined in previous studies that fall risk increased with increasing age (4-7). It has been reported in the population-based prospective studies that the yearly fall rate in the elderly is 30-60%, the older adults have a fear of

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falls and recurrent falls have been observed in almost half of those who have fallen (6-8). It has been stated that 50% of the older adults who receive institutional care fall at least once a year, recurrent falls have been observed in 40% of them and the prevalence of falls in the institutional environment is three times greater than the prevalence of falls in the society (9). The prevalence of falls was found to be 34% in a study conducted in nursing homes in Turkey (10).

Falls in the elderly cause many outcomes ranging from simple treatable health problems to life threats. According to a study conducted in the USA, 10% of the older adults who fall apply to emergency services and 6% of them are hospitalized due to that reason (6). Also, the expenses of the treatment directly performed due to falls are on averagely 5% of the total health expenditures (6). These results indicate the importance of determining falls in older adults and the fall prevention/protection programs. As a matter of fact, protection from falls is among the national priorities of many countries (11). WHO is focused on raising fall awareness in society, identifying fall risks, and developing evidence-based fall prevention programs suitable for cultures and strategies including policy determination in order to prevent falls in older adults.

Studies have revealed that the determination of falls and fall prevention programs will decrease the incidence of falls by 6-33% (6,11-14). Maintaining the quality of life of the older adults, providing an active life for them, and protecting and promoting their health are among the main purposes for the older adults living in society and institutions. For this reason; it is important to determine the prevalence of falls, fear of falling, and fall risk factors in older adults living in nursing homes.

Materials and Methods

This descriptive and correlational study was conducted to determine the prevalence of falls, fear of falling, and risk factors for falling in older adults living in nursing homes. The research was carried out in a nursing home affiliated with the Ministry of Family and Social Policies in a province in the Central Anatolia Region. There is only one central nursing home in this province. The study was conducted in this nursing home. In this nursing home, no screening has been done about the physical characteristics of the elderly and their risk of falling before.

The population of the study was composed of older adults living in a nursing home located in the Central Anatolian Region. No sampling calculation was made in the study. All the older adults living in the institution were intended to be reached. The older adults who met the inclusion criteria and agreed to participate in the study were included in the study between January and June 2019. Between these dates, 127 older adults stayed in the nursing home. The study was completed with 113 participants who met the criteria and agreed to participate.

Inclusion Criteria

- The older adults aged 65 and over, who

- were able to communicate,

- had no physical walking problem,

- Those who did not make any changes in the medications used by the elderly person during the study were included in the study.

Exclusion Criteria

- Had hearing impairment, dementia, delirium

- Had deformity preventing walking and had used assistive devices for walking.

Data Collection

The data of the study were collected using introductory information form, fall behavioral scale for older people (FaB), standardized mini-mental state examination (MMSE), timed up and go test (TUG), and Tinetti balance and gait assessment (TBGA).

Introductory information form is composed of 10 questions including socio-demographic characteristics, health-disease characteristics and falls a history of the older adults (number of falls in the recent year, place of falls, reasons for falls etc.).

FaB was developed by Clemson et al. (15) in English and its Turkish reliability and validity study was conducted by Ekşi Uymaz and Nahcivan (16). It is a 4-point Likert scale including 30 items and 10 subscales. Possible minimum and maximum scores to be obtained from the overall scale and its subscales get a point between one and four and while high scores indicate the safe/protective behaviours related to falls, low scores indicate risky behaviours. According to the results of the reliability and validity study of the scale in its original language, Cronbach's Alpha coefficient is 0.84 (17).

MMSE; the reliability and validity study of the test, whose standardized version was performed by Molloy and Standish (17), was conducted by Güngen et al. (18). The test was developed to perform the short-term cognitive assessment in older adults, especially in the examination of delirium or dementia. While the minimum score on the scale is "0", its maximum score is "30". Zero-twelve points are assessed as "severe", 13-22 points as "moderate" 23-24 points as "mild" "cognitive disorder" and 25-30 points are assessed as "no cognitive disorder" (18).

TUG was applied to assess the functional capacities of the cases. A standard chair is used for the test. Firstly, patients are asked to sit in a chair. Then, they are asked to stand up and walk with regular steps at a 3-meter distance, the length of which was determined in advance, and turn back and sit on the chair at the end of 3 meters. The walking time of the patients during the test is determined with a stopwatch in seconds (19).

TBGA was developed by Tinetti (20) under the name of performance-oriented assessment of mobility problems in elderly patients to perform the assessment for patients with high fall risk and its Turkish validity and reliability study was conducted by Ağırcan (21). TBGA assesses balance and gait under 2 main titles: The first 9 questions are related to balance and the following 7 questions are related to gait. As a result of the assessment performed by observation, a total score of 18 points and below indicates high fall risk, 19-24 points indicate moderate fall risk, and 24 points and above indicate low fall risk (21).

The information form and the scales were filled out by the researchers using the face-to-face interview method and measurements. The materials needed to collect data were obtained by the researchers and they were placed in a suitable room in the nursing home. The older adults who agreed to participate in the study were assessed in this room during the time scheduled for them. The interviews were carried out between 10:00-12:00 and 14:00-15:00. Privacy was paid attention and the older adults were individually interviewed. In data collection, 2 interviews were performed with an elderly person and each interview lasted for 25 minutes.

Statistics

Data were analyzed using statistical packaged software IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, New York, USA). Participants' demographics and clinical characteristics were summarized using either means and standard deviations, or frequencies and percentages as appropriate. Comparisons of baseline characteristics between fallers and non-fallers were made using One-Way ANOVA or non-parametric Mann-Whitney U tests as deemed appropriate. Multiple linear regression analysis assumptions are based on the relevant literature (15-17). In the normal distribution of numerical variance data, the Shapiro-Wilk normality test was used. According to this test (statistic =0.992; df =126; p=0.731) residuals are normally distributed. The data show homoscedasticity relative to the scatter plot. According to the normal P-P Plot of Regression and Scotter plot of Regression tests, linearity was achieved. Since the Durbin-Watson =1.883 value obtained from the study is between 1.5 and 2.5, there is no autocorrelation. Tolerance values are above 0.2 and VIF values are less than 10, so there is no multicollinearity. Multiple linear regression analysis was performed to determine the effects of age, and sex on the fall scores. For the model statistics in the regression analysis tables; F, p, and adjusted R^2 values, as well as the t statistics and p-values of beta coefficients, are given. The descriptive statistics were expressed in units (n) and percentages (%). The statistical significance level was accepted as $p<0.05$.

Ethical Considerations

Ethical Committee Approval from the Ethical Committee of Erciyes University Social and Human Sciences and institutional permission from the nursing home were obtained (2011, KAEK-80). Also, the older adults included in the study were informed and their written and verbal consent was received.

Results

The average age of the older adults included in the study was 77.5±8.8 and 44.2% of them were female. It was determined that the participants fell 1.9±1.08 times on average and 75.2% had the fear of falls (Table 1).

It was determined that 41.6% of the older adults fell at least once in the recent year, 31% of them fell while walking in and out of the building, and they fell mostly due to loss of balance and tripping (Table 2).

The difference in MMSE score accounted for 16.9% of the fear of falls and the number of falls in older adults ($F=11.001$; $p<0.001$; $R^2=0.169$) and the difference in TBGA accounted for 15.8% of the fear of falls and the number of falls of the older adults ($F=10.166$; $p<0.001$; $R^2=0.158$). The decrease in MMSE (β-3.617 and -1.655) and TBGA (β-4.107 and -1.428) scores increased the fear of falls and the number of falls ($p<0.001$). The difference in TUG score accounted for 10.5% of the fear of falls and the number of falls in older adults ($F=6.195$; $p=0.003$; $R^2=0.105$). It was determined that the number of falls and fear of falls increased as the TUG score increased (β-4.124 and 1.708) (Table 3).

Discussion

This study was conducted to determine the prevalence of falls, fear of falling, and risk factors for falling in older adults living in nursing homes. This study is important in terms of contributing to the literature and drawing attention as it was conducted in a developing region having no data on the falls in the older adults living in the institution. Although the differences in the region where the studies have been conducted, race and the healthcare system have varied the results, it has been observed that the number of falls and the rate of deaths due to falls increases consistently. Especially the older adults living in the institution are at risk (22,23). It is quite important to determine the falls in people over the age of 65 in these regions, raise awareness, conduct fall prevention studies, assess the older adults based on falls, gait, balance, fear of falls and the associated factors and draw the attention of the healthcare professionals in terms of public health applications.

Many people notice a decrease in their mobility as a result of ageing. Multiple chronic diseases and deficiencies are responsible for this decrease and they make older adults prone

Table 1. Demographics, cognitive and physical characteristics of the participants

Characteristics	Full sample n=113	Fallers n=47	Non-fallers n=66	p-value
Age (years), mean ± SD	77.5±8.8	79.7±8.4	76.0±8.7	0.026
Gender (female; n, %)	50, (44.2)	29, (61.7)	21, (31.8)	<0.001
Educational status (Primary education and below; n, %)	105, (92.9)	45, (95.7)	60, (90.9)	0.27
Number of chronic diseases, mean ± SD	2.1±0.9	2.4±1.0	1.9±0.8	0.020
Number of drugs used, mean ± SD	4.0±2.3	4.1±2.4	3.9±2.3	0.67
Period of living in the institution (more than 3 years; n, %)	45, (39.8)	16, (34.0)	29, (43.9)	0.19
Participating in social activities in the institution (unwilling; n, %)	87, (77.0)	32,(68.1)	55, (83.3)	0.04
Fear of falls (people with fear n, %)	85, (75.2)	43, (91.5)	42, (63.6)	<0.001
FaB scale, mean ± SD	2.6±0.4	2.9±0.3	2.5±0.4	<0.001
TUG, second mean ± SD	17.9±9.2	20.6±10.6	15.9±7.6	0.007
TBGA, score mean ± SD	18.9±6.8	16.6±6.0	20.5±6.9	0.001
MMSE, score mean ± SD	16.4±6.8	14.1±5.9	18.1±6.9	0.002

One-Way ANOVA or non-parametric Mann-Whitney U test was applied when appropriate. FaB scale fall behavioral scale for older people, TUG: The timed up and go, TBGA: Tinetti balance and gait assessment, MMSE: Mini-mental state examination, SD: Standard deviation

Table 2. History, characteristics, and fear of falls

	n	%
	n	%
Falls in the recent year		
Yes	47	(41.6)
No	66	(58.4)
Number of falls in the recent year		
Once	21	(18.6)
Twice	14	(12.4)
Three times	5	(4.4)
Four times and more	7	(6.2)
Place of falls*		
While walking in and out of the building	35	(31.0)
While getting up from bed	10	(8.8)
While getting up from a chair	4	(3.5)
While having a bath/in the toilet	11	(9.7)
While climbing up/coming downstairs	9	(8.0)
Reasons for falls*		
Tripping	16	(14.2)
Slipping	15	(13.3)
Loss of balance	17	(15.0)
Dizziness	16	(14.2)
Faint	2	(1.8)
Not remembering/not sure	9	(8.0)

*Marked more than once

to falls (20). Fall is responsible for two-thirds of all deaths due to unintentional injuries. In WHO 2018 report, it has been reported that age, gender and the status of living in a nursing home/care centre are the important risk factors for falls (23). Fall risk is higher for the older adults living in nursing homes and elderly care centres because there may be limitations different from the environment where the older adults are familiar (24). In a study conducted in China, the prevalence of falls in older adults was 19.3% and the prevalence of repeated falls was 4.75% (14). In other studies in the literature, it was found that the fall rate of the older adults living in nursing homes was higher compared to the older adults living in a home environment (25-27). It was determined in this study that older adults fell 1.9±1.08 times on average and 41.6% of them fell at least once in the recent year. It was determined in this study that the prevalence of falls increased with increasing age. Likewise, it was stated in the previous studies that the prevalence of falls increased with increasing age (5,28). The fact that more risk factors for falls in older adults (29-31) and the severity of these risk factors increases with increasing age is thought to increase the possibility of falls and, as a result, increase the falls prevalence with increasing age. It is known that gender is an important factor for falls together with age. It has been reported in the studies that women experience falls more compared to men and the female gender is a risk factor for falls (5,28). It was found in this study that the fall risk was higher in women, which is compatible with the literature.

The difference between this study and the fall studies in the literature is that falls in the older adults living in the institution

were assessed in a multi-directional manner, these assessments were associated with the number of falls/fear of falls, and it was aimed to emphasize that the fear of falls is as important as falls itself. Falls are an important health problem causing fear and anxiety, leading to loss of independence and affecting quality of life negatively for older adults (32). Fear of falls is estimated to be experienced by many older adults and it has been reported that the prevalence of fear of falls is not known exactly. Fear of falls causes limitation of movement in older adults or leads the older adults to fail to move (33,34). This fear causes physical and cognitive weakness in older adults and results in recurrent falls in them. Thus, fear of falls causes weakness, weakness causes the limitation of movement and falls, and falls causes fear again and these cause a vicious circle. It has been reported in the studies that fear of falls causes significant differences in the emotional and behavioural areas of individuals, the reduces physical ability and social interaction, and causes less participation in social activities (35,36). It was determined in this study that 75.2% of the older adults had a fear of falls and 41.6% fell at least once in a recent year, and 68% of these people were unwilling to participate in social activities. This result suggests that most older adults who have experienced falls have the fear of falls and they limit their lives due to this fear.

In the multiple linear regression model established in this study, the correlation between the number of falls and fear of falls was explained using MMSE, TUG and TBGA. TBGA and TUG are the tests that also provide an opinion about the performance during daily life activities such as standing up, walking, returning and sitting as well as balance and being used commonly in assessing balance. In a previous meta-analysis performed, TUG score between the ages of 60-99 has been reported to be 9.4 seconds on average. In another study, it was determined that the correlation between TUG score and falls was significant and this score was higher than 15 seconds, which increased falls 3 times more (37-40). According to the logistic regression analysis results of another study, it was reported that high TUG scores increased fall risk approximately two times (41). It was determined that the mean TUG in the older adults in this study was similar to the literature. Also, it was found in the multiple linear regression analysis that a decrease of one unit in TUG score caused an increase of 4.1 units in fear of falls and an increase of 1.7 units in the number of falls. It was determined that there was a negative correlation between TBGA mean score and fear of falls and the number of falls and the decrease in TBGA caused an increase in fear of falls and the number of falls. It was determined that there was a negative correlation between MMSE mean scores and fear of falls and the number of falls and the decrease of MMSE caused an increase in fear of falls and the number of falls. In a study conducted; elderly individuals had a moderate to high risk of falling according to TBGA. Higher MMSE score was found to be an independent variable for reduced risk of falling (42). In another study, MMSE and TBGA were examined in hospitalized elderly individuals and multifactorial regression analysis was performed. Participants had a significantly worse overall health performance with an increased risk of falling (43). These results demonstrate that TUG, TBGA and MMSE, which are important indicators of balance and daily life activities, are significant determinants in the number of falls and fear of falls.

Conclusion

Consequently, it was determined that the fear of falls and the number of falls were high in the older adults living in the institution. It was concluded that TUG, TBGA and MMSE were significant determinants in explaining the correlation between the fear of falls and the number of falls. It may be recommended in the service planning for the prevention of the falls of the older adults living in nursing homes that the assessment of their fear of falls is performed as well as performing regular fall assessments for them. Also, conducting studies with large sample groups in which different methods can explain the effect of TBGA and MMSE on the fear of falls and the number of falls may be useful.

Ethics

Ethics Committee Approval: Ethical Committee Approval from the Ethical Committee of Erciyes University Social and Human Sciences and institutional permission from the nursing home were obtained (2011, KAEK-80).

Informed Consent: Informed and their written and verbal consent was received.

Peer-review: Externally peer-reviewed.

Table 3. Multiple linear regression analysis

	MMSE			TUG			TBGA		
	β	t	p	β	t	p	β	t	p
Fear of falls	-3.617	-0.231	0.012	4.124	2.062	0.042	-4.107	-2.858	0.005
Number of falls	-1.655	-0.286	0.002	1.708	2.236	0.027	-1.428	-2.645	0.009
Model statistics	F=11.001; p<0.001; R^2=0.169			F=6.195; p=0.003; R^2=0.105			F=10.166; p<0.001; R^2=0.158		

* Adjusted for age and gender. MMSE: Mini-mental state examination, TUG: The timed up and go, TBGA: Tinetti balance and gait assessment

Authorship Contributions

Concept: B.Ö., Ö.C., N.Ş., S.A., Design: B.Ö., Ö.C., N.Ş., N.U., S.A., Data Collection or Processing: B.Ö., Ö.C., N.Ş., N.U., Analysis or Interpretation: B.Ö., Ö.C., N.Ş., N.U., Literature Search: B.Ö., Ö.C., N.U., Writing: B.Ö., Ö.C., N.Ş., N.U., S.A.

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ORIGINAL RESEARCH

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Is Infectious Meningitis/Encephalitis a Notable Problem in Older Adults Admitted to Emergency Department with Altered Mental Status?

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Abstract

Objective: Altered mental status (AMS) is challenging diagnosis. It was aimed to evaluate the underlying causes, reveal laboratory, microbiological and imaging findings, and determine the infectious process in older patients who presented with AMS.

Materials and Methods: This retrospective study was conducted at a training and research hospital. Sixty-five year and older patients who presented with AMS and underwent lumbar puncture, were included.

Results: Among 98 older patients with AMS, the median age was 75.0 years (interquartile range: 69.0-75.0) and 58.2% of patients were female. Of the patients, 26.5% meningitis/encephalitis, 33.6% other infection sources, and 39.8% other disorders were found, respectively. Cerebrospinal fluid (CSF) white blood cell and protein levels were found higher; CSF chloride levels were detected lower in meningitis/encephalitis group. In brain, magnetic resonance imaging ($p<0.001$) and electroencephalogram ($p=0.009$) were found more pathologies suggesting infection in meningitis/encephalitis patients, while brain computed tomography revealed no differences between meningitis/encephalitis and other diagnoses group. The need for intensive care was higher in the other disorder group ($p=0.02$) while admission to service was higher in the meningitis/encephalitis group ($p=0.03$).

Conclusion: Clinical characteristics failed to differentiate between meningitis/encephalitis and other diagnoses in older patients with AMS, and CSF analysis, cranial imaging methods were required for the final diagnosis.

Keywords: Altered mental status, emergency service, encephalitis, meningitis, older adults

Introduction

It is common for older adults to apply to the emergency department (ED) with altered mental status (AMS) (1,2). Up to 50% of hospitalized older patients and 2% of ED patients experience changes in consciousness at different levels (3). The presence of infections, malnutrition, electrolyte imbalance, exacerbation of underlying diseases, drug side effects, delirium, and many other disorders may cause AMS in the older patients (4). Sometimes, the underlying cause may not be found despite all the research.

In the patient who applies to the ED with AMS, the cause is tried to be found by vital signs, a medical history that can be obtained from the patients themselves, relatives or caregivers, physical examination, symptoms and findings, and imaging methods (5). Before the diagnosis is made, peripheral glucose, oxygen level, laboratory parameters such as urinalysis, electrocardiogram, simple electrolyte tests, renal function tests, and complete blood count should be obtained (6,7). Cranial computed tomography (CT) can also be applied for acute intracranial haemorrhage or other mass lesions. If there is no reason to explain the patient's AMS despite all these tests and AMS persists, additional testing

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such as arterial blood gas, thyroid tests, cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), and brain magnetic resonance imaging (MRI) may be requested. Although obtaining CSF by lumbar puncture (LP) and using it in the differential diagnosis is less and less preferred thanks to brain CT and MRI. However, urgent LP is still used for suspected central nervous system (CNS) infections (6,8).

In this study, it was aimed to 1) evaluate the underlying causes, 2) reveal laboratory, microbiological and imaging findings, and 3) determine the infectious process (meningitis and encephalitis) in older patients who presented to the ED with AMS.

Materials and Methods

Study Design and Population

This study was a single-center, retrospective cross-sectional cohort study. We included all aged 65 years and older patients with AMS who were consulted to infectious diseases (ID) specialists and underwent LP between February 1, 2019 and December 1, 2021. We excluded patients with a lack of data, no indication for LP or those who refuse the LP while in ED. This study was approved by the Medical and Health Research Ethics Committee of Ankara City Hospital (date: 09/06/2021, number: 1756).

Case Definitions and Classifications

Meningitis is an inflammation of the leptomeninges, that can also involve the parenchyma and is defined by the presence of an inflammatory process of the brain (6). Encephalitis is determined by the parenchymal inflammatory process of the brain in association with abnormal brain function (7). We classified patients with AMS meeting the European Society of Clinical Microbiology and ID guidelines recommendations for meningitis, which includes signs and symptoms (headache, fever, neck stiffness), CSF findings [glucose concentration <40 mg/dL, a CSF serum glucose ratio of <0.4, a protein concentration >200 mg/dL, and a white blood cell (WBC) count 1000/microL] and CSF culture results (6,8,9). Viral encephalitis diagnosis was made by the Infectious Disease Society of America Guidelines criteria (7).

Study Variables

We selected several variables associated with the reasons of AMS, including age, sex, comorbidities including diabetes mellitus, hypertension, malignancies, chronic lung disease, heart disease (arrhythmias, coronary artery disease, congestive heart failure), chronic liver disease, chronic kidney disease and history of stroke, psychiatric disorders, Alzheimer's disease; symptoms and clinical signs on admission (fever, blood pressure, cough, dyspnea, presence of sputum, digestive symptoms, weakness in body parts, dysuria, neck stiffness, headache, Kernig's and Brudzinski's sign, history of seizure, presence of deep and soft tissue infections), intubation and vasopressor use in the ED, laboratory parameter results of blood and CSF, urinalysis, culture results (blood, urine, sputum, CSF), bacterial and viral real-time polymerase chain reaction (RT-PCR) panel, identification of *Mycobacteria* in CSF, imaging technics performed in the ED, outpatient or hospitalized status, the length of hospital stay, causes of AMS and final outcomes from hospital automation systems.

