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About Us

Journal History

European Journal of Geriatrics and Gerontology is the official open access scientific publication organ of the Academic Association of Geriatrics. It is a double peer-reviewed journal published quarterly in April, August and December. Galenos Publishing House publish the journal from 2019.

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Aims and Scope

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;

Aging
Aging Biology
Alzheimer's Disease
Biogerontology
Bone health in older people
Cell Biology
Clinical Geriatrics
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Cognitive Disorders
Demography of Older Populations
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Psychological Gerontology
Sarcopenia
Sleep Disorders
Syncope
Social Gerontology
Stroke Medicine

Special features include rapid communication of important timely issues, surgeon' workshops, interesting case reports, surgical techniques, clinical and basic science review articles, guest editorials, letters to the editor, book reviews, and historical articles in geriatrics and gerontology.

The target audience of the journal includes physicians working in the fields of geriatrics and gerontology and all other health professionals who are interested in these topics.

The evaluation and publication processes of the European Journal of Geriatrics and Gerontology are shaped in acceptance with the guidelines of ICMJE (International Committee of Medical Journal Editors), COPE (Committee of Publication Ethics), EASE (European Association of Science Editors), and WAME (World Association of Medical Editors). The journal also is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

European Journal of Geriatrics and Gerontology is indexed in the TUBITAK/ULAKBIM, EBSCO, Index Copernicus, Gale, ProQuest, J-Gate, CABI, Türk Medline and Turkey Citation Index.

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The European Journal of Geriatrics and Gerontology accepts invited review articles, research articles, brief reports, case reports, letters to the editor, and images that are relevant to the scope of geriatrics and gerontology, on the condition that they have not been previously published elsewhere. Basic science manuscripts, such as randomized, cohort, cross-sectional, and case control studies, are given preference. All manuscripts are subject to editorial revision to ensure they conform to the style adopted by the journal. There is a double blind kind of reviewing system.

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CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for reporting studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of diagnostic accuracy studies: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Objective: The abstract should state the objective (the purpose of the study and hypothesis) and summarize the rationale for the study.

Materials and Methods: Important methods should be written, respectively.

Results: Important findings and results should be provided here.

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Other types of manuscripts, such as case reports, reviews and others, will be published according to uniform requirements. Provide at least 3 keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies, a CONSORT abstract should be provided (http://www.consort-statement.org).

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Original articles should have the following sections;

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1. List All Authors

Bonanni E, Tognoni G, Maestri M, Salvati N, Fabbrini M, Borghetti D, DiCoscio E, Choub A, Sposito R, Pagni C, Iudice A, Murri L. Sleep disturbancesin elderly subjects: an epidemiological survey in an Italian district. Acta Neurol Scand 2010;122:389-397.

2. Organization as Author

American Geriatrics Society 2015 Updated Beers Criteria Expert panel. American geriatrics society 2015 updated Beer criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63: 2227-2246.

3. Complete Book

Ham RJ, Sloane PD, Warshaw GA, Potter JF, Flaherty E. Ham's primary care geriatrics: a case-based approach, 6th ed. Philadelphia, Elsevier/Saunders, 2014.

4. Chapter in Book

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

5. Abstract

Reichenbach S, Dieppe P, Nuesch E, Williams S, Villiger PM, Juni P. Association of bone attrition with knee pain, stiffness and disability; a cross-sectional study. Ann Rheum Dis 2011;70:293-8. (abstract).

6. Letter to the Editor

Rovner B. The Role of the Annals of Geriatric Medicine and Research as a Platform for Validating Smart Healthcare Devices for Older Adults. Ann Geriatr. 2017;21:215-216.

7. Supplement

Garfinkel D. The tsunami in 21st century healthcare: The age-related vicious circle of co-morbidity - multiple symptoms - over-diagnosis - over treatment - polypharmacy [abstract]. J Nutr Health Aging 2013;17(Suppl 1):224-227.