Microbiological Evaluation

For this study, we obtained results of various microbiological laboratory tests available in the database, CSF white and red blood cell, CSF glucose, protein, sodium, chloride and lactate dehydrogenase levels and CSF Gram stain; viral meningoencephalitis pathogen RT-PCR panel [includes, *Herpes simplex virus* type-1 and *Herpes simplex virus* type-2 (HSV-1 and HSV-2), *Varicella-zoster virus* (VZV), *Mumps virus*, *Enterovirus*, *Human parechovirus*]; bacterial meningitis pathogen RT-PCR panel (includes, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*) and tuberculosis tests [acid-fast bacillus (AFB) stain and culture], and cultures of CSF, blood, urine, sputum. In our institution, viral and bacterial panels were performed with Siemens, Germany's Fast Tract Diagnostics Multiplex RT-PCR assay. Culture and AFB stain for *Mycobacterium tuberculosis* were performed using Ziehl-Neelsen staining and Middlebrook 7H9 Broth/Löwenstein-Jensen media.

Statistics

Nominal variables were presented as number and percentage, whereas continuous variables were presented as the median and interquartile range (IQR). The distribution of the continuous variables was performed by using the Kolmogorov-Smirnov test where appropriate. Mann-Whitney U test was applied to analyse non-normally distributed data, and Pearson's chi-square or Fisher's Exact tests were applied to examine categorical data. The p-value of <0.05 was considered significant. The IBM Statistical Package for the Social Sciences (SPSS) version 24 (Chicago, USA) was used to perform statistical analysis.

Results

We evaluated 105 older adults with AMS. Seven patients were excluded due to lack of follow-up data, and 98 patients were selected for the study. At least one cause was found to explain AMS in all patients (100.0%) who applied to the ED. The etiologies of patients with AMS were shown in Table 1.

The median age was 75.0 years (IQR: 69-85) in total patients. The median age was lower in the meningitis/encephalitis group [71.0 (66.7-77.2) vs 76.0 (70.2-84.0); p=0.03]. Fifty-seven (58.2%) included patients were female. Ninety-three (94.9%)

patients presented with comorbidities. The most common comorbidity was hypertension in 63 (64.3%) cases. Kernig's and Brudzinski's signs were assessed in 29 (29.6%) patients and were found negative. Ninety-five (96.9%) of patients underwent a neurologic assessment by neurologists. The demographics, clinical characteristics and on admission vitals of patients are presented in Table 2.

Of laboratory values taken during admission, CSF protein and CSF WBC levels were higher; CSF chloride and serum sodium levels were lower in meningitis/encephalitis patients. The CSF culture was sent from all patients, and 14 (14.3%) of patients' culture results were positive (Table 3). All bacteria grown in the culture of the other diagnoses group were skin contaminant, while *S. pneumoniae* (four patients; 15.4%), *Haemophilus influenzae* (one patient; 3.8%) and *Escherichia coli* (one patient; 3.8%) were isolated in CSF cultures of meningitis/encephalitis patients, respectively. CSF viral and CSF bacterial pathogen RT-PCR panels were obtained from 71 (72.4%) and 28 (28.6%) patients, respectively. The viral pathogen panel of 8 (8.2%) patients was positive (five patients, 5.1%, HSV-1 and three patients, 3.1%, VZV) (Supplementary Table 1). The patient with positive bacterial pathogen panel also had positive CSF culture result (one patient, 1.0%, *S. pneumoniae*). Tuberculosis tests were sent from 20 (20.4%) patients, all of them were negative.

To find the etiologies in patients with AMS, investigated in other suspected areas with imaging methods (thorax CT and abdominal imaging technics). Brain MRI showed abnormalities in patients with meningitis or encephalitis, while brain CT revealed no differences (p=0.01 vs p=0.48). In brain MRI and EEG, more pathologies suggesting infection were found in meningitis/encephalitis patients (p<0.001; p=0.009, Table 3).

The median time from admission to outcomes (i.e., discharge, intensive care unit admission, inpatient follow-up and death) was longer in the CNS infections group [17.5 days (IQR: 10.7-24.2) vs 10.5 days (IQR: 4.0-18.7)]. The admission rate to service for following-up was higher in meningitis/encephalitis patients (p=0.03), whereas patients with other diagnoses needed intensive care more frequently (p=0.02). The hospital admission rates among all patients and mortality rates among meningitis/encephalitis patients were 87.8% and 23.1% (total seven patients; six of them encephalitis, one of them meningitis), respectively (Table 3).

While the diagnosis of meningitis was made by culture results in 6 (75.0%) patients and a combination of clinical signs and symptoms, CSF findings and brain MRI in two (25.0%) patients; the diagnosis of encephalitis was made by CSF viral pathogen RT-PCR panel in 8 (44.4%) patients, brain MRI and EEG findings in 6 (33.3%) patients, and clinical signs and symptoms and CSF findings in four (22.2%) patients respectively. The patients' characteristics were summarised in Supplementary Table 1.

Discussion

In older adults, admission to the ED with AMS are frequently seen due to many conditions. Specific signs, such as fever, neck stiffness, headache and, nausea is less common in older adults with meningitis. In our study, clinical signs and symptoms different from other disorders that cause AMS were not observed in patients diagnosed with meningitis and encephalitis. Our results were coherent with other studies (10,11). In light of this, it is not possible to distinguish CNS infection in older people with AMS by only assessing signs and symptoms.

Meningitis/encephalitis patients were younger [71.0 years (IQR: 66.7-77.2) vs 76.0 years (IQR: 70.2-84.0)]. The risk of encephalitis and meningitis, and other CNS infections were increasing in individuals aged 65 years and over and had been

Table 1. Etiologies of elderly patients with AMS

Meningitis/encephalitis	n (%)	Non-infectious disorders	n (%)
Total	26/98 (26.5)	Total	39/98 (39.8)
Meningitis	8 (30.8)	Psychiatric disorders	12 (30.8)
Encephalitis	18 (69.2)	Cerebrovascular diseases	12 (30.8)
Other infections	n (%)	Kidney diseases	5 (12.8)
Total	33/98 (33.6)	Pulmonary diseases	4 (10.2)
Urinary tract infection	10 (30.3)	Cardiovascular diseases	3 (7.7)
Sepsis	8 (24.2)	Liver disease	1 (2.6)
Pneumonia	5 (15.1)	Endocrinological disorder	1 (2.6)
Viral infections	4 (12.1)	Dehidydration	1 (2.6)
Bacteremia	2 (6.1)		
Sinusitis	2 (6.1)		
Cellulitis	1 (3.0)		
Lung abscess	1 (3.0)		

Data were presented as n (%), AMS: Altered mental status

associated with worse clinical outcomes in other studies (10-13). To our knowledge, there were no other studies shown that patients who applied to the ED with AMS and were diagnosed with meningitis/encephalitis were younger.

CSF chloride [115.0 mEq/L (IQR: 114.0-121.0)] was lower whereas CSF protein [715.6 mg/dL (IQR: 421.0-1701.0)], and CSF WBC counts [0.5/microL (IQR: 0-125.0)] were higher in patients with meningitis/encephalitis. In studies, older meningitis patients had lower CSF glucose and higher median CSF WBC count and CSF protein (10,14,15). Elevated protein levels and red blood cell counts in CSF were also detected in patients with viral encephalitis (14-16). Studies have shown that lower chloride levels (<120 mEq/L) might be seen in tuberculous, cryptococcal and bacterial meningitis (17,18).

Cranial CT should be used in patients suspected of space-occupying lesions, patients with the possibility of brain herniation or according to guidelines recommendations (9,19,20). In this study, 98.0% of patients underwent cranial CT before performing LP, and there was no difference in terms of abnormalities in cranial CT between the two groups. It was

Table 2. The demographics, clinical characteristics and on admission vitals of patients

	Total 98 (100)	Meningitis/encephalitis 26 (26.5)	Other diagnoses 72 (73.5)	p-value
Median age (IQR), years	75 (69-85)	71 (66.7-77.2)	76 (70.2-84.0)	**0.03***
Female gender, n (%)	57 (58.2)	14 (53.8)	43 (59.7)	0.60†
Comorbidities, n (%)	93 (94.9)	24 (92.3)	69 (95.8)	0.61†
Hypertension	63 (64.3)	18 (69.2)	45 (62.5)	0.53†
Diabetes mellitus	34 (34.7)	9 (34.6)	25 (34.7)	0.99†
Malignancies	5 (5.1)	-	5 (6.9)	-§
Chronic lung disease	17 (17.3)	6 (23.1)	11 (15.3)	0.38†
Arrhythmia	11 (11.2)	1 (3.8)	10 (13.9)	0.28†
Coronary artery disease	27 (27.6)	9 (34.6)	18 (25.0)	0.35†
Congestive heart failure	14 (14.3)	6 (23.1)	8 (11.1)	0.19†
Chronic liver disease	4 (4.1)	2 (7.7)	2 (2.8)	0.29†
Chronic kidney disease	15 (15.3)	3 (11.5)	12 (16.7)	0.75†
History of stroke	27 (27.6)	9 (34.6)	18 (25.0)	0.38†
Alzheimer's disease	16 (16.3)	1 (3.8)	15 (20.8)	0.06†
Psychiatric disorder	5 (5.1)	1 (3.8)	4 (5.6)	0.32†
Signs and symptoms, n (%)				
Neck stiffness	11 (11.2)	1 (3.8)	10 (13.9)	0.28†
Seizure	11 (11.2)	4 (15.4)	7 (9.7)	0.47†
Headache	10 (10.2)	3 (11.5)	7 (9.7)	0.72†
Nause	12 (12.2)	3 (11.5)	9 (12.5)	1.0†
Vomiting	15 (15.3)	3 (11.5)	12 (16.7)	0.75†
Sudden weakness in body parts	9 (9.2)	2 (7.7)	7 (9.7)	1.0†
Dysuria	3 (3.1)	-	3 (4.2)	-§
Dyspnea	11 (11.2)	1 (3.8)	10 (13.9)	0.28†
Cough	8 (8.2)	4 (15.4)	4 (4.6)	0.20†
Sputum	7 (7.1)	4 (15.4)	3 (4.2)	0.08†
Soft tissue infection	2 (2.0)	-	2 (2.8)	-§
Vitals on admission, n (%)				
Fever (>38 °C)	35 (35.7)	10 (38.5)	25 (34.7)	0.73†
Arterial blood pressure (>140/80 mmHg)	33 (33.7)	9 (34.6)	24 (33.3)	1.0†
Oxygen saturation below 90%	24 (24.5)	5 (19.2)	19 (26.4)	0.47†
Intubation in ED	14 (14.3)	3 (11.5)	11 (15.3)	0.75†
Vasopressor use in ED	5 (5.1)	1 (3.8)	4 (5.6)	-§

Data were presented as median (IQR) or n (%). Differences between age groups were examined using Pearson's chi square† and Fisher's Exact† test for categorical data, and Mann-Whitney U test* was used to compare medians. §The p-value was not calculated due to the small number of patients. ED: Emergency department, IQR: Interquartile range

Table 3. The laboratory, microbiological, imaging findings and outcomes of patients				
	Total 98 (100)	Meningitis/encephalitis 26 (26.5)	Other diagnoses 72 (73.5)	p-value
Laboratory parameters				
CSF sodium (mEq/L)	144.7 (142.0-148.8)	143.6 (141.6-145.8)	145.0 (142.3-149.0)	0.18*
CSF chloride (mEq/L)	120.0 (116.0-124.5)	115.0 (114.0-121.0)	122.0 (118.0-127.2)	**<0.001***
CSF glucose (mg/dL)	75.0 (59.0-98.5)	73.0 (49.2-108.2)	76.0 (63-93)	0.52*
CSF LDH (U/L)	30.0 (22.5-44.5)	32.0 (18.0-77.7)	29.0 (23.0-44.0)	0.83*
CSF protein (mg/dL)	544.0 (378.2-799.1)	715.6 (421.0-1701.0)	496.1 (360.8-762.5)	0.03*
CSF cell count, n (%)	92/98 (93.9)	26/26 (100.0)	66/72 (91.7)	
Positive WBC count (>5 cell/mL)	22 (23.9)	11 (42.3)	11 (16.7)	**0.009†**
WBC count (microL)	0 (0-3.5)	0.5 (0-125.0)	0 (0-0)	**0.001***
Positive RBC count (cell/mL)	57 (58.2)	18 (69.2)	39 (59.1)	0.37†
RBC count (microL)	30.0 (0-240.0)	35.0 (0-382.5)	0 (0-242.5)	0.60*
Serum sodium (mEq/L)	139.0 (136.0-142.0)	137.0 (132.7-140.0)	139.0 (136.0-143.0)	**0.01***
Serum glucose (mg/dL)	135.0 (104.7-176.5)	141.0 (108.7-200.7)	134.0 (101.2-163.7)	0.22*
Serum chloride (mEq/L)	14.0 (14.3)	103.0 (101.0-106.2)	105 (100-114)	0.32*
Serum protein (g/L)	63.0 (58.0-68.2)	65.0 (58.0-71.0)	63.0 (58.0-67.0)	0.23*
Aspartate transaminase (U/L)	30.0 (21.0-46.2)	25.0 (20.5-44.2)	33.0 (21.0-49.0)	0.26*
Alanine transaminase (U/L)	20.5 (15.0-34.5)	20.5 (15.0-47.0)	20.5 (15.0-32.7)	0.32*
LDH (U/L)	285.5 (232.0-338.2)	276.5 (219.2-381.7)	286.5 (233.0-334.2)	0.92*
Creatinine (mg/dL)	1.05 (0.80-1.56)	0.95 (0.73-1.22)	1.15 (0.85-1.64)	0.87*
WBC ($x10^9$/L)	10.4 (8.1-15.1)	9.4 (7.9-19.2)	10.6 (8.2-14.7)	0.79*
Lymphocyte ($x10^9$/L)	1.2 (0.7-1.6)	1.2 (1.0-1.7)	1.1 (0.7-1.6)	0.09*
CRP (mg/L)	38.5 (13.8-97.1)	34.7 (4.7-105.7)	43.5 (17.0-100.4)	0.27*
Procalcitonin (µg/L)	0.14 (0.05-1.09)	0.10 (0.03-0.44)	0.20 (0.06-1.31)	0.09*
WBC in urine (p/HPF), n (%)	33/90 (36.7)	8/24 (33.3)	25/66 (37.9)	0.69†
Cultures, n (%)				
Positive urine culture	24/58 (42.1)	6/16 (37.5)	18/42 (42.9)	0.66†
Positive blood culture	15/61 (24.6)	3/19 (15.8)	12/42 (28.6)	0.35†
Positive sputum culture	6/12 (50.0)	0/1 (0.0)	6/11 (54.5)	1.0†
Positive CSF culture	14/98 (14.3)	6/26 (7.7)	8/72 (11.1)	0.19†
Imaging, n (%)				
Cranial CT taken	96/98 (98.0)	26/26 (100.0)	70/72 (97.2)	1.0†
haemorrhage	4 (4.2)	1 (3.8)	3 (4.3)	-§
Old infarction area	22 (22.9)	4 (15.4)	18 (25.7)	-§
Acute ischemic stroke	7 (7.3)	2 (7.7)	5 (7.1)	-§
Mass	2 (2.1)	1 (3.8)	1 (3.8)	-§
Normal	61 (63.5)	18 (69.2)	43 (61.4)	0.48†
Cranial CT suggests infection	-	-	-	NA
Brain MRI taken	82/98 (83.7)	23/26 (88.5)	59/72 (81.9)	0.55†
Diffusion restriction	14 (17.1)	6 (26.1)	8 (13.6)	-§
Meningeal enhancement	5 (6.1)	2 (8.7)	3 (5.1)	-§
Encephalitis	5 (6.1)	4 (17.4)	1 (1.7)	-§
Haemorrhage	1 (1.2)	-	1 (1.7)	-§
Normal	56 (68.3)	11 (47.8)	45 (76.3)	**0.01†**

Table 3. Continued

	Total 98 (100)	Meningitis/encephalitis 26 (26.5)	Other diagnoses 72 (73.5)	p-value
EEG suggesting infection	8/20 (40)	6/8 (75.0)	2/12 (16.7)	**0.009‡**
Abnormal findings on thorax CT	27/77 (35.1)	4/19 (21.0)	23/58 (39.7)	0.09†
Abnormal findings on abdominal imaging	1/38 (2.6)	0/11 (0.0)	1/27 (3.7)	-§
The time from admission to outcomes (IQR), days	12.0 (5.7-20.0)	17.5 (10.7-24.2)	10.5 (4.0-18.7)	**0.009***
Outcomes, n (%)	98 (100)	26 (26.5)	72 (73.5)	
Discharge	12 (12.2)	1 (3.8)	11 (15.3)	0.17†
ICU admission	54 (55.1)	11 (42.3)	43 (59.7)	**0.02‡**
Inpatient follow-up	32 (72.7)	14 (93.3)	18 (62.1)	**0.03‡**
Death	26 (25.5)	7 (26.9)	19 (26.4)	0.74†

Data were presented as median (IQR) or n (%). Differences between age groups were examined using Pearson's chi-square† and Fisher's Exact test‡ for categorical data, and Mann-Whitney U test* was used to compare medians. §The p-value was not calculated due to the small number of patients. LDH: Lactate dehydrogenase, CSF: Cerebrospinal fluid, WBC: White blood cell, RBC: Red blood cell, CRP: C-reactive protein, MRI: Magnetic resonance imaging, EEG: Electroencephalogram, CT: Computed tomography, NA: Not applicable

probably related to the overuse of CT scan and its inability to detect early cerebral changes in viral encephalitis. However, the detection of space-occupying lesions in only 2.1% of the patients in cranial CT scan results reminded us that more rational behavior should be considered in the selection of this imaging method, and that both time and cost-effectiveness should be considered. Management of the patients in line with the recommendations of the guidelines seem to be a more correct approach when choosing CT imaging. On the other hand, unlike our research, many other studies have shown abnormalities on cranial CT scan in patients with encephalitis and meningitis (10,16,21).

Pathological changes were detected in brain MRI in meningitis and encephalitis patients. In encephalitis patients, especially brain MRI and EEG findings may be helpful for diagnosis in our study. These results were similar to the literature; MRI and EEG were significantly more sensitive than brain CT for detecting viral encephalitis (10,16,21,22).

Looking at the outcomes of our study, patients with meningitis and encephalitis were followed-up more in the ward, the need for intensive care developed more frequently in the other diagnoses group, possibly due to exacerbation of the underlying disease and clinical risk factors associated with higher mortality rates such as sepsis, pneumonia, and cerebrovascular diseases. The mortality rate was 26.9% in older patients with CNS infection; results ranged from 14.0% (23) to 28.4% (24) in earlier studies. In addition, the median duration of hospital stay was found to be longer in patients with CNS infection [17.5 days (IQR: 10.7-24.2) vs 10.5 days (IQR: 4.0-18.7)], probably due to extended antibiotic or antiviral treatment duration, and arrangements need to be made to return to daily life.

There are not many studies evaluating the etiologies of AMS in older patients who underwent LP in ED admissions regarding to CNS infections. In the previous studies, all infectious causes were given without specifying age groups (25-27) or etiologies of AMS in older patients (5,28). Our study found infectious causes in 60.2% of the older patients with AMS who underwent LP; meningitis and encephalitis were present in 26.5% of the patients. The reasons for this high infectious causes rate compared to previous studies might be the advanced age of the patients, a low number of the study population, and consultation of ID specialists of patients with suspected infectious etiologies.

53.8% (14 patients) of meningitis and encephalitis patients were diagnosed based on microbiological methods. CSF analysis and imaging methods were required to diagnose older patients properly. This difficulty in diagnosing has been reported in other studies (22,23,29).

Study Limitations

Our findings should be interpreted in the light of several limitations. Single-center and retrospective study with a limited number of patients and lack of other CNS infections in the study population seem to be the main limitations. Also, malnutrition status and frailty in patients were not evaluated. These may have affected the study results. However, the advantage of the study was that older patients with AMS was evaluated by ID specialists and emergency care physicians in the ED. In this way, the diagnosis of CNS infection was made accurately, and the patients were evaluated by both specialists in terms of other foci of infections.

Conclusion

AMS is a challenging diagnosis in older patients admitted to ED and has many etiologies. Since these patients' first point of contact is ED, making an early and accurate diagnosis and prompt appropriate treatment is essential. Physical examination, clinical

signs and symptoms, CSF analysis and imaging methods may all need to be used as diagnostic work-up for urgent stabilization and initiation of treatments.

Ethics

Ethics Committee Approval: This study was approved by the Medical and Health Research Ethics Committee of Ankara City Hospital (date: 09/06/2021, number: 1756).

Informed Consent: Informed consent was not obtained because of retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.M.A., F.M.G., Ö.A., Concept: Ç.M.A., S.C., Design: Ç.M.A., S.C., Data Collection or Processing: Ç.M.A., F.M.G., Ö.A., Analysis or Interpretation: Ç.M.A., F.M.G., Ö.A., R.G., Literature Search: Ç.M.A., S.C., R.G., Writing: Ç.M.A., S.C., R.G.