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REVIEW

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Three Problematic Issues from a Geriatric Point of View: Cancer, Radiotherapy, and Malnutrition

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Abstract

Cancer management in older patients has become an important public health concern due to the aging population and increased incidence of cancer with advanced age. The treatment decision for older individuals should not be constrained due to their advanced chronological age. Integration of an oncogeriatric approach is a major key point to improve treatment outcomes in older patients with cancer. Thus, comprehensive geriatric assessment should be used to evaluate older patients with cancer. Malnutrition (MN) is common in patients with cancer and has a profound effect on treatment outcomes. Therefore, assessing patients' nutritional status and providing individualized nutritional intervention are essential. Radiotherapy (RT) is one of the most frequently used and effective treatment modalities against cancer in older adults and is a well-defined cause of MN. We herein highlight geriatric assessment requirements, including essential nutritional assessment in older patients with cancer. In addition to the general view, we focused on RT-related MN and its consequences. RT is better tolerated than surgery in older adults, but it may cause dehydration and MN due to RT-related diarrhea and mucositis. The clinicians should consider that in addition to its effect on the general clinical status, functionality, and surgical outcomes, the prognosis of RT is the worst in older individuals with MN.

Keywords: Assessment, cancer, geriatrics, malnutrition, radiotherapy

Introduction

Malignant neoplastic diseases are the most common cause of death after cardiovascular diseases. The incidence of cancers has been increasing globally (1,2). In 2020, there were approximately 19.3 million new cancer cases, including non-melanoma skin cancer worldwide. Nearly 10 million of these cases resulted in cancer-related death (3).

In Western countries, older people constitute one-fourth of the population. Older people in the community will increase in the coming years. It is predicted that in the next fifty years, the number of people aged 65 and over will be more than double, and over the age of 85 will be almost quadruple. Cancer, an indicator of cellular senescence, is more common with aging. About 60% of new cancer cases and 70% of cancer-related deaths are seen in those aged 65 years and over. Therefore, in the future, older cancer patients will represent a global health problem resulting in increased cancer incidence and mortality (1,4-6). New treatment modalities are being developed to improve the cancer-related prognosis.

Radiotherapy (RT) is an important therapeutic option in the treatment of cancers. It is applied for curative, palliative, or supportive intend in about 50-70% of cancer patients. It is an integral component of cancer treatment, and it is sometimes considered the only treatment option in cases where surgery and/or chemotherapy are risky/contraindicated in older patients. RT is a therapeutic modality applied in older adults considering their evaluation with a geriatric assessment (1). Older patients, as well as younger patients, may benefit from RT because provided that acute and late tolerance connected to RT is acceptable. Ideally, older patients should be evaluated with a comprehensive geriatric assessment (CGA) before initiation of therapy and then regularly.

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Considering the aging population and the increased incidence of cancers, the integration of the oncogeriatric approach into multidisciplinary decision processes is necessary (7). In older patients, treatment decisions should be made based on the performance score (PS), functional capacity, comorbid diseases, accompanying geriatric syndromes, frailty, medications, nutritional status, and the existing social support level. Older individuals can be managed with different treatment options, i.e., only RT, chemotherapy, surgery, their variable combinations, or palliative approach instead of a curative treatment (8). Kurtman et al. (9) drew attention to the characteristics of the tumor, accompanying risks, functional capacity, palliative need, and benefit/harm in RT applications in older patients. They underlined that more palliative approaches could be considered in older patients with low PS and functional capacity, high comorbidity score, poor nutritional status, and other poor prognostic factors (10).

In clinical practice, older patients are being frequently undertreated even when they do not have any other disease or functional problem just due to the consideration of their chronological age. For example, treatment choice has been stratified by only age in some cases; i.e., ≥80 years were directed to less intensive treatment (8,9). Obviously, the treatment decision of an older individual should not be constrained due to an advanced chronological age (8,9). Some studies reported that mortality and morbidity for different tumor types are similar for older and younger patients (10). Some comorbidities that may already be present in older adults may worsen treatment outcomes; nevertheless, the treatment plan should not be made just due to the presence of comorbidities. In this context, there is not any data that can justify and validate age discrimination that is being made during the treatment of older cancer patients, which can excuse the administration of less effective treatments to older patients (10).