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Supplementary Table 1. Characteristic of meningitis and encephalitis patients

Meningitis	Age/ gender	Co-morbid conditions	Presenting symptoms	CSF analyses	CSF culture result	Blood test results	Head CT	Brain MRI	Outcome
Patient 1	66/F	DM, HT, CAD, CKD, asthma	Fever, nausea, vomiting	Glucose: 1 mg/dL, protein: 3.337 mg/dL, WBC: 1.025 microL	*Streptococcus pneumoniae*	Glucose: 109 mg/dL, WBC: $2.4x10^9$/L, CRP: 85 mg/dL	Normal	Normal	Dead
Patient 2	65/F	DM, HT, psychiatric disorder	-	Glucose: 4 mg/dL, protein: 4.954 mg/dL, WBC: 1.000 microL	*Streptococcus pneumoniae*	Glucose: 215 mg/dL, WBC: $24.7x10^9$/L, CRP: 403 mg/dL	Normal	Diffusion restriction	Alive
Patient 3	70/M	HT, CAD	Neck stiffness	Glucose: 1 mg/dL, protein: 6447 mg/dL, WBC: 640 microL	*Streptococcus pneumoniae*	Glucose: 171 mg/dL, WBC: $19.5x10^9$/L, CRP: 237 mg/dL	Normal	Normal	Alive
Patient 4	71/M	HT, CAD	Fever, headache, cough	Glucose: 4 mg/dL, Protein: 1982 mg/dL, WBC: 100 microL	*Streptococcus pneumoniae*	Glucose: 96 mg/dL, WBC: $30.1x10^9$/L, CRP: 59 mg/dL	Old parenchymal haemorrhage	Normal	Alive
Patient 5	65/M	DM, HT, CAD	-	Glucose: 86, protein: 561 mg/dL, WBC: 8 microL	*Haemophilus influenza*	Glucose: 119 mg/dL, WBC: $8.96x10^9$/L, CRP: 4 mg/dL	Normal	Normal	Alive
Patient 6	67/M	DM, HT, stroke history	-	Glucose: 106 mg/dL, protein: 267 mg/dL, WBC: 40 microL	*Escherichia coli*	Glucose: 193 mg/dL, WBC: $22.1x10^9$/L, CRP: 183 mg/dL	Old infarction area	Diffusion restriction	Alive
Patient 7	67/M	DM, HT, COPD	Fever, headache, nausea, vomiting	Glucose: 21 mg/dL, protein: 2369 mg/dL, WBC: 540 microL	Negative	Glucose: 176 mg/dL, WBC: $13.0x10^9$/L, CRP: 74 mg/dL	Mass	-	Alive
Patient 8	65/F	HT	Fever, seizure	Glucose: 74 mg/dL, protein: 201 mg/dL, WBC: 10 microL	Negative	Glucose: 126 mg/dL, WBC: $6.3x10^9$/L, CRP: 40 mg/dL	Normal	Diffuse pachymeningeal hyperintensity	Alive
Encephalitis	**Age/ gender**	**Co-morbid conditions**	**Presenting symptoms**	**CSF analyses**	**CSF RT-PCR result**	**Head CT**	**Brain MRI**	**EEG**	**Outcome**
Patient 1	77/F	DM, HT	-	Glucose: 147 mg/dL, protein: 722 mg/dL, WBC: 200 microL, RBC:0 microL	*HSV-1*	Normal	Diffusion restriction	-	Dead
Patient 2	68/F	HT, heart failure, stroke history	-	Glucose: 115 mg/dL, protein: 303 mg/dL, WBC: 0 microL, RBC: 0 microL	*HSV-1*	New infarction area	Compatible with encephalitis	-	Dead
Patient 3	65/M	-	Fever, vomiting, cough	Glucose: 77 mg/dL, protein: 438 mg/dL, WBC: 30 microL, RBC: 10 microL	*HSV-1*	Normal	Compatible with encephalitis	Epileptiform activity	Alive
Patient 4	77/M	HT, CAD	-	Glucose: 72 mg/dL, protein: 302 mg/dL, WBC: 0 microL, RBC: 20 microL	*HSV-1*	Normal	Diffusion restriction	Epileptiform activity	Alive

Supplementary Table 1. Continued

Meningitis	Age/ gender	Co-morbid conditions	Presenting symptoms	CSF analyses	CSF culture result	Blood test results	Head CT	Brain MRI	Outcome
Patient 5	72/M	Stroke history	Fever, focal neurologic deficit	Glucose: 57 mg/dL, protein: 847 mg/dL, WBC: 200 microL, RBC: 0 microL	*HSV-1*	Normal	Compatible with encephalitis	Epileptiform activity	Alive
Patient 6	86/M	HT, COPD, heart failure, stroke history	-	Glucose: 52 mg/dL, protein: 544 mg/dL, WBC: 0 microL, RBC: 1.600 microL	*VZV*	Normal	Diffusion restriction	-	Dead
Patient 7	101/F	Heart failure, CKD	Dyspnea	Glucose: 105 mg/dL, protein: 746 mg/dL, WBC: 0 microL, RBC: 0 microL	*VZV*	Normal	-	-	Dead
Patient 8	75/F	DM, heart failure, asthma, stroke history	Fever	Glucose: 151 mg/dL, protein: 976 mg/dL, WBC: 0 microL, RBC: 1.000 microL	*VZV*	Old infarction area	Normal	-	Alive
Patient 9	80/M	HT, CAD, stroke history	Fever, focal neurologic deficit	Glucose: 87 mg/dL, protein: 709 mg/dL, WBC: 2 microL, RBC: 200 microL	-	Normal	Diffusion restriction	Compatible with encephalitis	Alive
Patient 10	71/M	DM, HT, CAD, arrhythmia, asthma	-	Glucose: 83 mg/dL, protein: 1070 mg/dL, WBC: 0 microL, RBC: 120 microL	Negative	Old infarction area	Compatible with encephalitis	-	Dead
Patient 11	78/F	DM, HT, CAD	Seizure	Glucose: 173 mg/dL, protein: 1.607 mg/dL, WBC: 1 microL, RBC: 83 microL	Negative	Normal	Normal	Compatible with encephalitis	Alive
Patient 12	69/F	HT, CKD	-	Glucose: 54 mg/dL, protein: 547 mg/dL, WBC: 0 microL, RBC: 0 microL	Negative	Normal	Prosthesis	Compatible with encephalitis	Alive
Patient 13	71/M	DM, HT, CAD, stroke history	Seizure	Glucose: 159 mg/dL, protein: 368 mg/dL, WBC: 0 microL, RBC: 80 microL	Negative	Normal	Compatible with encephalitis	Epileptiform activity	Dead
Patient 14	85/F	HT	Fever, cough	Glucose: 60 mg/dL, protein: 545 mg/dL, WBC: 0 microL, RBC: 0 microL	Negative	Normal	Normal	Compatible with encephalitis	Alive
Patient 15	76/F	CAD, heart failure, arrhythmia	-	Glucose: 62 mg/dL, protein: 681 mg/dL, WBC: 0 microL, RBC: 1.000 microL	Negative	Old infarction area	Normal	-	Alive

Supplementary Table 1. Continued

Meningitis	Age/ gender	Co-morbid conditions	Presenting symptoms	CSF analyses	CSF culture result	Blood test results	Head CT	Brain MRI	Outcome
Patient 17	65/F	-	Focal neurologic deficit	Glucose: 41 mg/dL, protein: 918 mg/dL, WBC: 0 microL, RBC: 0 microL	Negative	Normal	Normal	-	Alive
Patient 18	91/F	Stroke history, Alzheimer's disease	Fever, cough	Glucose: 64 mg/dL, protein: 1.100 mg/dL, WBC: 32 microL, RBC: 2 microL	Negative	Old infarction area	Normal	-	Alive

CSF: Cerebrospinal fluid, CT: Computed tomography, MRI: Magnetic resonance imaging, F: Female, M: Male, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CKD: Chronic kidney disease, WBC: White blood cell, CRP: C-reactive protein, COPD: Chronic obstructive pulmonary disease, RT-PCR: Real-time polymerase chain reaction, EEG: Electroencephalography, HSV-1: Herpes simplex virus-1, VZV: Varicella zoster virus, RBC: Red blood cell

ORIGINAL RESEARCH

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Impact of Malnutrition Status at Admission on Post-discharge Short Term Mortality in Palliative Care Unit

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Abstract

Objective: Malnutrition is an immense problem and highly prevalent in patients admitted to palliative care units. We aimed to determine the impact of nutritional status at admission and the risk factors for short-term (90-day) mortality after discharge.

Materials and Methods: This study included patients admitted to and discharged from the palliative care unit (PCU). A total of 118 patients were classified into two groups: Patients who died within 3-month after hospital discharge and patients who survived in the same period. The nutrition status of the patients was retrospectively assessed with NRS-2002.

Results: The mean age of the patients was 70.9±13.4. The overall post-discharge 90-day mortality was 40% (n=47). Age, gender, and length of stay in PCU were similar between the two groups. Majority of patients (97.5%) had an NRS score of 3 or above, and 70 patients (59%) had pressure ulcers at admission. Seventy-six patients (64%) were discharged with enteral nutrition (percutaneous endoscopic gastrostomy/nasogastric tube), and the rest were on oral nutrition. Nutritional risk score 2002 (NRS) and pressure ulcer rate on admission were higher in patients with 90-day mortality [4 (3-6) vs. 3 (2-5), p≤0.001 and 36 (76.6%) vs. 34 (47.9%), p=0.002, respectively]. In addition, patients had lower both systolic and diastolic blood pressure measurements on admission in the mortality group [108±12.8 vs. 118.6±14.2, p≤0.001 and 67.2±9.5 vs. 72.8±9.5, p=0.002, respectively]. When patients were divided into two groups, 28.8% were terminally ill. Length of hospitalization in the palliative care unit, discharge with enteral nutrition, and frequency of percutaneous endoscopic gastrostomy was lower; however, the number of patients with malignity, NRS 2002 score, and ninety-day post-discharge mortality was higher in the terminally ill group than in those non-terminally ill. At admission, high NRS 2002 score [odds ratio (OR): 4.03, 95% confidence interval (CI): 1.54-10.52; p=0.005] and low systolic blood pressure (OR: 0.94, 95% CI: 0.90-0.98; p=0.008) were independently associated parameters with short-term (90-day) mortality after discharge in multivariable analysis.

Conclusion: In addition to comorbid diseases, hemodynamic findings and nutritional status on admission may be associated with early post-discharge mortality in patients hospitalized in PCU.

Keywords: Palliative care, malnutrition, home discharge, pressure ulcer, blood pressure

Introduction

Palliative care is an approach that aims to improve the quality of life of the patients and their families facing the problems (physical, psychological, social, or spiritual) associated with life-threatening illnesses (1). Not only patients with terminal cancer but also those suffering from other life-limiting illnesses benefit from palliative care. It focuses on optimizing quality of life. To improve quality of life, ensuring nutrition should be one of the goals. Unfortunately, malnutrition is an immense problem and is highly prevalent in patients admitted to palliative care units. In order to assess the nutritional status of hospitalized palliative care patients, simple and practical screening procedures that detect individuals who are malnourished or at risk of developing malnutrition and who can receive specific nutritional support are adopted. It has been proposed numerous validated screening and assessment instruments, of which nutritional risk screening

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2002 (NRS) is a simple, effective, and validated nutritional screening method for hospitalized patients (2).

Malnutrition in hospitalized patients has various clinical and financial outcomes. Upon admission a considerable amount of patients present with malnutrition. Furthermore, not only malnourished inpatients but also normally nourished inpatients may face worsening nutritional status during the course of a hospital stay (3). As their conditions progress many palliative care patients with cardiovascular disease, chronic obstructive pulmonary disease, progressive neurological coniditions as well as advanced cancer experince nutritional problems.

There are scarce studies assessed the association between the nutritional status upon admission and early-late period post discharge clinical outcomes (4,5). Most of them were carried out with patients not require palliative or maintenance care. To the best of our knowledge there is no study assessing the nutritional status at admission and postdischarge outcomes in palliative care unit. Within this context, the main purpose of our study was to determine the impact of nutritional status at admission and the risk factors for short-term (90-day) mortality after discharge. We hypothesized that preexisting malnutrition in patients admitted to PCU would be associated with adverse outcomes following hospital discharge.

Materials and Methods

Study Design and Participants

This retrospective study was carried out in a palliative care unit (PCU) in a tertiary hospital according to the Declaration of Helsinki and the guidelines for Good Clinical Practice. The Ethics Committee of Bursa City Hospital approved the study protocol with number 2020-11/1 in 2020.

This study included patients admitted to and discharged from the PCU. All adult patients >17 years of age who were admitted to and discharged from the PCU in one-year period was recruited. Patients with recurrent admissions and who died during the hospitalization were not included in the study. A total of 118 patients were classified into two groups: Patients who died within 3-month after hospital discharge and patients who survived in the same period. Found by screening the patient ID number on the national health systemAt admission to the PCU, the following variables were recorded: Age, gender, length of hospitalization, chronic diseases, nutritional route, and clinics transferred from. Pressure ulcers/injuries were evaluated with the updated staging system which includes the following definitions: Stage 1-4, unstageable pressure injury, and deep tissue pressure injury (6). Participants were also divided into two groups terminally ill and non-terminally ill. Terminally ill patients had advanced phase solid tumors, for whom antiblastic therapy was no longer indicated, or had life-threatening non-curable diseases.

Each patient admitted to the present PCU was evaluated by a multidisciplinary palliative care team consisting of internal medicine specialist (geriatrician), physician assistant specializing in internal medicine, nurses, dietitian, physiotherapists, psychologist, social workers, and spiritual support specialists. If needed, from other clinics, consultation was requested.

Anthropometric Measurements

Anthropometric measurements were evaluated at the time a patient was admitted to PCU. Due to their clinical condition most participants could not stand on an upright platform scale to be weighed, we used self-reported weight and height from participants or their caregivers to calculate body mass index (7). For the other patients that weight and height could be measured, they were asked to take off their outer wear and shoes to stand on an adult weight scale with height measuring rod (Seca, Hamburg, Germany) for the measurement.

Nutritional Assessment

The nutrition status of the patients was retrospectively assessed with NRS-2002 within 48 hours of hospitalization. NRS-2002 was designed to detect the presence of undernutrition and the risk of developing undernutrition in hospitalized patients through two criteria: Impaired nutritional status and disease severity. NRS 2002 was calculated by summing nutritional status impaired score (0-3) to the severity of disease score (0-3), as well as a score of 1 for patients age >70. The final scoring of NRS-2002 ranges from 0 to 7, and a total score of ≥3 indicates that a patient is "at nutritional risk" (8).

Statistics

Statistical package for the social sciences (SPSS) version 21.0 was used for statistical analyses. Continuous variables were assessed by Kolmogorov-Smirnov test and histograms to find out if they had normal or skewed distribution. Normally distributed parameters were compared by the Student t-test and others by the Mann-Whitney U test. Categorical variables were compared by chi-square or Fisher's Exact tests, where appropriate. Categorical variables were presented as number and frequency. P-value <0.05 was considered statistically significant. Multivariate binary logistic regression was used to identify independent predictors associated with in-hospital mortality. Variables that remained significant ($p<0.05$) in the multivariate model were considered as independent predictors for post discharge short-term mortality. Hosmer-Lemeshow goodness of fit statistics was performed to assess model fit. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each predictor. All variables in Table 1 were determined by clinical significance and tested for multicollinearity; variables with $p<0.2$ after univariate analysis were entered into the multivariable logistic regression model. The final models were determined by backward elimination procedures with $p<0.05$ as model retention criteria.

Results

A total of 118 patients were included in the present data analysis. The mean age of the patients was 70.9±13.4 year and 47% were women. Twenty (16.9%) patients were transferred from other clinics, 17 (14.4%) from home, and 81 (68.6%) from intensive care units to PCU. Patients were hospitalized for a median of 23 days, ranging from 2-107 days (Table 1).

When patients were categorized into two groups (patients who died within 90-day after hospital discharge vs. patients who survived in the same period) the overall post-discharge 90-day mortality was found to be 40% (n=47). Age, gender, and length of stay in PCU were similar between the two groups. With regards to chronic illnesses, chronic obstructive pulmonary disease and malignity were found to be higher in the group with 90-day mortality [9 (19.1%) vs. 5 (7%), p=0.046 and 19 (40.4%) vs. 9 (12.7%), p=0.001, respectively]. NRS 2002 and pressure ulcer rate on admission were higher in patients with 90-day mortality [4 (3-6) vs. 3 (2-5), p≤0.001 and 36 (76.6%) vs. 34 (47.9%), p=0.002, respectively]. In addition, patients had lower both systolic and diastolic blood pressure measurements on admission in the mortality group [108±12.8 vs. 118.6±14.2, p≤0.001 and 67.2±9.5 vs. 72.8±9.5, p=0.002, respectively]. The results of the study regarding ninety day post-discharge mortality are shown in Table 1.

Majority of patients (97.5%) had a NRS score of 3 or above, and 70 patients (59%) had pressure ulcers at admission. Seventy-six patients (64%) were discharged with enteral nutrition [percutaneous endoscopic gastrostomy (PEG)/nasogastric tube], and the rest were on oral nutrition.

When patients were divided into two groups, 28.8% were terminally ill. Age and gender were similar between groups. In addition, length of hospitalization in palliative care unit, discharge with enteral nutrition, frequency of PEG were lower, but the number of patients with malignity, NRS 2002 score, and ninety-day post-discharge mortality were higher in terminally ill group than in those non-terminally ill. Characteristics of the non-terminally and terminally ill patients are denoted in Table 2.

Table 1. The results of the study regarding ninety day post-discharge mortality

	Ninety day post-discharge mortality		
	No (n=71)	**Yes (n=47)**	**p**
Age ± SD	70.8±13.9	71±12.8	0.954
Gender, female, n (%)	36 (50.7)	19 (40.4)	0.273
Length of hospitalization in palliative care unit	23 (3-75)	23 (2-107)	0.766
Length of hospitalization in intensive care unit*	42.5 (7-526)	74 (17-400)	0.007
Body mass index	24.5±3.2	24.6±2.8	0.770
Nutrition type at discharge Oral, n (%) Enteral, n (%)	 24 (33.8) 47 (66.2)	 18 (38.3) 29 (61.7)	0.618
Diabetes mellitus, n (%)	21 (29.6)	13 (27.7)	0.822
Hypertension, n (%)	33 (46.5)	19 (40.4)	0.517
Chronic obstructive pulmonary disease, n (%)	5 (7)	9 (19.1)	**0.046**
Coronary artery disease, n (%)	12 (16.9)	10 (21.3)	0.550
Heart failure, n (%)	6 (8.5)	3 (6.4)	0.679
Dementia, n (%)	16 (22.5)	9 (19.1)	0.659
Atrial fibrillation, n (%)	14 (19.7)	12 (25.5)	0.456
Parkinson disease, n (%)			
Malignity, n (%)	9 (12.7)	19 (40.4)	**0.001**
Metastatic cancer, n (%)	1 (10)	13 (68.4)	**0.005**
Cerebrovascular disease, n (%)	34 (47.9)	15 (32.6)	0.102
Percutaneous endoscopic gastrostomy, n (%)	36 (50.7)	17 (36.2)	0.120
Pressure ulcer, n (%)	34 (47.9)	36 (76.6)	**0.002**
NRS 2002, median (minimum-maximum)	3 (2-5)	4 (3-6)	**<0.001**
Systolic blood pressure ± SD	118.6±14.2	108±12.8	**<0.001**
Diastolic blood pressure ± SD	72.8±9.5	67.2±9.5	**0.002**

*n=78, NRS 2002: Nutritional risk screening, SD: Standard deviation

A binary logistic regression analysis was performed to detect the possible parameters that affect short term post-discharge mortality. Multivariate analysis revealed that, at admission, high NRS 2002 score (OR: 4.03, 95% CI: 1.54-10.52; p=0.005) and low systolic blood pressure (OR: 0.94, 95% CI: 0.90-0.98; p=0.008) were independently associated parameters after adjustment for length of hospitalization in intensive care unit, chronic obstructive pulmonary disease, malignity, cerebrovascular disease, presence of percutaneous endoscopic gastrostomy, NRS 2002 score, presence of pressure ulcer and systolic blood pressure. The results of logistic regression analysis are summarized in Table 3.

Discussion

In this retrospective study, we found that nearly 40% of patients died within three months after hospital discharge from the palliative care unit. We also determined that low systolic blood pressure and a high NRS-2002 score at admission are independently associated risk factors with 3-month mortality after hospital discharge. As far as we know, this study is the first to show the association between nutritional status and short-term mortality after discharge from the palliative care unit.

Palliative care has recently been known as care for patients with neoplasm not responsive to curative treatment or a disease that is life-threatening (definitions from World Health Organization 1990 and 2002) (9). This definition, however, is not synonymous with end-of-life care. For example, patients may receive palliative care earlier in their illnesses while still receiving remedial treatment. Furthermore, having palliative care doesn't necessarily mean that they're likely to die soon-some people have had palliative care for years. For instance, many patients are discharged from our PCU and being followed up for years. Indeed, once a patient is admitted to PCU, home discharge must be among the significant care goals in the PCU, if available (10). After dividing our study sample as terminally ill and non-terminally ill, the vast majority of patients were non-terminally ill. The low number of terminally ill patients in our study may be because the majority of these patients died during hospitalization, and we included patients (majority of non-terminally) who could be discharged from the hospital. As expected, the number of patients with malignity and ninety-day post-discharge mortality was higher, and nutritional status was worse in the terminally ill group than in those non-terminally ill. In addition, the length of hospitalization of the terminally ill patients was lower than those of the terminally ill, which

Table 2. Characteristics of the non-terminally and terminally ill patients

	Non-terminally ill (n=84)	Terminally ill (n=34)	p
Age ± SD	72.1±13	67.9±14.1	0.122
Gender, female, n (%)	42 (50)	13 (38.2)	0.246
Length of hospitalization in palliative care unit	25 (2-107)	16 (3-93)	**0.013**
Nutrition type at discharge Oral, n (%) Enteral, n (%)	 22 (26.2) 62 (73.8)	 20 (58.8) 14 (41.2)	**0.001**
Percutaneous endoscopic gastrostomy, n (%)	46 (54.8)	7 (20.6)	0.001
Malignity, n (%)	1 (1.2)	27 (79.4)	<0.001
NRS 2002	3 (2-5)	4 (2-6)	0.003
Ninety day post-discharge mortality Yes, n (%) No, n (%)	 21 (25) 63 (75)	 26 (76.5) 8 (23.5)	**<0.001**
Systolic blood pressure ± SD	116±14.4	71.1±10	0.055
Diastolic blood pressure ± SD	110.4±14.7	69.4±9.7	0.401

NRS 2002: Nutritional risk screening, SD: Standard deviation

Table 3. Independent predictors of ninety day post-discharge mortality

	Unadjusted		Adjusted	
Risk factors	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Systolic blood pressure	0.94 (0.91-0.97)	**<0.001**	0.94 (0.90-0.98)	**0.008**
NRS 2002 score	5.36 (2.66-10.79)	**<0.001**	4.03 (1.54-10.52)	**0.005**
Pressure ulcer	3.56 (1.57-8.09)	**0.002**	5.47 (0.98-30.30)	0.052

The p-value of the Hosmer-Lemeshow test was 0.898, the following factors were entered into the multivariate logistic regression analysis: Length of hospitalization in intensive care unit, chronic obstructive pulmonary disease, malignity, systolic blood pressure, NRS 2002 score, cerebrovascular disease, presence of PEG, presence of decubitus ulcer. CI: Confidence interval, OR: Odds ratio, NRS 2002: Nutritional risk screening, PEG: Percutaneous endoscopic gastrostomy

is consistent with the study in which individuals requiring palliation did not prefer institutional care and preferred discharging and staying home during the last period of life (11).