Comprehensive geriatric assessment (CGA) accepted as the standard for estimating life expectancy, morbidity, and mortality in cancer patients aged 70 years and over (1,2). Carnofsky performance status and Eastern Cooperative Oncology Group performance measures are associated with the treatment toxicity; nevertheless, these scales alone cannot predict outcomes as successful as CGA in the older population (1,2). There are very few studies in which the geriatrician and oncologist have worked together to manage the treatment plan. In the ELCAPA study, geriatricians made recommendations that may modify the treatment plan in older cancer patients through CGA. Subsequently, 20.8% of the patients required a reduction in the treatment intensity (11). In a study by Mohile et al. (6), 161 patients (57 men, 104 women; median age 82.4 years), 50% of whom had advanced cancer, were involved and referred for CGA at a university hospital. After the discussion at the oncogeriatric multidisciplinary consultation, cancer treatment was changed in 79 (49%) patients, including delayed treatment in 5 patients, less intensive treatment in 29 patients, and more intensive treatment in 45 patients. Horgan et al. (12) reported that eligible older people are not referred to geriatric evaluation, while a geriatric assessment might have changed the initial treatment decision. On the other hand, clinicians need controlled studies to determine whether the treatment modifications based on CGA can improve treatment outcomes. Implementation of multidisciplinary expertise, including social workers, physical therapists, occupational therapists, and nutritionists, can help develop CGA-guided interventions in older individuals with cancer. Accordingly, the risks can be identified, and a CGA-guided treatment plan can be determined. As a simple example, a geriatrician or a pharmacologist can assess the currently used medications, correct the inappropriate medication use, and thereby reduce the potential side effects due to medications.

Nutrition is one of the major issues to be evaluated during the oncologic assessment (13). Malnutrition (MN) results from a deficiency in energy, protein, and micronutrient intake, causes changes in body composition and adversely affects the patient's bodily functions and clinical status (14,15). It has been reported that, in many cancers, 15-40% of the patients had already lost weight and become malnourished before the initiation of the treatment (13). Moreover, the MN incidence may increase further during the treatment of cancer. Specifically, considering RT, the prevalence of MN is estimated between 15-80% during RT application (13,15). This rate is higher in some types of cancers treated with RT, such as head and neck, esophagus and other gastrointestinal system, pancreaticobiliary, and lung cancers (13-15). While RT is tolerated better than surgery in older population, the risk of dehydration due to RT-related diarrhea and mucositis and the resulting MN status should be carefully considered (7,16). Consequent cachexia developing in cancer settings directly brings about 20% of all cancer-related deaths (2,6).

Diagnosis of Malnutrition in Older Cancer Patients, Including Those Treated with Radiation Therapy

Considering the risk of MN in cancer patients, it is essential for oncologists to assess the patients' nutritional status and provide individualized nutritional intervention promptly to optimize clinical outcomes. In this regard, oncologists should evaluate the patients' nutritional status before treatment, determine the potential risk factors that may lead to weight loss, and detect the risk of MN immediately. Thus, MN should be screened and detected in the early reversible phase before refractory cachexia occurs (14,15). Previous studies noted that the weight loss was lesser when a nutritional evaluation and management was performed before, during, and after cancer treatment (2,14). Consequently, the clinicians can aid in the maintenance and/

or improvement of mental and physical functions, reduction of treatment and disease-related complications, decreasing disease severity, lower use of resources, and shortened hospitalization duration (14).

If an older patient has weight loss (>5% in six months or >10% over six months) or has a markedly reduced body mass index (BMI) (i.e., BMI<20 kg/m^2), or involuntary loss of muscle mass, she/he should be considered having MN symptoms and signs. MN can be defined and recognized by variable definitions. The most recent definition is the global consensus approach [global leadership initiative on malnutrition (GLIM)] for the diagnosis of MN. Global leadership initiative on malnutrition (GLIM) suggests that the diagnosis of MN is made when there is at least one phenotypic criterion (i.e., involuntary weight loss, low BMI, or decreased muscle mass) and one etiological criterion (i.e., reduced food intake/malabsorption or acute/chronic disease-related inflammation) (2,8). 2021 updated European Society of Parenteral and Enteral Nutrition Guidelines for clinical nutrition in cancer patients recommended the use of the following scales for the assessment of nutrition in cancer patients: Nutritional risk screening-2002, malnutrition universal screening tool (MUST), mini nutritional assessment (MNA), and malnutrition screening tool (MST). The Academy of Nutrition and Dietetics recommends using of MST and MUST (17). Among these evaluation methods, MUST (in the outpatient setting) and MNA (in both outpatient and inpatient settings) are preferred in older cancer patients (2,14,15). Global leadership initiative on malnutrition (GLIM) definition and evaluation can be preferred in older adults as well. Obviously, the diagnostic approach to detect MN does not differ according to the chosen treatment modality, including RT.

Causes of Malnutrition in Older Cancer Patients, Including Those Treated with Radiation Therapy

Patient-specific, disease-specific, and treatment-specific factors may lead to MN. Radiotherapy (RT) generally has side effects specific to the region where it is applied, and adverse nutritional effects appear due to these side effects.

The patient and disease-specific factors include poor pre-treatment nutritional status, current micronutrient, antioxidant, and mineral deficiencies, low BMI, poor PS, advanced age, caucasian race, female gender, genetic polymorphisms, comorbidities, smoking, fatigue, weight loss, loss of appetite, anorexia, anxiety, depression, dyspnea, pain, advanced cancer, type of cancer, localization of cancer, gastrointestinal system obstruction, impaired absorption of nutrients, metabolic changes due to hormones secreted in cancers, immune-activation via the released cytokines, insulin resistance that develops as a result of the inflammatory process, increased catabolism associated with cancers, and low prealbumin and albumin levels (2,13-15,18).

Treatment-specific factors that may cause MN are anorexia, fatigue, surgery, chemotherapy, and RT-related systemic and local toxicities, mucositis, xerostomia, dysphagia, esophagitis, diarrhea, enteritis, nausea/vomiting, hematological side effects, anxiety, depression, micronutrient, antioxidant, and mineral deficiencies, taste changes and the intend and extend of the treatment (curative, palliative, external, brachytherapy, stereotactic body radiation therapy, etc.). Radiotherapy-related treatment toxicity augments, especially when it is applied with concurrent chemotherapy. These may lead to weight loss and MN by reducing nutrient intake (13,15,18-20). Identifying and treating the side effects that may affect the nutritional status of older patients receiving treatments, including RT, will reduce the possibility of interrupting the therapy and have the capacity to improve tumor control.

Consequences of Malnutrition in Older Cancer Patients with a Specific Emphasis on Those Treated with Radiation Therapy

Malnutrition (MN) has been shown to be associated with a decreased functional capacity due to muscle loss, augmentation of symptoms, decreased quality of life and treatment tolerance, worse prognosis, and reduced survival (13,15). On the other hand, MN causes the progression of many diseases that may be simultaneously present in the patient other than cancer, and it is a unique factor in the development of sarcopenia, cachexia, and frailty, which are themselves associated with increased morbidity and mortality (8). Malnutrition (MN) may cause adverse alterations in absorption, protein binding, hepatic metabolism, and renal excretion of drugs and their metabolites during systemic therapies. In malnourished patients, decreased plasma protein concentration may significantly increase the likelihood of toxicity of agents with high protein binding, such as prednisolone, etoposide, cisplatin, paclitaxel, and irinotecan metabolites. In addition, MN may disrupt some metabolic pathways in the liver, reducing the clearance of drugs and prolonging their half-life. Thus, it has been claimed that since patients will be exposed to more drugs, toxicity may increase, and the necessity to interrupt the treatment will occur more frequently in patients suffering concomitantly from MN (15).

Malnutrition (MN) influences the patient's tolerance to the treatment. Weight loss indicates that the patient may not tolerate a curative treatment, complete the treatment, thereby can not receive adequate treatment, and, hence, weight loss increases mortality risk (21,22). Specifically, the prognosis of RT is the worst in older individuals with MN. Many studies have been published reporting that MN had an adverse effect on treatment and decreased favorable response to the introduced treatment. Increased RT toxicity, changing, stopping, or interrupting the RT plan may be negative factors that change the use of a curative or palliative procedure and decrease the response to RT, especially when combined with chemotherapy (13,15).

Another point is that MN escalates surgical morbidity and post-surgical complications. It can delay wound healing, worsen muscle functions, and increase the risk of postoperative complications, thus prolonging hospital stay and increasing the financial burden (15).