When acutely ill, despite normally nourished patients may put up with short-term starvation, malnourished patients may not, and early nutrition support as soon as possible is indicated especially for non-terminally ill patients. Valid and quick detection of malnutrition is essential in hospitalized palliative care patients. In our study, at admission, a significant number of patients, approximately 97.5 percent, had a score of 3 and over, suggesting that they were malnourished or at risk of nutrition. So, nutritional treatment may be of utmost importance, even in the palliative care unit. There are several ways to deliver nutrition and hydration to patients, of which the oral route is the preferred method; nasogastric tubes, PEG, and parenteral nutrition are the others. In our study, most patients (64%) were discharged with enteral nutrition (either PEG or nasogastric tube). PEG tubes, unlike nasogastric tubes, are effective on a long-term basis and possess less risk of aspiration (12). However, providing comfort with PEG tubes for palliative care patients is controversial. Some authors believe that PEG placement for nutritional supplementation is inconsistent with the goal of palliative care which prioritizes comfort without any pain (13). In contrast, others state that these problems (pain, discomfort, and infection) can be dealt with through good nursing management and care (14). In our study, a considerable amount of patients, nearly 4 out of 10 discharged with a PEG. In addition, we found no difference concerning mortality between patients having PEG or not.

Pressure ulcers are more prevalent in palliative care units compared with the general population and those in nursing homes. They are physically and psychosocially distressing for the patients and their carers and associated with significant morbidity and mortality (15). Pressure ulcer prevalance varies from 17 to 47% in palliative care (16). In our study sample, not consistent with previous studies, 59% had pressure ulcers, which may be attributable to the majority of patients transferred from intensive care unit. Moreover, we found that mortality group had significantly higher pressure ulcer rate at admission. These findings are concordant with those reported previously, in which increased mortality rate was reported in patients with pressure ulcer (17).

The results of our analysis demonstrated that low admission both systolic and diastolic blood pressure is an independent predictor of post-discharge mortality in palliative care unit. Patients with low blood pressure may more likely to have advanced disease, low cardiac output and organ perfusion, responding unfavorably to treatment. This finding is in keeping with other studies evaluating the relationship between blood pressure at admission and mortality (18).

Study Limitations

The present study has some potential limitations. First of all, a retrospective method was used for data collection. This might lead to bias owing to missing information and the unavailability of information on confounders in clinical records. Secondly, measurements of skeletal muscle mass and muscle strength, as well as calf circumference, which are powerful indicators of malnutrition, could not be performed due to the design of the study in the patients included in this study. Furthermore, since this study was conducted in a single site, its results may not be widely generalized.

Conclusion

The current study showed that in addition to comorbid diseases, hemodynamic findings, presence of pressure ulcer, and nutritional status on admission may be associated with early post-discharge mortality in patients hospitalized in PCU.

Information: This study has been accepted by the Scientific Committee to be presented during the ASPEN Nutrition Science and Practice Conference which was held from 26 to 29 March, 2022 in Seattle/United States of America and 18. Uludağ İç Hastalıkları Ulusal Kış Kongresi which was held from 03 to 06 March 2022 in Bursa/Turkey. Abstract of this study has been published in the abstract book of these conferences.

Ethics

Ethics Committee Approval: This retrospective study was carried out in a palliative care unit (PCU) in a tertiary hospital according to the Declaration of Helsinki and the guidelines for Good Clinical Practice. The Ethics Committee of Bursa City Hospital approved the study protocol with number 2020-11/1 in 2020.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.D., N.S.K., Concept: O.D., Design: O.D., Data Collection or Processing: O.D., N.S.K., Analysis or Interpretation: O.D., N.S.K., Literature Search: O.D., N.S.K., Writing: O.D., N.S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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The Validation of the Turkish Version of the PRISMA-7 Questionnaire; A Case-finding Instrument for Detecting Older Adults Living with Frailty

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Abstract

Objective: Numerous easy-to-apply and reliable tools have been developed for frailty detection with realizing the obvious importance of it. We aimed to evaluate the reliability and validity of the PRISMA-7 questionnaire in the Turkish community-dwelling older population, incorporating the geriatrician perspective.

Materials and Methods: Upon application of the exclusion criteria, a total of 97 older patients were enrolled. All participants underwent a comprehensive geriatric assessment. After the necessary permissions were obtained, the Turkish version of PRISMA-7 was properly translated into Turkish with a forward-backward translation approach. The adaptation was made complied with the guideline recommendations. A reference tool, the Turkish version of the clinical frailty scale (CFS), was used for validation.

Results: Median (interquartile range) age of participants was 72 (10) years, and 61 (62.9%) were female. According to CFS, 17.5% (n=17) patients were in the frail group, and 82.4% (n=80) were in the Robust/Vulnerable group. When we evaluated the concordance of PRISMA-7 and CFS, there was a moderate concordance (Cohen's kappa: 0.589, p<0.001). At its optimal cut-off for differentiating frail from non-frail patients (≥3), the PRISMA-7 questionnaire had a sensitivity of 94.1% and a specificity of 82.5% (area under the curve: 0.956, p<0.001). For PRISMA-7 inter-rater and retest reliabilities, Cohen's kappas were 0.615, p=0.03 & 1.0, p<0.001, respectively.

Conclusion: The Turkish version of PRISMA-7 is a valid and reliable frailty evaluation instrument for the Turkish geriatric population.

Keywords: Frailty, PRISMA-7 questionnaire, Turkish validation, older adults

Introduction

Frailty is characterized by a reduction in physiological reserve and in resistance to physical and psychological stressors (1). Because of the rapid aging of the population, the prevalence of frailty is projected to increase (2). However, frailty prevalence can change depending on the screening method and population. In addition, it has been reported that in community-dwelling older adults, frailty prevalence may vary from 4% to 59.1% (3). People living with frailty have an increased risk of mortality, hospitalization, falls, and institutionalization (1). In other words, frailty is a major public health concern that can initiate a vicious cycle of many negative outcomes, including death (4). Moreover, early identification of the people living with frailty may enable a proper intervention that will enhance life quality and prevent negative consequences (5).

With realizing the obvious importance of frailty, numerous easy-to-apply and reliable tools have been developed for its detection. Based on two basic approaches, physical frailty and cumulative deficit evaluation tests have been developed to assess frailty. The fried frailty index, Edmonton Frailty scale, clinical frailty scale (CFS), and Program of Research to Integrate the Services for the Maintenance of Autonomy-7 (PRISMA-7) questionnaire

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are among the most commonly used tools (6). The PRISMA-7 identifies frailty by utilizing a combination of seven simple self-reported components. The questions pertain to age, general health, activities, and social support, and each response receives a score of one or zero (7). PRISMA-7 has been translated into a number of languages and validated in a number of nations. Moreover, a previous study in the primary care setting tried to validate the Turkish version of PRISMA-7. However, since the study mentioned above used a reference tool that is also non-validated, it undermines that validation's credibility.

This study aimed to evaluate the validity and reliability of the PRISMA-7 questionnaire in the Turkish community-dwelling older population, incorporating the geriatrician perspective.

Materials and Methods

Participants

In this cross-sectional study conducted over a three-month period, one hundred twenty (120) older patients were evaluated after being admitted to the geriatrics outpatient clinic (November 2021-January 2022). The inability to communicate or answer questions and the presence of an acute illness were determined as exclusion criteria. Therefore, patients aged 65 years and older without exclusion criteria were included in the study. A total of 97 patients aged 65 and older were included in the study. The participants' demographic information (age, gender, education, occupation, and place of residence), chronic diseases, multimorbidity (two or more chronic diseases), geriatric syndromes, medications, polypharmacy (using five or more drugs), smoking, falls, and fracture history from the previous year were collected.

Comprehensive Geriatric Assessment (CGA)

Standardized tools were utilized to perform an optimal CGA. The Katz activities of daily living scale was used to assess the patient's functional status (8). It scored the patient over 6 points based on how independently they performed basic daily tasks and care, with a higher score indicating greater independence (9,10). The Lawton-Brody ınstrumental activities of daily living scale was utilized to assess patients' instrumental daily living activities (11). The mini-mental state examination test, which assesses orientation, memory, attention, calculation, recall, language, motor function, and perception skills, was used to gauge the participants' cognitive status (12). The nutritional screening was made using the mini nutritional assessment short-form; scores >11 points indicate normal nutrition status, 8-11 points indicate malnutrition risk, and 7 points indicate malnutrition (13). Using the Yesavage geriatric depression scale, the patient's mood was evaluated. The evaluation was conducted over 15 points, and patients with more than 5 points were clinically evaluated for depression (14).

The handgrip measurements were performed using the Takei grip strength dynamometer to determine the patients' muscle strength. The dominant hand was measured three times while seated, with the elbow bent at 90 degrees and the hand in the neutral position. In the analysis, the highest of the three repeated measurements was used. Low handgrip strength (HGS) was stated as less than 16 kg for women and more than 27 kg for men, respectively. The physical performance was evaluated by measuring the gait speed. During the 4-meter walking test, the patient was told to walk at a normal pace (with an auxiliary device, if one was used) and stop at a designated point. The elapsed time was recorded in seconds, and the patient's walking speed was then calculated in meters per second. Values below 0.8 m/s were deemed indicative of poor physical performance (15).

Study Tool

PRISMA-7 questionnaire is a tool recommended by the British Geriatric Society (2014) to quickly and simply screen frailty (16). It contains seven simple self-reported questions to detect frailty: Older than 85 years; male; health problems that limit activities; support of another person needed; health problems requiring staying at home; social support; and the use of a cane/walker/wheelchair. Each question is answered as "yes" or "no", and the "yes" answer is scored as 1 point and the "no" answer as 0 points. A total score ≥3 deems as frailty (7). In order to verify the intra- and inter-observer reliability, a sample of 20 participants (10 participants for intra-observer, 10 participants for interobserver reliability) was selected.

Translation

The necessary permissions were obtained from the authors who created the PRISMA-7 questionnaire. The process of forward-backward translation approach and adaptation was made complied with the recommendations of the ISPOR task force for translation and cultural adaptation report (17). Initially, the original PRISMA-7 tool was translated into Turkish by two native Turkish speakers who are also experts in translation and speak English fluently. All authors have reviewed and approved the Turkish version. Then, a professional, native English-speaking translator completed the backward translation without knowledge of the screening tool. Finally, the Turkish version of the PRISMA-7 instrument was administered to a convenient sample of community-dwelling older adults in order to assess cultural adaptation.

Reference Tool

The CFS, a tool created to measure frailty in the second phase of the Canadian Study of Health and Aging, was chosen as the reference instrument. CFS is a frailty screening instrument based on the "cumulative deficit evaluation" model (18). CFS describes frailty by assigning a score between 1 and 9 (1: Very fit; 2:

Well; 3: Well with the treated comorbid disease; 4: Apparently vulnerable; 5: Mildly frail; 6: Moderately frail; 7: Severely frail; 8: Very severely frail; and 9: Terminally ill) according to the physician's clinical opinion. Each point on this scale corresponds to a written description of frailty and is accompanied by a visual classification chart. Scores more than five are considered frail (19). The reliability and validation study of the Turkish version of CFS was conducted by Özsürekci et al. (20).

Statistics

Version 24.0 of SPSS was used to conduct the statistical analysis. To ascertain whether or not variables are normally distributed, visual (histogram, probability plots) and analytical methods were used to investigate the variables. For variables with a normal distribution, descriptive statistics were presented as mean and standard deviation (SD), for variables with an asymmetric distribution, as median [interquartile range (IQR)], and for nominal variables, as the number of cases and percentage (%). Additionally, the Spearman correlation test was run for the variables in the correlation analysis without a normal distribution.

The sample size was calculated using two rater kappa statistics (21) by providing 90% power to determine the correct kappa when two categories according to the CFS scale, Robust+Vulnerable and Frail frequencies in Turkey (20), were 64.0% and 36.0%, respectively.

To evaluate the construct validity of the PRISMA-7, the CFS was accepted as the reference tool. The CFS was classified as robust/vulnerable (scores <5) and frail (scores ≥5) when assessed in its concordance with the PRISMA-7. Cohen's Kappa was utilized to investigate the construct validity and inter-rater reliability of the PRISMA-7. Cohen's Kappa was also utilized to assess test-retest reliability. Sensitivity, specificity, as well as positive and negative predictive values were determined. P-values less than 0.05 were accepted as statistically significant.

Results

Ninety-seven older adults with a median (IQR) age of 72 (10) years were enrolled in the study, of whom 61 (62.9%) were female. Among the participants, 72.2% (n=70) of patients were hypertensive, 51.5% (n=50) had diabetes mellitus, 18.6% (n=18) had coronary heart disease, 12.4% (n=12) had atrial fibrillation, and 10.3% (n=10) had chronic respiratory diseases. The most common geriatric syndromes in this study were polypharmacy, with a prevalence of 55.7% (n=54), and urinary incontinence, with a prevalence of 41.2% (n=40). The mean (± SD) body mass index was 30.06 (±5.82) kg/cm^2. Mean (± SD) HGS was 18.09 (±5.08) and 27.58 (±7.57) for females and males, respectively. The mean (± SD) gait speed was 0.93 (±0.35) m/sn. The median (IQR) CFS score was 3.0 (1.0). According to CFS, 17.5% (n=17) patients were in the Frail group, and 82.4% (n=80) were in the Robust/Vulnerable group. Demographic characteristics, comorbidities, nutritional status, and CGA parameters were summarized in Table 1.

When we evaluated the concordance of PRISMA-7 and CFS, there was a moderate concordance (Cohen's kappa: 0.589, p<0.001) (Table 2). At its optimal cut-off, for differentiating frail from non-frail patients (≥3), calculated using the maximal accuracy approach, the PRISMA-7 questionnaire had a sensitivity of 94.1% and a specificity of 82:5% (area under the curve: 0.956, p<0.001) (Figure 1). For PRISMA-7 inter-rater and retest reliabilities, Cohen's kappas were 0.615, p=0.03 & 1.0, p<0.001, respectively (Table 3).

According to the reference scale, the positive predictive value of PRISMA-7 determined was 53.33%, and the negative predictive value was 98.51% (Table 2). The total prevalence of each component of PRISMA-7 was presented in Table 4.

Discussion

Since frailty is an important problem for aging populations, screening tools that can detect it simply and quickly become prominent. Furthermore, it is clear that frailty screening tools require cross-cultural adaptations. Therefore, this study aimed to evaluate the validity and reliability of the PRISMA-7 questionnaire in the Turkish community-dwelling older population by comparing it with CFS. Our results revealed that the Turkish version of PRISMA-7 and CFS have a good and positive concordance for evaluating frailty.

According to the Turkish Statistical Institute data presented in 2021, the ratio of individuals aged 65 and over has increased to 9.7% (22). Furthermore, since it is expected to increase to 12.9% in 2030 in Turkey (23), it is obvious that frailty will be an essential concern in Turkey as an aging country. Considering that frailty reflects a health burden, particularly in the geriatric population, detecting and intervening at the earliest stages is crucial. In this study, PRISMA-7 was chosen to be evaluated whether it is a proper tool to screen frailty for older adults in Turkey since it is an easy-applicable and brief form to perform in geriatrics outpatient clinics.

The prevalence of frailty may vary depending on the environment and the instruments used for screening. In the Frail TURK project, a study designed to assess frailty in the population aged 65 and over in Turkey, Fried Frailty criteria were used, and 39.0% of 1126 participants were defined as frail (23). Similarly, in the validation study of the Turkish version of CFS, frailty frequency was reported as 35.6% (20). In concordance with the previous studies, 30.9% of participants in our study were frail, according to the Turkish version of PRISMA-7.

Table 1. Demographical characteristics and comprehensive geriatric assessments of patients

		Total participants n=97	Robust (n=67, 69.1%)	Frail (n=30, 30.9%)	p
Demographics					
Age, median (IQR)		72.0 (10.0)	71.0 (8.0)	76.0 (14.0)	<0.001
Sex (female), n (%)		61 (62.9)	40 (59.7)	21 (70.0)	0.33
Illiterate, n (%)		21 (21.6)	13 (19.4)	8 (26.7)	0.42
Marital status (married), n (%)		60 (61.9)	45 (67.2)	15 (50.0)	0.11
BMI mean ± SD		30.06±5.82	29.25±4.84	29.49±7.55	0.46
Smoking, n (%)		38 (39.2)	27 (40.3)	11 (36.7)	0.74
Chronic diseases					
Diabetes mellitus, n (%)		50 (51.5)	39 (58.2)	11 (36.7)	0.05
Hypertension, n (%)		70 (72.2)	45 (67.2)	25 (83.3)	0.10
Coronary artery disease, n (%)		18 (18.6)	12 (17.9)	6 (20.0)	0.81
Congestive heart failure, n (%)		6 (6.2)	4 (6.0)	2 (6.7)	1.0
Atrial fibrillation, n (%)		12 (12.4)	7 (10.4)	5 (16.7)	0.51
Cerebrovascular event, n (%)		10 (10.3)	6 (9.0)	4 (13.3)	0.49
Chronic kidney disease, n (%)		4 (4.1)	2 (3.0)	2 (6.7)	0.59
Chronic obstructive pulmonary disease-asthma, n (%)		10 (10.3)	7 (10.4)	3 (10.0)	1.0
Malignancy, n (%)		11 (11.3)	4 (6.0)	7 (23.3)	0.03
Hypothyroidism, n (%)		10 (10.3)	4 (6.0)	6 (20.0)	0.07
Multimorbidity ≥2, n (%)		70 (72.2)	47 (70.1)	23 (76.7)	0.51
Comprehensive geriatric assessment-geriatric syndromes					
Dementia, n (%)		4 (4.1)	-	4 (13.3)	0.008
Depression, n (%)		29 (29.9)	17 (25.4)	12 (40.0)	0.15
Osteoporosis, n (%)		22 (22.7)	13 (19.4)	9 (30.0)	0.25
Falls, n (%)		22 (22.7)	12 (17.9)	10 (33.3)	0.09
Polypharmacy, n (%)		54 (55.7)	32 (47.8)	22 (73.3)	0.02
Drug number, median (IQR)		5.0 (4.0)	4.0 (3.0)	6.0 (4.0)	0.008
Urinary incontinence, n (%)		40 (41.2)	22 (32.8)	18 (60.0)	0.01
Katz index of independence in activities of daily living, median (IQR)		6.0 (1.0)	6.0 (0.0)	6.0 (1.0)	0.002
Lawton-Brody instrumental activities of daily living scale, median (IQR)		8.0 (0.0)	8.0 (0.0)	6.0 (4.0)	<0.001
Mini nutritional assessment-short form, median (IQR)		13.0 (4.0)	14.0 (2.0)	10.0 (6.0)	<0.001
Mini-mental state exam, median (IQR)		28.0 (5.0)	28.0 (5.0)	26.0 (8.0)	0.008
Yesevage geriatric depression scale, median (IQR)		2.0 (6.0)	2.0 (5.0)	4.5 (6.0)	0.01
SARC-F, median (IQR)		1.0 (3.0)	0.0 (1.0)	4.0 (6.0)	<0.001
Grip strength mean ± SD	Female	18.09±5.08	18.30±4.05	15.21±5.68	0.004
	Male	27.58±7.57	28.55±7.76	24.68±6.54	0.19
Gait speed (m/sn), mean (SD)		0.93±0.35	1.04±0.30	0.67±0.31	<0.001
PRISMA-7, median (IQR)		2.0 (2.0)	2.0 (1.0)	4.0 (2.0)	<0.001
Clinical frailty scale, median (IQR)		3.0 (1.0)	3.0 (1.0)	5.0 (2.0)	<0.001

N: Number, IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, PRISMA-7: Program of Research to Integrate the Services for the Maintenance of Autonomy-7

Table 2. PRISMA-7 and reference test (CFS) concordance results

		PRISMA-7 questionnaire		Kappa	Approximate significance
		Robust	Frail		
Clinical frailty scale	Robust+vulnerable	66 (98.5)	14 (46.7)	0.589	<0.001
	Frail	1 (1.5)	16 (53.3)	-	-
Inter-rater reliability		-	-	0.615	0.03
Retest reliability		-	-	1.0	<0.001

Spearman Rho CFS-prisma: 0.577, p<0.001, Sensitivity: 94.12%, Specificity: 82.50%, Positive likelihood ratio: 5.38, Negative likelihood ratio: 0.07, Positive predictive value: 53.33%, Negative predictive value: 98.51%, CFS: Clinical frailty scale, PRISMA-7: Program of Research to Integrate the Services for the Maintenance of Autonomy-7

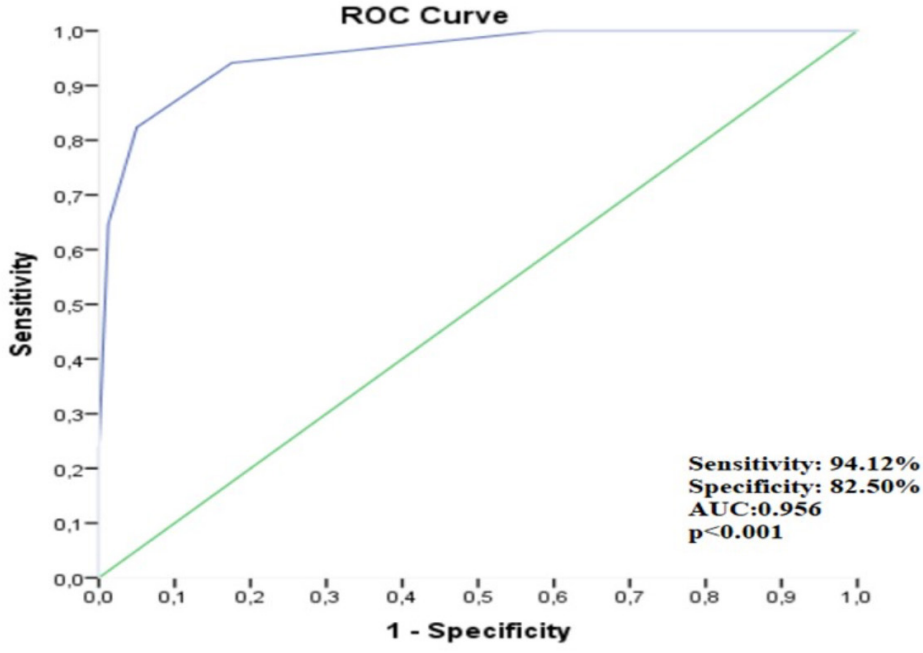

Figure 1. Receiver operating characteristics (ROC) curve demonstrating the accuracy of Turkish version of PRISMA-7 questionnaire

AUC: Area under the curve, PRISMA-7: Program of Research to Integrate the Services for the Maintenance of Autonomy-7

Table 3. Inter-rater and retest reliability results of the components of PRISMA-7

	Inter-rater reliability	Retest reliability
	Cronbach's alpha	Cronbach's alpha
Age >85 years	1.0	1.0
Male gender	1.0	1.0
In general, do you have any health problems that require you to limit your activities?	0.78	0.89
Do you need someone to help you on a regular basis?	0.78	0.89
In general, do you have any health problems that require you to stay at home?	0.78	0.78
If you need help, can you count on someone close to you?	1.0	1.0
Do you regularly use a stick, walker or wheelchair to move about?	1.0	1.0
Total score	0.78 (0.12-0.95)	0.91 (0.65-0.98)

PRISMA-7: Program of Research to Integrate the Services for the Maintenance of Autonomy-7

Table 4. Total prevalence of the components of PRISMA-7	
	Prevalence n (%)
Age >85 years	10 (10.3)
Male gender	36 (37.1)
In general, do you have any health problems that require you to limit your activities?	30 (30.9)
Do you need someone to help you on a regular basis?	21 (21.6)
In general, do you have any health problems that require you to stay at home?	18 (18.6)
If you need help, can you count on someone close to you?	93 (95.9)
Do you regularly use a stick, walker or wheelchair to move about?	17 (17.5)
PRISMA-7: Program of Research to Integrate the Services for the Maintenance of Autonomy-7	

Although CGA is the standard method for frailty evaluation, numerous frailty screening instruments have been created based on the physical frailty and cumulative deficit accumulation frailty models. Since CFS is focused on both biological theory and clinical judgment, it distinguishes from other methods based on cumulative frailty. Since, recently, the associations between social, cognitive and physical frailty were revealed, combining cognitive and physical function items is one of the advantages of CFS (19). Furthermore, a valid and reliable Turkish version of CFS was presented in a recent study (20). Therefore, CFS was chosen as a standard tool for this validation study. A previous study conducted in primary care in Turkey, tried to validate PRISMA-7 by comparing it with CFS. Unfortunately, when the study mentioned above was carried out, there was no validated version of the CFS (24). As this main limitation makes proper validation necessary, we re-performed an appropriate validation study by comparing the Turkish version of the PRISMA-7 questionnaire to the valid Turkish version of CFS.

International guidelines also advise using the PRISMA-7, one of the quick and practical tools for identifying frailty in older adults (25,26). Additionally, some studies have been carried out to evaluate how accurately it predicts the risk of negative outcomes in frail adults (27). The suitability of PRISMA-7 was also investigated in primary care, which is an important step in assessing frailty. In a study carried out by Hoogendijk et al. (28), five instruments (i.e., the Groningen frailty indicator, prescription of multiple medications, clinical judgement of the general practitioner, the self-rated health of the older adult and PRISMA-7) have been compared, and PRISMA-7 has been the most accurate one of these tools for identifying frailty in primary care. It has also been demonstrated to be useful in a hospital ward as a screening instrument to define elderly older adults who may benefit from further geriatric assessment during their hospitalization (29). Although this study was not primarily designed to assess the power of the Turkish version of PRISMA-7 for detecting adverse health outcomes related to frailty, future studies may evaluate this predictive value in both outpatient and hospital settings.

Study Limitations

This study has several limitations as well. Although there is no universally accepted strategy for performing a cross-cultural adaptation of questionnaires, our methodology adhered to commonly stated guidelines. In addition, the lack of a standard instrument for the accurate evaluation of frailty hinders comparability. Since reviews on frailty tools constantly document the clinical and diagnostic power of the CFS, we used CFS as a reference tool to alleviate this limitation.

Conclusion

The Turkish version of PRISMA-7 is a valid and reliable frailty evaluation tool for the Turkish geriatric population.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee in the Department of Medicine at Hacettepe University (GO-21/1313). All processes were carried out in compliance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, as well as the ethical standards of the institutional and/or national research committee.

Informed Consent: All participants provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O.B., S.C., Concept: A.O.B., M.K., B.B.D., C.B., Design: A.O.B., M.K., M.G.H., M.C., C.B., Data Collection or Processing: A.O.B., S.C., M.G., Analysis or Interpretation: A.O.B., S.C., B.B.D., M.G.H., M.C., C.B., Literature Search: A.O.B., Writing: A.O.B., S.C., C.B.

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ORIGINAL RESEARCH

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Demographic and Neuropsychologic Profiles of Patients with Neurodegenerative Dementia: Results from A Tertiary Referral University Hospital

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Abstract

Objective: Although the prevalence of dementia is increasing globally, the data related to dementia patients living in North Cyprus is very limited. The aim of this study was to evaluate the demographic and neuropsychological characteristics of patients diagnosed with neurodegenerative dementia.

Materials and Methods: The data of 105 patients with neurodegenerative dementia, who were followed up in the neurology departments of the Dr. Suat Günsel University of Kyrenia Hospital and Near East University Hospital between 2018 and 2021, were collected both retrospectively and prospectively. The patients underwent diagnostic procedures by neurologic examination, neuropsychologic evaluation based on the measures of attention and executive functions, memory, language, mood and visuospatial perception and neuroimaging. All the results were evaluated statistically according to the dementia subgroups.

Results: Out of 105 patients, 58 were female and 47 were male. The mean age was 74.34±10.41. The most common dementia type was Alzheimer's dementia (AD) (77/105), followed by Lewy body dementia (LBD) (15/105) and frontotemporal dementia (FTD) (13/105). The initial median mini mental state examination (MMSE) score was 20. There was a positive correlation between years in higher education and lower MMSE scores. Out of the 105 patients, 81 spoke Turkish and 13 spoke English as a native language. Depression occurred more frequent in earlier stages and milder cases. The visuospatial functions were affected more in LBD and FTD patients when compared to AD patients. Prosopagnosia was significant for the differential diagnosis of Parkinson's dementia from other forms of dementia. Also, a decrease in categorical fluency was observed in patients with higher depression scores.

Conclusion: These results are important as this is the first study determining the detailed dementia subgroups and neuropsychologic profiles of dementia patients living in North Cyprus.

Keywords: Dementia, neurodegeneration, prosopagnosia, aging, Alzheimer's disease

Introduction

There is a growing probability of chronic and age-associated diseases like dementia. The global prevalence of dementia in the general population older than 60 years of age is 5-7% (1). The majority of these patients live in low and middle income countries. The strongest known risk factor is age, but dementia does not develop as a normal part of aging. The most common type of dementia is Alzheimer's disease (AD) accounting for 60-70% of all dementia patients (2,3).

Lewy body dementia (LBD) is an umbrella term covering two clinical entities, namely Parkinson's disease dementia (PD) and Dementia with Lewy bodies (DLB), making it the second most

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common type of neurodegenerative dementia after AD (4,5). DLB accounts for 24.7% of people with dementia (6). According to the DLB consortium, they are distinguished by the relative timing of motor Parkinsonism (7).

DLB should be diagnosed when dementia occurs before or concurrently with Parkinsonism, whereas PD is the dementia that occurs in the context of well-established Parkinson's disease (6).

Patients with Parkinson's disease (which is the second most common neurodegenerative disease) have a 2.5-6 times higher risk of developing dementia than people without disease (8). The cognitive involvement with executive and visuospatial impairments is typical in these patients (9).

Frontotemporal dementia (FTD) predominantly affects frontal and/or temporal lobes with three prototypes semantic dementia, progressive non-fluent aphasia and behavioral variants (10). Primary progressive aphasia (PPA) is in the frontotemporal spectrum group, where the prominent clinical feature is difficulty with language (11), whereas the behavioral variant of FTD requires three of six discriminating features consisting of disinhibition, apathy, loss of empathy, compulsive behaviors, hyperorality and dysexecutive neuropsychological profile (12).

After the consensus clinical diagnostic criteria were established in 2011, FTD was classified as a behavioral variant, whereas semantic and progressive non-fluent aphasia variants were classified under the umbrella of PPA (11,12).

FTD accounts for 20% of all cases of degenerative dementia. According to some sources, the prevalence of FTD is similar to that of AD with 15 cases per 100.000 in 45-64 age group (13,14).

The aim of this study is to determine the demographic findings and neuropsychological profiles of patients with neurodegenerative dementia living in North Cyprus.

Materials and Methods

Patient Selection and Diagnostic Evaluation

The data of 105 patients with neurodegenerative dementia who were followed up in the neurology departments of the Dr. Suat Günsel University of Kyrenia Hospital and Near East University Hospital between 2018 and 2021 were collected. The study was conducted both retrospectively (including the patients without any missing data in the system) and prospectively for newyl diagnosed patients.

All the patients underwent neuropsychological assessment by a single certified neuropsychologist. All patients had dementia blood screen and structural imaging was performed preferentially with MRI.

The diagnostic procedure included movement disorder society PDD criteria, DLB consortium criteria, National Institute of neurological disorders and stroke association criteria and FTD consortium new highly sensitive revised criteria (4,7,12,15-18). The final diagnosis was made by the neurologist.

Neuropsychological Assessment

The neuropsychologic tests were performed on all patients in Turkish or English according to the patient's native language. These assessments were focused on the main measures of attention and executive functions, memory, language, mood and visuospatial perception.

The neuropsychological test battery included 14 tests namely the mini-mental state test (19), digit span test (20,21), trails making test (22), verbal fluency (23), clock drawing test, stroop color word interference test (24), similarities (WAIS-R subtest) (25), Luria test, Benton line judgment orientation test (26), Benton facial recognition test (27), figure copying test, Boston naming test (28), Oktem verbal memory processes test (29) and geriatric depression scale (30).

According to the Turkish validated version of the mini mental state examination (MMSE), the cut-point for cognitive function was as follows: 24-30 points: Normal range, 23-18: Mild dementia, 17-0: Severe dementia (31).

The trail making test has been standardized in the Turkish alphabet in the B form, where the letters are in the range of A-I and the normal values of the test for participants aged 50 and over were determined by Cangoz et al. (32).

The standardized clock drawing test for the Turkish sample aged 50 and over was used for Turkish speaking patients (33).

Also, valid and reliable Turkish forms of the stroop color word interference test (34), Benton facial recognition test (35), and Boston naming test (36) were used.

For the Geriatric depression scale, the Turkish validity-reliability study was conducted by Ertan et al. (37) and the cut-off score was determined to be 14.

The inclusion criteria: The patients who were diagnosed with neurodegenerative dementia according to the above-mentioned criteria and underwent the neuropsychologic test battery that was performed by the same educated neuropsychologist.

The exclusion criteria: Patients were excluded if they had any psychiatric disorder, secondary causes of dementia like normal pressure hydrocephalus or Limbic encephalitis, mild cognitive impairment or neuroimaging evidence of another disorder that could explain their symptoms or had no neuroimaging available.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the University of Kyrenia Ethics Committee (date: 25.01.2022, no: GÜ/ETK-22-20).

Statistics

The normality of the data was evaluated using histograms, q-q plots and the Shapiro-Wilk test. Correlations between categorical variables were evaluated using the chi-square test and Monte-Carlo method. Age and group comparisons were made by using the Student's t-test. The level of statistical significance was set at $p<0.05$. Analysis of the data was performed using SPSS 22 statistical software.

Results

The study included 105 patients with degenerative dementia. Out of these 105 patients, 58 (55.2%) were female and 47 (44.8%) were male. The mean age at diagnosis was 74.34±10.41. The causes of dementias were AD in 77 (73.3%), FTD in 13 (12.4%), DLB in 6 (5.7%) and PD in 9 (8.6%) patients.

The initial median MMSE score at diagnosis was 20 (ranging from 14 to 23). According to the MMSE scores, 43 (41.7%) of them had severe dementia, and 37 (35.9%) had mild dementia at the time of diagnosis. The MMSE score was normal in 23 (22.3%) patients.

The years of education were between 0-5 years in 26 (25.7%), 6-11 years in 45 (44.6%) and 12 years and above in 30 (29.7%) of the patients.

Depression was observed in 26 (36.1%) of the patients. There was also a statistically significant association between geriatric depression and MMSE scores ($p<0.05$). Higher depressive scores were observed in milder dementia cases.

There was a statistically significant positive correlation between years in higher education and lower MMSE scores ($p<0.05$).

Out of 105 patients, 81 (77.1%) of them spoke Turkish and 13 (%13.3) spoke English as a native language. Ethnic backgrounds included 61 (62.2%) Turkish Cypriots with permanent residency in North Cyprus, whereas the others comprised a mixture of citizens and residents from Turkey, England, Russia and Turkmenistan.

Detailed descriptive statistic results of the Benton facial recognition, Benton line judgement orientation, clock drawing, Boston naming, similarities, verbal fluency, figure copying, Trails making, Stroop color Word interference, Oktem verbal memory processes, Attention and Fluency tests are shown in Table 1.

When the dementia subgroups and visuospatial, attention and executive functions were compared, a statistically significant association was observed. The visuospatial functions were affected more in LBD, FTD and PD compared to AD ($p<0.05$) (Table 2).

The Benton facial recognition test was statistically significant for the differential diagnosis of PD from other types of dementia

Table 1. The neuropsychologic test results of the patients

Variables (Neuropsychologic domains and tests)	Descriptive statistics n (%)
Benton facial recognition test	
Normal	23 (53.5)
Borderline	6 (14.0)
Impaired	7 (16.3)
Advanced impaired	7 (16.3)
Benton line judgement orientation test	
Normal	14 (35.9)
Impaired	25 (64.1)
Clock drawing test	
Normal	35 (38.9)
Impaired	55 (61.1)
Boston naming test	
Normal	26 (56.5)
Impaired	19 (41.3)
Similarities (WAIS-R subtest)	
Normal	23 (39.7)
Impaired	35 (60.3)
Lexical fluency	
Normal	16 (29.6)
Impaired	38 (70.4)
Figure copying	
Normal	49 (56.3)
Impaired	38 (43.7)
Luria's test	
Normal	14 (30.4)
Impaired	32 (69.6)
Trail making test	
Normal	5 (8.5)
Impaired	54 (91.5)
Stroop color word interference test	
Normal	2 (13.3)
Impaired	13 (86.7)
Oktem verbal memory processes test	
Normal	9 (10.1)
Impaired	80 (89.9)
Basic attention	
Normal	37 (40.7)
Impaired	54 (59.3)
Complex attention	
Normal	4 (4.7)
Impaired	82 (95.3)
Categorical fluency	
Normal	6 (40.0)
Impaired	9 (60.0)
Semantic fluency	
Normal	4 (26.7)
Impaired	11 (73.3)

(p<0.05) (Table 3). There was no other correlation between the other tests and dementia subgroups.

When the geriatric depression scales were compared with the diagnosis and different neuropsychologic domains; a decrease in categorical fluency was positively associated with higher depressive scores (p<0.05). No other relation was observed among dementia subtypes, other neurodomains and depression.

Discussion

In the study group, the most common etiology of neurodegenerative dementia was AD (73.%). The second most common type of dementia was LBD with 14.3% and 12.4% FTD respectively. There was a higher number of female patients (55.5%) and all these findings are parallel to the current literature.

Men have a higher risk of developing DLB (5) and the male predominance of FTD in the US, Greece and Turkey was reported in previous studies (38). However, there was a female predominance (17/28) in our LBD and FTD group.

The study population was relatively well educated as 74.6% had secondary or higher education. It is known that the sensitivity of MMSE is low in highly educated populations (39,40). In our patient group, we also observed a relation between higher education years and lower MMSE scores (p<0.05). MMSE cannot distinguish dementia syndromes and some patients who meet the criteria may score in the normal range (41). This is also in line with our findings as 22.3% of the patients were considered to be in the normal range according to the MMSE scores.

Late-life depression and dementia may share common neurobiology in older patients. Depression is considered as a prodrome and/or risk factor for dementia (42). Depression was observed in 26 (36.1%) of the patients.

In a recent published study, early stage Alzheimer's patients had higher MMSE and more depressive symptoms (43). This finding is similar to ours as there was an association between geriatric depression and MMSE scores (p<0.05). Higher depression scores were observed in cases of milder dementia and higher MMSE scores in our study group.

Patients with neurodegenerative dementia have different neuropsychological profiles, which can only be distinguished in the early phases of dementia. For example, in typical AD, episodic memory is impaired whereas executive functions and behavior are relatively spared. On the other hand, in FTD, episodic memory is typically spared, whereas executive functions (working memory, planning, generation, abstraction, problem solving and mental flexibility) and behavior are impaired (12,44). In DLB, executive, visuospatial and attention deficits are more prominent compared to other types of dementia (5,45,46). This finding is similar to our finding in that the visuospatial functions were affected

Table 2. The relation between dementia subgroups and attention, executive and visuospatial functions

Variables	Diagnosis				p
	AD (n=77)	LBD (n=6)	FTD (n=13)	PD (n=9)	
Visuospatial functions					
Normal	28 (45.9)	0 (0.0)	2 (16.7)	2 (25.0)	0.039
Impaired	33 (54.1)	6 (100.0)	10 (83.3)	6 (75.0)	
Attention and executive functions					
Normal	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.999
Impaired	68 (97.1)	6 (100.0)	13 (100.0)	9 (100.0)	

AD: Alzheimer's dementia, LBD: Lewy body dementia, FTD: Frontotemporal dementia, PD: Parkinson disease dementia

Table 3. The relation between dementia subgroups and prosopagnosia

Variables	Diagnosis				p
	AD (n=77)	LBD (n=6)	FTD (n=13)	PD (n=9)	
Benton facial recognition					
Normal	18 (60.0)	2 (100.0)	3 (50.0)	0 (0.0)	0.020
Borderline	5 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	
Impaired	4 (13.3)	0 (0.0)	2 (33.3)	1 (20.0)	
Advanced impairement	3 (10.0)	0 (0.0)	0 (0.0)	4 (80.0)	

AD: Alzheimer's dementia, LBD: Lewy body dementia, FTD: Frontotemporal dementia, PD: Parkinson disease dementia

more dominantly at the time of diagnosis in patients with LBD, FTD and PD compared to the patients with AD ($p<0.05$) (Table 2).

Prosopagnosia is widely reported in patients with posterior cortical atrophy (pathologically considered as AD) and FTD, but is less expected in PD (47,48). A very interesting case of index patient was reported with a novel PSEN mutation causing early onset AD with prosopagnosia and Parkinsonism together (49). According to a recent study, prosopagnosia was the most unique symptom of right temporal variant of FTD. This finding was not seen in AD and less in FTD group (50). According to our findings, prosopagnosia was a statistically significant finding for the differential diagnosis of Parkinson's dementia from other types of dementia ($p<0.05$). Similarly, it has previously been reported in different studies that unfamiliar face recognition memory and facial expression recognition may be impaired in the course of Parkinson's disease (47,51). The mechanism proposed here, is the addition of the posterior-cortical defect over frontal executive impairment (52). Also, cases who developed paroxysmal prosopagnosia episodes before progressing from Parkinson's disease to PD were reported in the literature (48).

In our study group, when depression was compared with the dementia subgroup and neuropsychologic domains; no association was found between depression and dementia subgroups. Some studies suggest that action naming is more affected in FTD, whereas object naming is more disturbed in AD (53).

According to our findings, a decrease in categorical fluency was positively associated with higher depressive scores ($p<0.05$).

It is also important to emphasize that neuropsychological profiles are not always definite rules. Forexample approximately 10% of patients with FTD may show episodic memory deficits at initial presentation (54,55).

Another point is that the large FTD consortium study was carried out mainly on Western European and North American behavioral FTD patients whose native language is English and it may not effectively diagnose those speaking other languages (56).

Study Limitations

In our patient group, only 13.3% of the patients spoke English as their native language and 37.8% of them had migration backgrounds. It is known the patients with migration backgrounds may also cause different challenges, including language skills and cultural characteristics, leading to difficulties in evaluating cultural and language sensitive cognitive tests causing under diagnosis (57,58). This may be one of the limitation of our study. Another limitation is that our battery did not include specific tests such as the social recognition test (which is highly reccommended in recent studies) in FTD patients. Our sample size is also limited to the patients at two different tertiary referral centers.

Conclusion

Our study revealed the first data of patients with neurodegenerative dementia in North Cyprus. The most common type was AD, followed by LBD and FTD. Depression occurred more in patients in the earlier stages. The visuospatial functions were affected more in LBD and FTD patients and prosopagnosia was significant for the differential diagnosis of PD from other forms of dementias.

Ethics

Ethics Committee Approval: This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the University of Kyrenia Ethics Committee (date: 25.01.2022, no: GÜ/ETK-22-20).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.G., S.E.M., S.D., F.Ç., Design: P.G., S.E.M., S.D., F.Ç., Data Collection or Processing: P.G., S.E.M., S.D., F.Ç., Analysis or Interpretation: P.G., S.E.M., Literature Search: P.G., S.E.M., Writing: P.G., F.Ç.

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ORIGINAL RESEARCH

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Potentially Inappropriate Medication Use in Older Adults Intensive Care Patients According to TIME-to-STOP Criteria

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Abstract

Objective: It was aimed in this study, to determine the prevalence and pattern of potentially inappropriate medication (PIM) use according to TIME-to-STOP criteria in older adults hospitalized in the intensive care unit (ICU). In addition, the results were compared with the results of our previous study, evaluated by 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list.

Materials and Methods: In this descriptive study, the data of patients aged 65 and over (n=139) hospitalized in the University Hospital ICU between 8 June 2020 and 11 January 2021, were evaluated retrospectively. The relationship between dependent and independent variables was evaluated with chi-square, Mann-Whitney U and t-test analyses.

Results: The number of patients with at least one PIM use according to TIME-to-STOP criteria was 67 (48.2%) [80.6%, 59.7%, 48.2% in Beers, STOPP/v2 and EU(7)-PIM list, respectively]. PIM use showed no significant difference in terms of demographic and clinical characteristics. The groups causing the highest rates of PIM use were antipsychotic, propulsive and sedative-hypnotic drugs. The presence of PIM use and prognosis showed no relationship; mortality was significantly higher in patients using midazolam and digoxin.

Conclusion: According to TIME-to-STOP criteria, at least one PIM use was detected in approximately half of the older adults hospitalized in the ICU. In TIME-to-STOP criteria and 3 other screening criteria, there were differences between the prevalence of PIM, the drugs regarded as PIM or the PIM evaluation criteria. It is considered that there is a need to extend the scope of TIME-to-STOP criteria for ICU patients.

Keywords: Potentially inappropriate medication, intensive care unit, older adults, TIME-to-STOP criteria, explicit criteria

Introduction

"Potentially inappropriate medication (PIM) use" was defined as using the drugs having a greater risk of harm in older adults than the expected benefit, which should be avoided if safer alternatives are available (1). Various criteria were developed for the evaluation of PIM use in the older adults and to guide physicians in selecting safe drugs in the clinical practice: Explicit (criteria-based) and implicit (judgment-based) criteria (2).

Physician's clinical evaluation is considered by implicit criteria, while evaluating prescriptions (3). Explicit criteria however, provide information and guidance on optimal drug use by presenting lists of drugs that should be avoided (4). The first of such criteria developed for this purpose is "Beers criteria", defined by the American Geriatrics Society in 1991 (5).

Since then, many countries developed their own PIM use criteria. In Europe, STOPP/START criteria, EU(7)-PIM list, NORGEP-NH criteria, PRISCUS List; in Brazil CBMPII criteria; in China, Chinese PIM criteria are some of those (6-11). Although there are many studies to date, conducted especially with Beers criteria and STOPP/START criteria in our country, considering differences in diagnosis-treatment guidelines, prescribing habits and the drug market, PIM use criteria specific to Turkey is required. Criteria Set of Turkish Inappropriate Medication Use in the Elderly (TIME-to-START and TIME-to-STOP), based on STOPP/START criteria,

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was established under the leadership of the Rational Drug Use Study Group of the Turkish Academic Geriatrics Society (12). It was developed by a multidisciplinary team of experts using the "Delphi technique". Thus, TIME criteria was enabled to be used not only in Turkey but also in other countries, especially in Europe. The criteria were presented in Turkish with a view to guide the non-geriatrician physicians while planning treatment for older adults in daily clinical practice and to make it easy to understand. Furthermore, a mobile application was developed so that healthcare professionals could easily access TIME criteria at any time (4).

Older adults ICU patients are more frail and have more comorbidities with respect to other patients. On the other hand, treatment protocols can greatly vary during ICU stay due to acute development of the diseases and their critical nature, where many drugs are used, typically for a short period of time (13). Moreover, the involvement of several physicians in treatment, with insufficient coordination between them and insufficient time for consultation may also lead to increased PIM use in older adults in the ICUs (14). Several studies conducted with this patient group using different criteria revealed the prevalence of PIM use as 48-98% (15-18).

In our previous study, a prospective study on older adults hospitalized in the ICU, we determined the prevalence of PIM use as 80.6%, 59.7% and 48.2%, according to 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list, respectively (18). In the present study, analyzing our previous study data according to the recently published TIME-to-STOP criteria. We aimed to determine a) the prevalence of PIM use in ICU patients and affecting factors, b) the drug groups most frequently evaluated as PIM, c) the relationship between the 28-day mortality rates and the length of stay in the ICU with PIM use. Another aim was to compare the PIM use results obtained by TIME-to-STOP criteria in this study with the results of our previous study, evaluated by 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list.

Materials and Methods

This is a cross-sectional study. The data of our previous study (data of 139 patients aged 65 and over, hospitalized in Dokuz Eylül University Research and Application Hospital Internal Medicine ICU and Anesthesia ICU between 8 June 2020-11 January 2021) were evaluated retrospectively (18).

Evaluated data of patients: demographic characteristics (age, gender, body mass index, number of comorbidities), administration of mechanical ventilation (MV) and/or renal replacement therapy (RRT), mortality data (yes/no), length of ICU stay (days), laboratory findings (serum creatinine, GFR, sodium, potassium) and medication use data (active ingredients, daily dose and use number), Charlson Comorbidity Index (predicts one-year mortality), Glasgow Coma Scale (evaluates the state of consciousness by scoring responses to eye/verbal/motor stimuli), acute physiology and chronic health evaluation II score (APACHE II, evaluates the disease severity) and mortality (death occurred in the first 28 days after ICU admission).

PIM use was evaluated by TIME-to-STOP criteria for drugs used by patients during their ICU stay (12). Polypharmacy was defined as the use of 5 or more medications.

Statistics

Descriptive statistics were implemented for the demographic data of each hospitalization of the patients and the presence of PIM use. Results were given as number (n), percentage (%) and mean (standard deviation). The relationship between the dependent variable (presence of PIM use) and independent variables (demographic data, clinical characteristics) was evaluated by chi-square analysis. Independent variables were analyzed in two different groups according to the median values.

The relationship between the presence of PIM use, drugs, and 28-day mortality was evaluated by chi-square analysis and Fisher's Exact test. The relationship between the presence of PIM use and the average number of days of stay in the ICU was evaluated by using the Student's t-test for parametric data and the Mann-Whitney U test for non-parametric data. All data were analyzed by the SPSS-24 (SPSS INC., Chicago, IL, USA) statistical program and $p<0.05$ was considered statistically significant.

The research was initiated after the approval of the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylül University and carried out in accordance with the principles of the Declaration of Helsinki.

Results

Mean age of 139 patients included in the study was 76.7 ± 7.7 (65-102) years and 51.1% (n=71) of them were male. Respiratory system diseases was the most common diagnosis of hospitalization, with a rate of 38.1%. MV support was used in 89.2% (n=124) of the patients. Mean length of ICU stay was 12.2 ± 9.9 days. Polypharmacy occured in 90.6% (n=126) of the patients. Mortality occured in 32.4% patients in this period.

Patients with at least one PIM use according to the TIME-to-STOP criteria was 48.2% (n=67) (Figure 1). There was no statistically significant difference between the presence of PIM use and demographic and clinical characteristics, according to TIME-to-STOP criteria, ($p>0.05$) (Table 1). Polypharmacy was not statistically significantly affecting the presence of PIM according to TIME-to-STOP criteria ($p=0.057$).

According to TIME-to-STOP criteria, the most common drugs evaluated as PIM were antipsychotics (quetiapine or haloperidol)

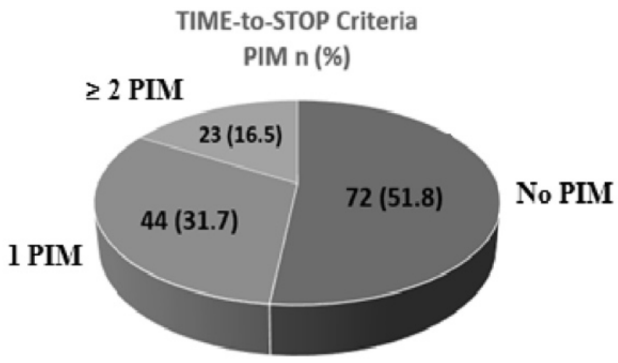

Figure 1. Potentially inappropriate drug use (PIM use) in elderly patients (n=139) hospitalized in the intensive care unit, according to TIME-to-STOP criteria

Table 1. Factors affecting PIM use according to TIME-to-STOP criteria

	TIME-to-STOP criteria Presence of PIM use (n=67)	p-value
Age (years) (n) 65-74 (65) 75-84 (50) ≥85 (24)	 32 (49.2) 23 (46.0) 12 (50.0)	0.925
Gender (n) Female (68) Male (71)	 34 (50.0) 33 (46.5)	0.678
Body mass index (n) <25 (62) ≥25 (77)	 29 (46.8) 38 (49.4)	0.763
Mechanical ventilation (n) Yes (124) No (15)	 58 (46.8) 9 (60.0)	0.333
Renal replacement therapy (n) Yes (26) No (113)	 13 (50.0) 54 (47.8)	0.839
Charlson comorbidity index (n) ≤6 (65) >6 (74)	 28 (43.1) 39 (52.7)	0.294
Glasgow Coma scale (n) ≤9 (70) >9 (69)	 33 (47.1) 34 (49.3)	0.801
APACHE II (n) ≤22 (70) >22 (69)	 28 (40.0) 39 (56.5)	0.052
Number of drugs (n) ≤10 (70) >10 (69)	 29 (41.4) 38 (55.1)	0.107

PIM: Potentially inappropriate medication, the relationship between the dependent and independent variables was evaluated by chi-square analysis

in 26.6% (n=37), propulsives (metoclopramide) in 25.2% (n=35) and sedatives-hypnotics (midazolam) in 7.2% of the patients (Figure 2).

According to TIME-to-STOP criteria, no significant relation was found in the 28-day mortality rate and length of ICU stay in the presence of PIM use (Table 2). As for the drugs evaluated as PIM according to TIME-to-STOP criteria, mortality was significantly higher in patients using midazolam and digoxin (Table 3). There was no significant difference in terms of length of ICU stay. There was no significant relation between polypharmacy and the 28-day mortality rate or length of ICU stay (p>0.05).

Comparison of the PIM use results obtained by the TIME-to-STOP criteria with the results of our previous study, evaluated by the 2019 Beers, STOPP/v2 criteria and EU(7)-PIM List (18).

One or more PIM use was determined in 48.2% of the patients by TIME-to-STOP criteria, in 80.6% by Beers criteria, in 59.7% by STOPP/v2 criteria and in 48.2% by EU(7)-PIM List (Supplement 1).

The presence of PIM use was not associated with demographic and clinical features according to TIME-to-STOP criteria, while receiving RRT as well as high number of drugs were the common variables significantly affecting the presence of PIM use according to the other three criteria (Supplement 2).

Antipsychotic drugs were common to all four criteria, ranking among the top three PIM. The most common drugs evaluated as PIM in intensive care patients were: Enoxaparin (29.5% of patients), metoclopramide (25.2% of patients), and antipsychotics (haloperidol or quetiapine, 24.5% of patients), according to the 2019 Beers criteria. Furthermore, benzodiazepine and opioid combinations, having clinically significant drug-drug interaction potential and should be avoided according to the Beers criteria, were used in 58.3% of the patients. According to STOPP/v2 criteria, 26.6% of the patients used haloperidol or quetiapine, 20.9% enoxaparin and 18.0% amiodarone, which were evaluated as PIM. According to EU(7)-PIM list, drugs evaluated as PIM at most were amiodarone in 23.7% of the patients, metoclopromide in 19.4%, and haloperidol in 10.8% (Supplement 3).

According to four criteria, there was no significant difference between 28-day mortality rate of the patients with and without PIM use. The length of ICU stay was significantly longer in the presence of PIM use, only in 2019 Beers criteria (Supplement 4).

Discussion

This is the first study evaluating prevalence of PIM use in older adults hospitalized in the ICU, by the TIME criteria. We found PIM prevalence as 48.2% according to TIME-to-STOP criteria. This value was lower than the PIM prevalence we found by the 2019 Beers and STOPP/v2 criteria in our previous study, but similar to the PIM prevalence we found by EU(7)-PIM list. However, there

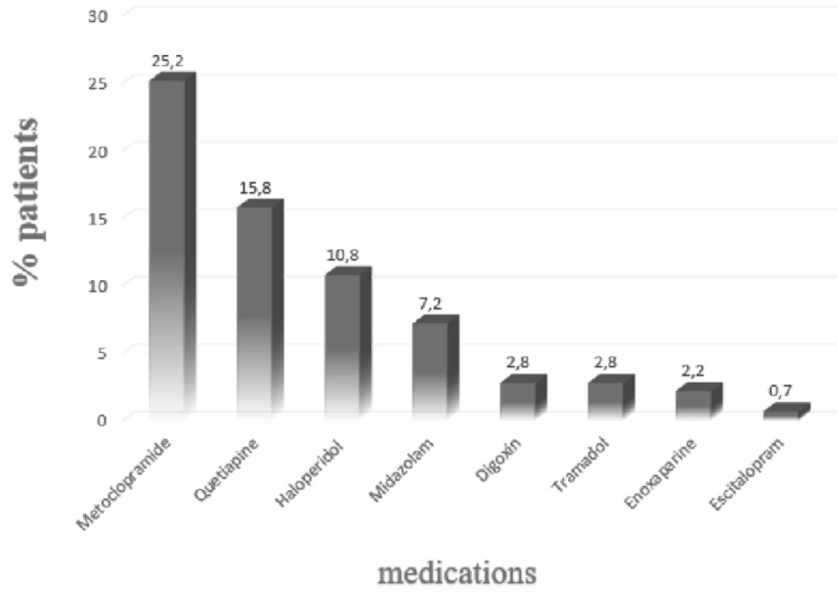

Figure 2. The most common drugs evaluated as PIM in elderly patients hospitalized in the intensive care unit, according to the TIME-to-STOP criteria

Table 2. The relationship between the PIM use presence and 28-day mortality and length of ICU stay, according to TIME-to-STOP criteria

		Mortality n (%)	p-value	Length of ICU stay (day) mean (SD)	p-value
TIME-to-STOP criteria	PIM (n=67)	26 (38.8)	0.743	12.6 (10.9)	0.590
	No PIM (n=72)	26 (36.1)		11.7 (9.1)	

PIM: Potentially inappropriate medication, the relationship between the presence of PIM use and 28-day mortality was evaluated by chi-square analysis. The relationship between the presence of PIM use and the average number of days of stay in the ICU was evaluated by using the Student's t-test

Table 3. The relationship between the drugs evaluated as PIM and 28-day mortality, according to TIME-to-STOP criteria

PIM use according to TIME-to-STOP criteria		Mortality n (%)	p-value
Metoclopramide	**Yes (n=35)** **No (n=114)**	15 (42.9) 37 (35.6)	0.441
Quetiapine	**Yes (n=22)** **No (n=117)**	6 (27.3) 46 (39.3)	0.284
Haloperidol	**Yes (n=15)** **No (n=124)**	3 (20.0) 49 (39.5)	0.140
Midazolam	**Yes (n=10)** **No (n=129)**	8 (80.0) 44 (34.1)	**0.006**
Digoxin	**Yes (n=4)** **No (n=135)**	4 (100.0) 48 (35.6)	**0.018**
Tramadol	**Yes (n=4)** **No (n=135)**	1 (25.0) 51 (37.8)	0.603
Enoxaparin	**Yes (n=3)** **No (n=136)**	2 (66.7) 50 (36.8)	0.556

PIM: Potentially inappropriate medication, the relationship between the presence of PIM use, drugs, and 28-day mortality was evaluated by chi-square analysis and Fisher's Exact test

were differences regarding the medications evaluated as PIM use and the evaluation criteria (18).

TIME criteria are recently published, so the studies using TIME for evaluating PIM use are still limited in the literature. PIM rate was 21.5-38% in older adults presented to geriatric outpatient clinics, 11.7% in older adults treated in the palliative care service (19-21). The high prevalence of PIM use and different drug groups accepted as PIM use in our study when compared to other studies in the literature were attributed to our sample group being composed of ICU inpatients.

In this study, antipsychotics were the group of drugs most frequently evaluated as PIM use according to TIME-to-STOP criteria. In our previous study, antipsychotics ranked first according to the STOPP/v2 criteria, and were among the drug groups with the most common causes of PIM use according to the 2019 Beers criteria and the EU(7)-PIM list. Using antipsychotics in the treatment of delirium in ICU inpatients is controversial. Routine use of haloperidol or atypical antipsychotics in most of the adult patients at critical state and developing delirium is conditionally recommended because their undesirable effects outweigh their potential benefits (22). Antipsychotics are considered directly as PIM use in the older adults due to their anticholinergic and extrapyramidal side effects in TIME-to-STOP, 2019 Beers and STOPP/v2 criteria, while they are considered as PIM use when received above the recommended dose in EU(7)-PIM list. PIM use rate of antipsychotics in older adults treated in the ICU was 8.3% according to 2012 Beers criteria, and 14.9% in hospitalized older adults according to CBMPII criteria (16,23). The higher incidence of delirium in ICU patients and the frequent use of antipsychotics in such cases may be a contributing factor in increased rates of PIM use in our study (24). Antipsychotics increase ICU length of stay and mortality (25), and may cause extrapyramidal side effects (26). More effective and safe alternatives are needed (27).

Metoclopramide was one of the drugs most commonly regarded as PIM in our study. For metaclopromide, PIM use rate was about 3-22% in non-ICU patients according to Beers 2012 criteria, and 29% in ICU patients (16,28-30). The criterion for evaluating metoclopramide as PIM use is similar in TIME-to-STOP, 2012 and 2019 Beers criteria, and it is recommended to avoid using this drug due to its extrapyramidal side effects (12,31,32). However, the criterion for evaluating metoclopramide as PIM is different in EU(7)-PIM list (dose adjustment is recommended) and in STOPP/v2 criteria (in patients with Parkinsonism) (6,7). Off-label use of metoclopramide, such as facilitating enteral feeding in the ICU, is common but it may increase the risk of side effects including parkinsonism and tardive dyskinesia in older adults (33).

Midazolam was the third most common drug of PIM use. According to TIME-to-STOP criteria, using benzodiazepines in acute and chronic respiratory failure was evaluated as PIM use, similar to STOPP/v2 criteria. Therefore, the rate of PIM use due to midazolam was the same rate found by STOPP/v2 criteria in our previous study. According to 2019 Beers criteria, under the title of drug-drug interactions, concomitant use of benzodiazepines (midazolam) and opioids (fentanyl) is accepted as PIM use due to the risk of toxicity. However, benzodiazepines and opioids are the essential drugs increasing patients' compliance with the ventilator and reducing anxiety and agitation during MV support (34). The prevalence of PIM use was found to be high according to 2019 Beers criteria, considering that approximately 90% of the patients received MV support (18). According to EU(7)-PIM list, dose adjustment is recommended for midazolam, and it was not accepted as PIM because the patients included in our study received lower doses. Midazolam is preferred over other benzodiazepines since it is short-acting (35). However, the use of midazolam in the ICU was found to cause delirium, prolongation of ICU length of stay, and an increased risk of mortality (36-38). For patients receiving mechanical ventilator support, guidelines recommend primarily propofol or dexmedetomidine instead of midazolam if analgesia and continuous sedation are required (22).

Digoxin, tramadol and enoxaparin were the other drugs accepted as PIM according to TIME-to-STOP criteria. Digoxin-related PIM use factors and the rates we obtained were similar for TIME-to-STOP and the other three criteria. It is primarily used in the treatment of atrial fibrillation, favored in heart failure with normal ejection fraction, and generally used above the recommended dose (0.125 mg/day), which were the PIM use factors for digoxin. The rate of digoxin-related PIM use (using above the recommended dose) was reported as 5.3-14.6% according to different criteria in non-ICU older adults (39-41). Lower rate (2.8%) determined in our study may be attributed to the low number of patients using digoxin. In-patients of cardiology ICU and cardiovascular surgery ICU were not included in this study.

According to TIME-to-STOP and 2019 Beers criteria, tramadol was one of the drugs to be be avoided when kidney functions failed, and PIM use rate was the same in both criteria. In STOPP/v2 criteria, first choice use of opioids for pain relief was recognized as PIM use, whereas in EU(7)-PIM list, their overdose use. Two studies with older adults admitted to the hospital, the rate of tramadol-related PIM use was 7-18% (42,43). In the study by Noronha et al. (44) in the geriatric oncology clinic, the rate of tramadol-induced PIM use was found to be 30% according to Beers criteria, and this high rate of PIM use may be related to the patient group and their frequent use of analgesics. In our study, tramadol was not administered in patients with malignancy only, but with moderate to severe pain, additionally. However, opioid-related PIM use rate was lower due to using primarily paracetamol or non-steroidal anti-inflammatory drugs for pain relief.

In our previous study, amiodarone was one of the common drugs causing PIM use according to all three criteria (16-24%). It was accepted as PIM use in 2019 Beers and STOPP/v2 criteria for being used as the first treatment choice of atrial fibrillation, however, in EU(7)-PIM list, due to the need for dose adjustment. Atrial fibrillation was reported to be common in ICUs, and increasing mortality (45). Therefore, immediate control of atrial fibrillation is vital. Given that amiodarone is not common in primary care, its use was excluded from the criteria while developing TIME-to-STOP criteria. For this reason, amiodarone could not be evaluated as PIM use in our study. However, amiodarone use is quite common in the ICU. It may be suggested to add it to TIME-to-STOP criteria list in case it is desired to cover a broader scope of patient group.

The number of drugs used and having RRT were recognized as risk factors for PIM use according to 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list, and although the rate of PIM use was higher in TIME-to-STOP criteria, the difference was not significant. Renal functions and GFR decreased in patients receiving RRT (46). Using enoxaparin in patients with low GFR was the most commonly evaluated PIM use in 2019 Beers and STOPP/v2 criteria. Thus, preferring enoxaparin as an antithrombotic during RRT led to a high rate of enoxaparin-induced PIM use, leading RRT indirectly to be a risk factor for PIM use. In the TIME-to-STOP criteria, using enoxaparin under serious bleeding risks is considered as a PIM use, independent of renal function tests, which may explain low levels of enoxaparin-related PIM use rates and the reason why RRT was not a significant risk factor for PIM use. It may be recommended to add a note on dose adjustment to TIME-to-STOP criteria in patients with severe renal impairment.

In our study, the length of ICU stay and the mortality rate were found to be higher in the presence of PIM use with respect to TIME-to-STOP criteria, but not significant. In the study by Özkan (47), drugs used in cardiovascular system diseases showed a significant relationship between PIM use and mortality according to TIME-to-STOP criteria. PIM use rates due to midazolam and digoxin caused a significant increase in mortality in our study. The studies conducted on patients sedated with midazolam in the ICU, revealed significantly increased mortality with midazolam in comparison to other sedative agents (38,48). Likewise, in many large-scale studies and meta-analyses, digoxin was shown to significantly increase all-cause mortality when used for both heart failure and atrial fibrillation (49,50). Our results show similarity to the literature in this respect.

Study Limitations

Small sample size and being conducted in a single-center are the limitations the study. Although this was a retrospective analysis, the data collection was implemented prospectively in the previous study and there was no data loss.

Conclusion

It was determined in this study that approximately half of the older adults hospitalized in the ICU had at least one PIM use according to TIME-to-STOP criteria. Antipsychotics and propulsive drugs were the most frequently observed PIM. TIME-to-STOP criteria were not found to be effective in determining the prognosis, but there was a correlation between digoxin- and midazolam-related PIM use and mortality. Furosemide, fentanyl and amiodarone, which were among the 10 most frequently used drugs for ICU patients throughout the study period and regarded as PIM according to other three criteria along with a caution notice added for older adults in the short product information, were not included in TIME-to-STOPP criteria, indicating the need to extend the current criteria for older adults. Another recommendation would be the extension of TIME-to-STOP criteria so that the information regarding dose adjustment of enoxaparin in patients with severe renal impairment are also included.

Ethics

Ethics Committee Approval: The research was initiated after the approval of the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylül University and carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Our previous study (18), consent was obtained from the participants or their relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.M.Y., F.D.A., N.G., Concept: S.O., N.M.Y., F.D.A., N.G., A.G., Design: S.O., N.M.Y., F.D.A., N.G., A.G., Data Collection or Processing: S.O., N.M.Y., F.D.A., Analysis or Interpretation: S.O., N.M.Y., F.D.A., N.G., A.G., Literature Search: S.O., N.M.Y., F.D.A., N.G., A.G., Writing: S.O., A.G.

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Supplement 1. PIM use prevalence in ICU patients according to the TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list (18)

TIME to STOP criteria (n=139)		2019 BEERs criteria (n=139)		STOPP v2 criteria (n=139)		EU(7)-PIM list (n=139)	
n (%)		n (%)		n (%)		n (%)	
No PIM 1 PIM ≥2 PIM	72 (51.8) 44 (31.7) 23 (16.5)	No PIM 1 PIM ≥2 PIM	27 (19.4) 45 (32.4) 67 (48.2)	No PIM 1 PIM ≥2 PIM	56 (40.3) 57 (41.0) 26 (18.7)	No PIM 1 PIM 2 PIM	72 (51.8) 47 (33.8) 20 (14.4)
Prevalence of PIM use	67 (48.2)	Prevalence of PIM use	112 (80.6)	Prevalence of PIM use	83 (59.7)	Prevalence of PIM use	67 (48.2)

PIM use: Potentially inappropriate medication use
Demirer Aydemir F, Oncu S, Yakar NM, Utkugun GA, Gokmen N, Comert B, Ucku R, Gelal A. Potentially inappropriate medication use in elderly patients treated in intensive care units: A cross-sectional study using 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List. Int J Clin Pract 2021;75:e14802.

Supplement 2. Variables significantly affecting the presence of PIM use according TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM List

	TIME-to-STOP criteria PIM use presence (n=67)	p-value	2019 Beers criteria PIM use presence (n=112)	p-value	STOPP/v2 criteria PIM use presence (n=83)	p-value	EU(7)-PIM List PIM use presence (n=67)	p-value
Age (years) (n) 65-74 (65) 75-84 (50) ≥85 (24)	 32 (49.2) 23 (46.0) 12 (50.0)	0.925	 49 (75.4) 42 (84.0) 21 (87)	0.328	 37 (56.9) 29 (58.0) 17 (70.8)	0.471	 30 (46.2) 25 (50.0) 12 (50.0)	0.903
Gender (n) Female (68) Male (71)	 34 (50.0) 33 (46.5)	0.678	 56 (82.4) 56 (78.9)	0.604	 41 (60.3) 42 (59.2)	0.891	 35 (51.5) 32 (45.1)	0.450
Body mass index (n) <25 (62) ≥25 (77)	 29 (46.8) 38 (49.4)	0.763	 50 (80.6) 62 (80.5)	0.985	 36 (58.1) 47 (61.0)	0.722	 28 (45.2) 39 (50.6)	0.520
Mechanical ventilation (n) Yes (124) No (15)	 58 (46.8) 9 (60.0)	0.333	 101 (81.5) 11 (73.3)	0.453	 73 (58.9) 10 (66.7)	0.561	 60 (48.4) 7 (46.7)	0.900
Renal replacement therapy (n) Yes (26) No (113)	 13 (50.0) 54 (47.8)	0.839	 26 (100.0) 86 (76.1)	0.005	 21 (80.8) 62 (54.9)	0.015	 19 (73.1) 48 (42.5)	0.005
Charlson Comorbidity index (n) ≤6 (65) >6 (74)	 28 (43.1) 39 (52.7)	0.294	 44 (67.7) 68 (91.9)	<0.001	 34 (52.3) 49 (66.2)	0.095	 26 (40.6) 41 (55.4)	0.083
Glasgow Coma scale (n) ≤9 (70) 9 (69)	 33 (47.1) 34 (49.3)	0.801	 62 (88.6) 50 (72.5)	0.016	 38 (54.3) 45 (65.2)	0.189	 41 (58.6) 26 (37.7)	0.014
APACHE II (n) ≤22 (70) >22 (69)	 28 (40.0) 39 (56.5)	0.052	 47 (67.1) 65 (94.2)	<0.001	 38 (54.3) 45 (65.2)	0.189	 24 (34.3) 43 (62.3)	0.001
Number of drug (n) ≤10 (70) >10 (69)	 29 (41.4) 38 (55.1)	0.107	 48 (68.6) 64 (92.8)	<0.001	 36 (51.4) 47 (68.1)	0.045	 24 (34.3) 43 (62.3)	0.001

PIM: Potentially inappropriate medication, the relationship between the dependent and independent variables was evaluated by chi-square analysis

Supplement 3. Drug groups evaluated as PIM in elderly ICU patients and related criteria according TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM List (18)

Drugs	PIM use criteria according to TIME to STOPP	% (n)	PIM use criteria according to 2019 Beers	% (n)	PIM use criteria according to STOPP/ v2	% (n)	PIM use criteria according to EU(7)-PIM	% (n)
Antipsychotics Haloperidol Quetiapine	Neuroleptics/antipsychotics for hypnotic purpose (increased confusion, hypotension, extrapyramidal side effects, risk of fall).	15.8% (n=22) 10.8% (n=15)	Avoid antipsychotics for behavioral problems of dementia or delirium unless non-pharmacological options have failed or are not possible and the older adult is threatening substantial harm to self or others	13.7% (n=19) 10.8% (n=15)	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia	15.8% (n=22) 10.8% (n=15)	N/A Anticholinergic and extrapyramidal side effects Above the recommended dose	N/A 10.8% (n=15)
Propulsives Metoclopramide	Metoclopramide or trimethobenzamide as the first line antiemetic treatment of older adults (due to the extrapyramidal side effects and restlessness).	25.2% (n=35)	Metoclopramide can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	25.2% (n=35)	Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).	N/A	Antidopaminergic and anticholinergic effects, may worsen peripheral arterial blood flow and precipitate intermittent claudication, above the recommended dose	19.4% (n=27)
Sedative-hypnotic Midazolam	Benzodiazepines with acute or chronic respiratory failure i.e. PO_2 <60 mmHg and / or pCO_2> 50 mmHg (risk of exacerbation of respiratory failure).	7.2% (n=10)	Midazolam and fentanil Drug-drug interactions	58.3% (n=81)	Benzodiazepines with acute or chronic respiratory failure i.e. pO_2 <8.0 kPa ± pCO_2 >6.5 kPa (risk of exacerbation of respiratory failure).	7.2% (n=10)	N/A	N/A
Glycosides Digoxin	Digoxin as first line treatment for atrial fibrillation. Digoxin for heart failure with preserved EF. Digoxin at a dose greater than 0.125 mg/day	2.8% (n=4)	Digoxin for first-line treatment of atrial fibrillation or of heart failure	2.8% (n=4)	Digoxin for heart failure with preserved systolic ventricular function.	1.4% (n=2)	Elevated glycoside sensitivity in older people; risk of intoxication Above the recommended dose	2.8% (n=4)

Supplement 3. Continued

Drugs	PIM use criteria according to TIME to STOPP	% (n)	PIM use criteria according to 2019 BEERs	% (n)	PIM use criteria according to STOPP/v2	% (n)	PIM use criteria according to EU(7)-PIM	% (n)
Opioids Tramadol	Extended-release tramadol if eGFR <30 mL/min/1.73 m^2	2.8% (n=4)	Potentially inappropriate medications based on kidney function	2.8% (n=4)	Use of oral or transdermal strong opioids as first line therapy for mild pain	7.9% (n=11)	More adverse effects in older people above the recommended dose	4.3% (n=6)
Antithrombotic Enoxaparin	Factor Xa inhibitors with concurrent significant bleeding risk.	2.2% (n=3)	Potentially inappropriate medications based on kidney function	29.5% (n= 41)	Factor Xa inhibitors if eGFR <15 (risk of bleeding). Any duplicate drug class prescription. Factor Xa inhibitors with concurrent significant bleeding risk.	20.9% (n=29)	N/A	N/A
Antiarrhythmics Amiodarone	Excluded criteria (reason: The drugs are not commonly used in primary care in local practice)	N/A	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	15.8% (n=22)	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	18.0% (n=25)	Associated with QT interval problems and risk of provoking torsades de pointes Above the recommended dose	23.7% (n=33)

PIM: Potentially inappropriate medication, N/A: Not applicable

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Supplement 4. Relationship of PIM use presence with 28-day mortality rate and length of ICU stay according TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list (18)

		Mortality n (%)	p-value	Length of ICU stay (day) Mean (standard deviation)	p-value
2019 Beers criteria*	PIM (n=112)	46 (41.1)	0.069	13.1 (10.4)	0.028
	No PIM (n=27)	6 (22.2)		8.4 (6.6)	
STOPP/v2 criteria*	PIM (n=83)	33 (39.8)	0.486	11.8 (9.5)	0.660
	No PIM (n=56)	19 (33.9)		12.6 (10.6)	
EU(7)-PIM list*	PIM (n=67)	28 (41.8)	0.303	13.1 (11.1)	0.295
	No PIM (n=72)	24 (33.3)		11.3 (8.8)	
TIME to STOPP criteria	PIM (n=67)	26 (38.8)	0.743	12.6 (10.9)	0.590
	No PIM (n=72)	26 (36.1)		11.7 (9.1)	

Demirer Aydemir F, Oncu S, Yakar NM, Utkugun GA, Gokmen N, Comert B, Ucku R, Gelal A. Potentially inappropriate medication use in elderly patients treated in intensive care units: a cross-sectional study using 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List. Int J Clin Pract. 2021; 75(11):e14802. doi: 10.1111/ijcp.14802

The relationship between the presence of PIM use and the average number of days of stay in the ICU was evaluated by using the Student's t-test for parametric data and the Mann-Whitney U test for non-parametric data.

The relationship between the presence of PIM use and 28-day mortality was evaluated by chi-square analysis

ORIGINAL RESEARCH

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Use of Absorbent Products in Older Men and Women Are Associated with Depressive Symptoms: A Retrospective Study from a University Hospital

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Abstract

Objective: Urinary incontinence (UI) is defined as the involuntary leakage of urine. UI is a challenging geriatric syndrome and most of the patients use absorbent products or diapers to hold urine and protect their clothes. We aimed in this study to evaluate the relationship between the use of absorbent products and the presence of depressive symptoms in patients with UI.

Materials and Methods: One-hundred and fifty-nine (159) community-dwelling older adults with UI who applied to our hospital outpatient clinic of geriatrics were included in the study. A comprehensive geriatric assessment was performed on the patients, and the risk of depression was evaluated with the Yesavage geriatric depression scale (GDS). Those with a GDS score of 5 and above were considered as presence of depressive symptoms.

Results: Depressive symptoms were determined in 71 patients (44.6%). 91.2% of the patients were female, and the mean age was 73.6±6.4 years. The patients were divided into two groups according to the presence of depressive symptoms. The rate of use of absorbent products was 68.6% in the group with depressive symptoms and 45.9% in the group without depressive symptoms, and the difference was statistically significant ($p<0.05$). Use of absorbent products increases the risk of depression regardless of sex, living alone, multimorbidity, and severity and the type of incontinence (odds ratio: 2.65, 95% confidence interval: 1.27-5.57, $p=0.010$).

Conclusion: The use of absorbent products in patients with UI is associated with the depressive symptoms. These patients should be screened for depression and evaluated for appropriate treatment options for incontinence and depression.

Keywords: Absorbent products, urinary incontinence, depression, older adults

Introduction

Urinary incontinence (UI), in other words, involuntary leakage of urine is a commonly seen health problem in adults (1), however, this geriatric syndrome is not properly treated because it is normalized with increasing age and mostly kept quiet with embarrassment. It is estimated that nearly half of the adult women experienced UI, on the other hand only 25-61% of those who had symptomatic UI seek medical care (2). The prevalence of UI in women aged 60 years and older was 50 to 70% (3). Furthermore, not just older women who suffered from UI, the risk of UI in men is also increasing with the aging process. The prevalence of UI in men aged 65 years and older is reported between 11 to 34% (4,5). Even though it is accepted as UI has no effect on survival, a meta-analysis showed that the presence of UI increases the risk of mortality by 20% in institutionalized patients (6). It was demonstrated that patients with UI have decreased quality of life (7), sexual dysfunction (8), increased morbidity (9,10), anxiety and mood disorders (11), and increased caregiver burden (12).

There is increasing evidence in the literature that UI had an impact on quality of life, social isolation, and limitations in lifestyle. These limitations in the lifestyle include decreased fluid

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intake, avoidance of places with no public toilets, and exercises such as weight-lifting. Social relationships can also be affected by UI, as embarrassment and incontinence are accepted as issues that should not be talked about (13). In a study conducted in Finland, it was found that the risk of depression rises 4.5 times in patients with UI (14). Another large-scale study revealed that the presence of depressive symptoms has increased two times in older adults with UI (15). Men with lower urinary tract dysfunction symptoms were investigated for anxiety and depression and quality of life, men with UI had experienced higher rates of anxiety and depression (16).

Different studies investigate the impact of the type, frequency, and duration of UI on depressive symptoms. Patients with urge incontinence have more psychological burdens than those with stress incontinence (7). Using standardized questionnaires, Macaulay et al. (17) investigated the psychological factors of 211 women, and it was discovered that women suffering from sensory urgency had worse self-esteem and were more nervous than those suffering from stress incontinence. Patients with bladder overactivity were just as worried and had low on self-esteem as patients with sensory urgency, but they also had unpleasant thoughts and anxieties and performed worse on psychometric tests (17). Another large-scale study conducted on more than 3000 women with the ages between 30-90 years old stated that the type of UI (urge/mixed) UI and severity of UI (moderate-to-severe) UI were each associated with increased odds of major depression in women with UI (18).

Pharmacological and non-pharmacological approaches are available in the management of UI. Since there is no absolute cure for UI, many patients wear absorbent products to avoid the distress of socially disabling leakage and odor problems. The use of pads in different countries ranges from 29% to 52% (19). There are different types of absorbent products for light, moderate, and heavy UI, besides disposable and reusable products, and body-worn and underpad designs. Although the exact number of pad users is uncertain, the cost of containment products to health care facilities is substantial. In addition, it is necessary to be able to balance the clinical benefit of the use of absorbent products with unfavorable effects.

The negative psychological impact of UI in patients is studied repeatedly, nevertheless, there is limited evidence in the relation between the use of absorbent products for urine leakage and depression. In this study, we aimed to reveal the association between depressive symptoms and the use of absorbent products in patients with UI.

Materials and Methods

Study Population and Study Design

The study was conducted as a retrospective cross-sectional study between 01 January 2020 and 31 December 2021. One-hundred and fifty-nine patients who applied between these two-year time periods who had UI and were referred to a geriatric nurse for non-pharmacological lifestyle modifications were included in the study. Patients with UI were referred to the geriatric nurse after the recovery from reversible UI reasons. The transient causes of UI are delirium, infection, atrophic vaginitis, pharmaeuticals, psychological disorders, excessive urine output, reduced mobility and stool impaction (20). All the participants were evaluated with a comprehensive geriatric assessment.

Comprehensive geriatric assessments of the patients were recorded from the electronic files of the participants retrospectively. Frailty was defined according to the clinical frailty scale (CFS) (12). CFS was defined according to clinical judgment by the physician of the patient between 1 (very fit) to 9 (terminally ill). Patients whose scale was equal to or more than 4 were accepted as patients living with frailty. Polypharmacy was defined as the usage of 5 or more medications (13). Fall event was recorded if the patient had fallen unintentionally in the previous year. Difficulty in falling asleep, frequent awakening during the night, or awakening early in the morning were categorized as insomnia. The risk of malnutrition was evaluated by mini-nutritional assessment-short form (MNA-SF) (21). MNA-SF scores between 8-11 were defined as the risk of malnutrition and, scores lower than 8 were accepted as malnutrition. The presence of depression risk was assessed by 15-item Yesavage geriatric depression scale (YGDS) (22) and 5 and higher scores were evaluated as depression. Six-item Katz activities of daily living (ADL) score and 8-item Lawton-Brody instrumental activities of daily living (IADL) score were used for assessing the functionality of the patients' (23). The cognitive status of patients was evaluated by MMSE and clock-drawing test (24,25). In mini-mental status examination (MMSE) test, six different cognitive domains, orientation, memory registration, attention, delayed recall, language, and motor functions were evaluated.

UI was accepted as involuntary urine leakage by the expression of patients or their caregivers, after the recovery of reversible UI reasons. The type of UI and its severity defined by Incontinence severity index (ISI) (26), and frequency were also recorded from the files of the interview of the geriatric nurse. ISI consists of two questions, regarding frequency and amount of leakage. It categorizes UI into slight, moderate, severe, and very severe. First question is "How often do you experience urinary leakage?" and the answer is one of them: Never, I do not leak urine (0 point), Less than once a month (1 point), A few times a month (2 point), A few times a week (3 point), Every day and/or night (4 point). Second question is "How much urine do you lose each time?". Answer is one of them: None, I do not leak urine (0 point), Drops (1 point), Small Splashes (2 point) and More (3 point). The total score is calculated by the multiplication of the scores of first and second question. A total score more than 8 is accepted as severe UI (26).

Ethical Approval

The study protocol was in adherence with the principles in the Declaration of Helsinki. The Ethics Committee of Hacettepe University approved the study protocol with the decision number 2022/18-01.

Statistics

The data of two groups according to the presence of diaper use were analyzed. Normality tests were performed. Categorical variables were stated as number (n) and percentage (%), and continuous variables as median (IQR) or mean ± standard deviation (SD) values according to the normal distributions or not. To evaluate the relationships between categorical variables, a chi-square test was used. Multivariable logistic regression analysis was wielded to investigate the relationship between diaper use and the presence of depressive symptoms. Age, living alone, multimorbidity, use of diaper, and severity of incontinence were included in the regression model. A value of $p<0.05$ (two-sided) was accepted as statistically significant. The data obtained in the study were analyzed statistically using IBM SPSS Statistics vn. 24.0 software (IBM Co., Armonk, NY, USA).

Results

The final analysis was made on 159 patients. The study population was categorized into two groups according to the presence of depressive symptoms. The mean age of the study population was 74.26±6.6 years and the female ratio was 91.2%. No difference was observed between groups regarding age, sex, education, living alone, duration, and type and severity of incontinence. The most commonly encountered type of UI was the mixed UI in both groups following by urge IU. No statistically significant differences observed in type of UI between two groups (p=0.841). Furthermore, when the frequency of geriatric syndromes was examined, no statistically significant difference was observed between the groups including frailty, dementia, history of falls and polypharmacy. Basic ADL scores were similar in patients with depressive symptoms and no depressive symptoms. Instrumental ADL scores were statistically lower in patients with depressive symptoms (p=0.004). Patients with depressive symptoms had lower MNA-SF scores, and the difference is statistically significant (p<0.001). Insomnia was more frequently seen in patients with depressive symptoms (p=0.002). Patients with depressive symptoms had used diapers or other absorbent products more frequently than patients who had no depressive symptoms (68.6% vs 45.9%, p=0.05). The results were shown in Table 1. In the multivariable logistic regression analysis (Table 2), it was found that the use of diapers was significantly associated with the presence of depressive symptoms independent of patient's sex, living alone, multimorbidity, and severity and type of UI (odds ratio: 2.65, 95% confidence interval: 1.27-5.57, p=0.010).

Discussion

UI is a frequent geriatric syndrome in older adults, wrongly normalized and comprehended as a natural cause of aging, especially in older women. Nevertheless, UI causes psychological problems such as anxiety and mood disorders, social isolation, and as a result, decreased quality of life. Even though the relationship between the experience of UI and depression is frequently explored, on the other hand, limited studies showed regarding the effect of absorbent product use on depressive symptoms in individuals with incontinence. Previous studies reveal patients with urge incontinence more frequently encounter with psychological problems. Furthermore, the severity of UI affects the presence of depressive symptoms. According to our findings, in older men and women with UI use of absorbent products is significantly associated with depressive symptoms regardless of sex, living alone, multimorbidity, and the severity and the type of UI. Increasing age was found to reduce the risk of the presence of depressive symptoms with respect to our data, we interpreted this situation as a result of the acceptance of incontinence with advancing age.

Providing confidentiality (no one will notice UI or odor), convenience, and skin protection from moisture are some reasons why patients prefer absorbent products. A study from Poland conducted on patients with stress UI also found that the use of absorbent products increases with the severity of UI, furthermore, women with severe UI pursue medical help more than others. A study exploring the effect of absorbent product use on the distress caused by UI in women diagnosed with heart failure revealed that absorbent products were commonly used in women with severe UI. The authors have concluded that using absorbent products indirectly affects UI discomfort by changing how women see the necessity of seeking UI treatment (27).

Differently from the aforementioned study, we found that the use of these products was associated with the presence of depressive symptoms regardless of the severity of UI.

The use of absorbent products had another effect on UI besides providing confidentiality. It has been shown that with the use of absorbent products there is an increase in the rate of accidents and a decrease in the rate of successful voids (28). Absorbent products are preferred since the inadequate treatment. Even though older patients stated that they would choose UI medications over absorbent products (29), caregivers would like to use these products according to Johnson et al. (30). On the other hand, absorbent products, especially diapers, can be a reasonable option in some instances, such as for older people living with frailty or dementia (31).

There are also some studies with conflicting results on the effect of the use of absorbent products on the quality of life. The perceived risk of poor pad efficacy, absence of discreteness,

Table 1. The characteristics and demographic features of the study population

	Depressive symptoms absent (n=88)	Depressive symptoms present (n=71)	p-value
Age, years mean ± SD	74.2±6.4	72.9±6.3	0.18
Sex, female n (%)	80 (90.9)	65 (91.5)	0.89
Education, >5 years	13 (14.8)	11 (15.5)	0.95
Living status, alone	13 (14.8)	19 (26.8)	0.06
Type of incontinence, n (%)			0.841
Urgency	36 (40.9)	30 (42.3)	
Mixed	45 (51.1)	37 (52.1)	
Stress	4 (4.6)	3 (4.2)	
Other	3 (3.4)	1 (1.4)	
Duration of incontinence, >1 year, n (%)	57 (71.3)	55 (82.1)	0.12
Severe incontinence, n (%)	38 (48.7)	40 (57.1)	0.11
Absorbent product use, n (%)	39 (45.9)	48 (68.6)	0.005
Pharmacological treatment for incontinence, n (%)	8 (9.2)	7 (10.0)	0.87
Multimorbidity, n (%)	76 (86.4)	57 (80.3)	0.30
Comprehensive geriatric assessment			
	Depressive symptoms absent (n=88)	**Depressive symptoms present (n=71)**	**p-value**
Living with frailty, CFS, n (%)	46 (52.3)	42 (59.2)	0.39
Dementia, n (%)	9 (10.2)	8 (11.3)	0.83
Basic ADL, median (IQR)	5.0 (1.0)	5.0 (1.0)	0.12
Instrumental ADL, median (IQR)	8.0 (1.0)	7.0 (2.0)	0.004
MMSE, median (IQR)	27.0 (6.0)	26.0 (6.0)	0.31
MNA-SF, median (IQR)	14.0 (2.0)	12.0 (4.0)	0.000
Polypharmacy, n (%)	59 (67.0)	48 (54.5)	0.75
History of falls, n (%)	18 (20.5)	9 (12.7)	0.24
Insomnia, n (%)	22 (25.0)	34 (47.8)	0.002
Use of diuretics, n (%)	42 (47.7)	32 (45.7)	0.80

CFS: Clinical frailty scale, ADL: Activities of daily living, MMSE: Mini-mental state examination, MNA-SF: Mini-nutritional assessment-short form, SD: Standard deviation

Table 2. Logistic regression analysis of possible independent factors effecting depressive symptoms

Model 1	OR	95% confidence interval	p-value
Absorbent product use	2.57	1.33-4.98	0.005
Model 2			
Absorbent product use	3.13	1.27-7.72	0.013
Insomnia	5.36	1.99-14.40	0.001
Model 3			
Age	0.94	0.88-0.99	0.047
Absorbent product use	2.65	1.27-5.57	0.010

*The model 1 is the unadjusted model, Model 2 includes use of absorbent products, insomnia, nutritional status and IADL score. Model 3 includes age, sex, living alone, multimorbidity, type and severity of UI, and use of absorbent products, OR: Odds ratio

and the requirement for complicated pad care regimes were all related to high anxiety levels reported in a study aiming to investigate the both positive and negative "treatment effects" of absorbent products (32). Therefore, it is not appropriate to make a plain comment when the use of absorbent products has a positive or negative effect on quality of life in individuals with UI. As a result of the retrospective design of our study, patients' quality of life and self-perceptions regarding the use of absorbent products could not be evaluated.

Study Limitations

There are some limitations to our study. Because of the retrospective design of our work, the cause-effect relationship was not revealed between the use of absorbent products and the presence of depressive symptoms. The type of absorbent products was not recorded, and also there was no information about how long and how often the patients used these absorbent products because of the retrospective design of the study and this is another limitation. However, some strong aspects of our work are also present, all patients had an interview with the geriatric nurse and all patients were evaluated with a comprehensive geriatric assessment. Another strength is that our work is a novel study in this area showing depressive symptoms with the use of absorbent products.

Conclusion

In this study, a significant relationship was found between the use of absorbent products and the presence of depressive symptoms in UI, a geriatric syndrome that is mostly hidden and normalized by older adults. Prospective long-term studies are needed to show the cause-effect relationship more clearly.

Ethics

Ethics Committee Approval: The study protocol was in adherence with the principles in the Declaration of Helsinki. The Ethics Committee of Hacettepe University approved the study protocol with the decision number 2022/18-01.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.G., M.Ö., S.C., A.O.B., B.B.D., Design: M.G., M.Ö., S.C., A.O.B., B.B.D., Data Collection or Processing: M.G., M.Ö., S.C., A.O.B., Analysis or Interpretation: M.G., S.C., A.O.B., C.B., M.G.H., M.C., B.B.D., Literature Search: M.G., S.C., A.O.B., C.B., M.G.H., M.C., B.B.D., Writing: M.G., S.C., A.O.B., C.B., M.G.H., M.C., B.B.D.

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CASE REPORT

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Lercanidipine-induced Chyloperitoneum in a Geriatric Patient with Peritoneal Dialysis

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Abstract

Peritoneal dialysis is one of the renal replacement therapy modality for patients with end-stage renal disease. Hypertension is a common comorbidity in these patients and calcium channel blockers are the most commonly prescribed drugs. Chyloperitoneum is a non-infectious cause of cloudy peritoneal effluent. Lercanidipine is a lipophilic, third generation calcium channel blocker and a widely used antihypertensive agent. Herein, we presented a case of geriatric peritoneal dialysis patient admitted to hospital cloudy effluent after the use of lercanidipine for hypertension. The peritoneal effluent returned to normal after after the cessation of lercanidipine.

Keywords: Chyloperitoneum, geriatrics, hypertension, lercanidipine, peritoneal dialysis

Introduction

Peritoneal dialysis (PD) is the most common type of home dialysis in which the peritoneal membrane is used to remove uremic toxins and fluid overload, especially in geriatric end-stage renal disease patients (ESRD). Chyloperitoneum is a rare condition characterized by milky peritoneal fluid containing high amounts of lymphatic fluid and triglycerides. It is important to make a differential diagnosis to rule out other possible causes. The most common causes include cancers such as lymphomas, tuberculosis, cirrhosis, lymphatic obstructions, pancreatitis, trauma, nephrotic syndrome, and drugs (1,2). Calcium channel blockers (CCBs) are the most commonly reparted among drug. In the presence of hypertension in elderly ESDR patients, CCBs are often preferred in the treatment. In this article, we present a patient with PD who was admitted to the hospital with chyloperitoneum after using lercanidipine for hypertension.

Case Report

A 78-year-old female patient with ESRD secondary to hypertensive nephrosclerosis had been receiving continuous ambulatory peritoneal dialysis (CAPD) treatment for 3 months. She was reffered our unite with cloudy peritoneal effluent (Figure 1). In her physical examination, she was oriented and cooperative, blood pressure was 150/90 mmHg, heart rate was 84 beats/minute and rhythmic, body temperature was 36.7 °C and respiratory rate was 20 per minute. There were no findings of acute abdomen. Also, the exit site of the catheter was clean. Her medications are valsartan 320 mg once a day, amlodipine 10 mg once a day, calcium acetate 700 mg three times a day, epoetin alfa 4000 IU twice a week. She has approximately 800 mL/day of urine. CAPD treatment consisted of four cycles of 2 L with 1.36% glucose solution per day. Our patient was not using icodextrin and therefore turbid waste could not bind to this dialysate component. There was no history of peritonitis, abdominal pain, fever, nausea and vomiting. Fibrin clots were not prominent and blood particles and leukocytes were not present in the effluent. Gram staining showed no features. Triglyceride concentration in peritoneal effluent was 65 mg/dL and other blood laboratory results are shown in Table 1. Routine cultures of waste dialysate were negative for bacteria, fungi and mycobacteria. No malignant cells were found in cytological examination. There were no clinical features suggestive of acute pancreatitis, solid organ malignancy, or lymphoma. Abdominal contrast-enhanced computed tomography imaging revealed a normal pancreas. The patient's laboratory results are summarized in Table 1. In her anamnesis, it was learned that the patient

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who applied to the emergency department with the complaint of irregular hypertension 3 days ago took lercadipine instead of amlodipine. This drug was suspected and stopped. After discontinuing of drug, the dialysis fluid became translucent within 24 hours.

Discussion

Hypertension is the most common comorbidity in ESRD patients. CCBs are also the most commonly prescribed antihypertensive drugs (approximately 70% of cases) in this particular patient group. CCBs use in this group is associated with a decrease in all-cause and cardiovascular mortality rates (3). Chyloperitoneum

Figure 1. Cloudy peritoneal effluent

Table 1. Laboratory results

		Normal range
White blood cell	5.07 x10^3/µL	4.6-10.2 x10$^{3/}$µL
Hemoglobin	10.9 g/dL	12.2-18.1 g/dL
Platelets	240 x10^3/µL	142-424 x10^3/µL
Urea	111 mg/dL	15-45 mg/dL
Creatinine	6.2 mg/dL	0.5-1.1 mg/dL
Sodium	139 mmol/L	136-148 mmol/L
Potassium	4.47 mmol/L	3.5-5.2 mmol/L
Calcium	9.1 mg/dL	8.5-10.6 mg/dL
Phosphorus	4.1 mg/dL	2.3-4.7 mg/dL
Albumin	3.8 g/dL	3.5-5.5 mg/dL
Cholesterol	163 mg/dL	0-200 mg/dL
Triglyceride	117 mg/dL	0-150 mg/dL
Parathormone	198.9 pg/mL	15-65 pg/mL
Ferritin	374.9 ng/mL	30-400 ng/mL
C-reactive protein	1.8 mg/L	0-6 mg/L

associated with CCBs has been previously reported on a case-by-case basis in the literature. In these publications, the use of dihydropyridine and non-dihydropyridine group CCBs was found in CCBs-related chyloperitoneum cases. While most of the cases in the literature developed chyloperitoneum in patients who received CCBs treatment for the first time, in some studies, chyloperitoneum developed when the prescribed CCBs type (4) or döşe (5) was changed.

Lercanidipine is a widely used third generation dihydropyridine type and lipophilic CCBs. Although rare, chyloperitoneum may cause development in patients receiving PD. Although the underlying mechanism of CCB-related chyloperitoneal development has not been clearly revealed, it can be explained by the deterioration of lymphatic functions that provide increased ultrafiltration and triglyceride excretion from the peritoneal membrane (6). Highly lipophilic CCBs, especially lercanidipine, easily penetrate the lipid layer of the cell membrane and act on intestinal smooth muscle cells and calcium channels in lymphatic vessels (7). Showed in a recently published systematic review that the prevalence of lercanidipine-related chyloperitoneal development is 25.97%. In addition, analyzes conducted in the study did not show a significant relationship with features such as advanced age, gender, duration of PD treatment or serum triglyceride concentrations in the development of lercanidipine-related chyloperitone (8,9).

Conclusion

In conclusion, CCBs should be considered as an important etiological factor in the development of chyloperitoneum in PD patients. In this situation, removal of the relevant drug or switching to a less lipophilic CCBs may be effective. Misconception of CCB-associated non-infectious chyloperitoneum as infectious can result in both unnecessary laboratory testing and an increase in the cost burden of inappropriate antibiotic prescriptions.

Ethics

Informed Consent: Informed consent was obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.P., F.D.Y., Ö.B., Concept: İ.P., F.D.Y., Ö.B., Design: İ.P., F.D.Y., Ö.B., Data Collection or Processing: İ.P., F.D.Y., Ö.B., Analysis or Interpretation: İ.P., F.D.Y., Ö.B., Literature Search: İ.P., F.D.Y., Ö.B., Writing: İ.P., F.D.Y., Ö.B.

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LETTER TO THE EDITOR

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Selenium's Role on Thyroid Autoimmunity and Cognitive Dysfunction in Elderly

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Abstract

Selenium is a trace element essential for the human body. The amount of this element, which is found in nature and in the human organism, varies depending on the geographical region and intake with food. Selenoproteins play an important role in maintaining the immune system, antioxidant system, hormone synthesis and living metabolism. Selenium can affect thyroid autoantibodies in autoimmune thyroid diseases and participate in the biosynthesis of thyroid hormones in the body. There are also studies showing that selenium is a protective factor for cognitive dysfunction, especially for the elderly population.

Keywords: Aging, clinical geriatrics, cognitive disorders, selenium, thyroid autoimmunity

Dear Editor,

Selenium in the Human Organisms

Selenium (Se) is a micronutrient first described in 1817; the name Se is derived from the Greek word "Selene", which means moon, by analogy with the shiny and gray appearance of this compound when melted. Se levels in the body depend on population characteristics, nutrient intake, and primarily on the composition of the surrounding soil in the living region (1). Se is an essential bioelement required for the functioning of all organisms. The optimal daily dose of Se has been determined as 55 µg. Se is found in trace amounts in the human organism and normal plasma serum Se levels vary between populations due to many factors (2-4). Skeletal muscles in the body are the main organs containing 46.9% of the total content of Se, while the kidneys contain only 4% of Se. The indicator of Se sufficiency is serum Se concentration of 60-120 ng/mL. The maximum Se concentration is reached in adulthood. The concentration of this element in the serum gradually decreases after the age of 60 (5,6). An excess of Se can cause severe anemia, hair loss, and the development of blindness. The ideal Se level in the organism is in a very narrow range. The recommended daily dose of Se is different depending on the geographical region, as we mentioned earlier. The World Health Organization recommends a daily dose of 55 µg of Se for adults. In addition, a daily dose of 400 µg is considered safe in terms of side effects. The Food and Nutrition Board in the USA has recognized that the amount of Se needed varies with age and is 40-70 µg for adult men and 45-55 µg for adult women (7). The recommended daily dose for children is 25 µg (Table 1) (8).

The main sources of Se in the diet are foods such as grains, meat and dairy products, fish, seafood and nuts. Fruits and vegetables contain relatively low Se. The Se content in 100 grams of some foods using the US department of agriculture database is given in Table 2 (9).

The Importance of Se in Biologically Active Compounds and Thyroid Autoimmuniy

Glutathione peroxidase, selenoprotein P, and thyroxine 5-deiodinase are selenoenzymes commonly found in mammals. Glutathione peroxidase and selenoprotein P catalyze redox reactions and have antioxidative effects (10). Glutathione reductase is another Se-containing enzyme. This enzyme is involved in the decomposition of organic peroxides and hydrogen. Glutathione reductase is responsible for maintaining the appropriate level of reduced glutathione to protect cells from

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peroxide accumulation and damage (11). Se aids in the proper synthesis, activation and metabolism of thyroid hormones. This enzyme is responsible for the conversion of thyroxine (T4) deiodation to its active form known as 3,3,5-triiodothyronine (T3) or the inactive form-rT3 isomer. Deiodination occurs in peripheral tissues, particularly in the kidneys, liver, and skeletal muscles. This process can be disrupted by a lack of Se in the organism. This indicates the important role of Se in the metabolism of thyroid hormones. Therefore, it is useful to consider the levels of this element in the presence of thyroid diseases (12). Se acts synergistically with vitamin E. There are studies showing that the synergistic effect of Se and vitamin E helps to protect organs against the destructive effects of free radicals (13). Low Se levels have been found in the African region of Zaire, where myxoedema is endemic. To gain a clear understanding of the role of Se, study was planned with a group of students in Zaire. After Se supplementation, increased serum thyroxine and decreased triiodothyronine concentrations were detected in the students (14). There are studies showing that low Se intake is associated with the risk of developing antithyroid antibodies. There are also publications showing that Se supplementation can reduce antithyroid antibody titers (15). Furthermore, in the presence of autoimmune thyroid disease, there is the possibility of a potential reduction in the required levothyroxine replacement dose for hypothyroidism and/or preventing the progression of subclinical hypothyroidism, but not all studies agree with this conclusions (16). There is still no high-quality level of evidence for its use except from the treatment of mild Graves' orbitopathy (17). Therefore, more studies are needed to confirm the effect of Se in autoimmune thyroid diseases.

Table 1. Recommended daily intake of selenium

Age (years)	Selenium (µg/day)
1-3	15-20
4-13	30-40
14-50	55-70
51 +	70-100

Table 2. Selenium contents of foods

Foods	Selenium (µg/100 gr)
Brazil nuts (selenium enriched)	1917.6
Tuna (fresh, dry-heat cooked)	108.2
Oysters (raw)	76.9
Mussels (steamed)	64.0
Flounder (dry-heat cooked)	55.4
Shrimp (steamed)	49.5
Salmon (dry-cooked)	46.8
Noodles (enriched and cooked)	20.6
Crab (steamed)	44.3
Beef (lean, steamed)	36.0
Chicken meat (baked in the oven)	30.3
Rice (brown, long grain, cooked)	10.3
Sunflower seeds (dry)	53.0
White bread	28.8
Milk (skimmed)	16.3

Cognitive Dysfunction and Se

The difficulty of precisely measuring dietary Se is one of the main problems in studies. In addition, the fact that the Se content in the soil is different in different regions, the lack of specific food composition tables for this trace element in many countries, the loss of up to 40% by evaporation, and the varying amounts due to cooking/processing of foods make it difficult to provide standardization in studies (18). Unfortunately, data on Se levels and disease associations in the elderly patient population are very rare. However, some studies of age-related differences in Se concentration show that Se concentrations are lower in older adults than in younger adults (19). In a study which is conducted with 219 healthy patients with the 20 years folow up period and 58.32 median age at baseline it was shown that Se concentrations decreased significantly during aging reagardless of gender. Average Se concentrations dropped from 85.19 (17.15) µg/L to 79.28 (17.69) µg/L after about 20 years (20).

Studies on the relationship between trace elements and cognitive function are limited and there is some controversy. Although Se is shown as a protective factor for cognitive dysfunction in most studies, there are results that argue the opposite. In a study conducted with 1006 patients in the geriatric population with a mean age of 71 in 2022, lower levels of whole blood Se were found in patients with mild cognitive impairment than in healthy individuals. Especially in female patients, this difference was more pronounced (21). In another study with a 9-year follow-up, cognitive decline was associated with a decrease in plasma Se over time. The greater the reduction in plasma Se, the greater the likelihood of cognitive decline. However, no relationship was found between short-term 2-year Se changes and cognitive changes (22). In another study conducted in Australia, Se concentration was not found to be associated with cognitive performance in older adults. However, it was suggested that this lack of association may be due to optimization of selenoprotein synthesis as a result of adequate Se intake in the study population (23).

In conclusion, serum Se level and dietary Se are directly related, and a desired serum Se level can play a role in preventing many chronic diseases, including autoimmune thyroid diseases. In this letter, we wanted to present evidence and raise awareness about these situations. But it is clear that high-quality evidence is needed. Rich sources of Se, such as oilseeds, nuts, chicken, fish, turkey, seafood, cereals and eggs, should be taken daily with

an adequate and balanced diet. The ideal reference ranges for Se concentrations in various geographic regions are not clear, and thyroid tissue-specific biomarkers need to be identified for functional evaluation of Se. There is a decrease in Se levels with aging, and this decrease in particular has been associated with a decrease in cognitive functions.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.S., Y.B., Design: G.S., Y.B., Data Collection or Processing: G.S., Y.B., Analysis or Interpretation: G.S., Y.B., Literature Search: G.S., Y.B., Writing: G.S., Y.B.

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