Conclusion

The integration of the oncogeriatric approach is a major key point to improve outcomes in older cancer patients. Malnutrition (MN) is common in the cancer setting and has a profound effect on treatment outcomes. It is essential to assess the patients' nutritional status generally via MUST or MNA and provide individualized nutritional intervention. Radiotherapy (RT) is one of the most frequently used and effective treatment modalities in older adults. While RT is tolerated better than surgery in older adults, it is a well-defined cause of MN. The clinicians should consider that, in addition to its effect on general clinical status, functionality, and surgical outcomes, the prognosis of RT is the worst in older individuals with MN as well.

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References

1. Muelas Soria R. [Nutritional impact of radiotherapy in oncogeriatric patients. Can radiation oncologists minimize the radiotherapy impact on the nutritional status of the elderly patient?]. Nutr Hosp 2020;37:1.
2. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Oldervoll L, Ravasco P, Solheim TS, Strasser F, de van der Schueren M, Preiser JC, Bischoff SC. ESPEN practical guideline: Clinical Nutrition in cancer. Clin Nutr 2021;40:2898-2913.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-249.
4. American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2019-2021. Atlanta: American Cancer Society; 2019.
5. Blasiak J, Chojnacki J, Pawlowska E, Szczepanska J, Chojnacki C. Nutrition in Cancer Therapy in the Elderly-An Epigenetic Connection? Nutrients 2020;12:3366.
6. Mohile SG, Klepin HD, Rao AV. Considerations and controversies in the management of older patients with advanced cancer. Am Soc Clin Oncol Educ Book 2012:321-328.
7. Durdux C, Boisserie T, Gisselbrecht M. [Radiation therapy in elderly patients]. Cancer Radiother 2009;13:609-614.
8. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, Kiesswetter E, Maggio M, Raynaud-Simon A, Sieber CC, Sobotka L, van Asselt D, Wirth R, Bischoff SC. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr 2019;38:10-47.
9. Kurtman C, Gareveran MS, Gümüştepe E. Geriatric Radiotherapy. Ankara Eğt. Arş. Hast. Derg 2016;49:122-127.
10. Monfardini S, Balducci L, Overcash J, Aapro MS. Surgical and Radiation Oncology in Elderly Patients with Cancer October 25, 2020. The ASCO post. https://ascopost.com/issues/october-25-2020/surgical-and-radiation-oncology-in-elderly-patients-with-cancer/.
11. Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N, Krypciak S, Bastuji-Garin S, Culine S, Paillaud E. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol 2011;29:3636-3342.
12. Horgan AM, Leighl NB, Coate L, Liu G, Palepu P, Knox JJ, Perera N, Emami M, Alibhai SM. Impact and feasibility of a comprehensive geriatric assessment in the oncology setting: a pilot study. Am J Clin Oncol 2012;35:322-328.
13. Ravasco P. Nutrition in Cancer Patients. J Clin Med 2019;8:1211.
14. Reber E, Schönenberger KA, Vasiloglou MF, Stanga Z. Nutritional Risk Screening in Cancer Patients: The First Step Toward Better Clinical Outcome. Front Nutr 2021;8:603936.
15. Santarpia L, Contaldo F, Pasanisi F. Nutritional screening and early treatment of malnutrition in cancer patients. J Cachexia Sarcopenia Muscle 2011;2:27-35.
16. Huguenin P, Glanzmann C, Lütolf UM. Acute toxicity of curative radiotherapy in elderly patients. Strahlenther Onkol 1996;172:658-663.
17. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36:11-48.
18. Cacicedo J, Casquero F, Martinez-Indart L, del Hoyo O, Gomez de Iturriaga A, Navarro A, Bilbao P. A prospective analysis of factors that influence weight loss in patients undergoing radiotherapy. Chin J Cancerm 2014;33:204-210.
19. Donaldson SS, Lenon RA. Alterations of nutritional status: impact of chemotherapy and radiation therapy. Cancer 1979;43(5 Suppl):2036-2052.
20. Richards J, Arensberg MB, Thomas S, Kerr KW, Hegazi R, Bastasch M. Impact of Early Incorporation of Nutrition Interventions as a Component of Cancer Therapy in Adults: A Review. Nutrients 2020;12:3403.
21. Barthelemy N, Streel S, Donneau AF, Coucke P, Albert A, Guillaume M. Screening for malnutrition in lung cancer patients undergoing radiotherapy. Support Care Cancer 2014;22:1531-1536.
22. Ge T, Lin T, Yang J, Wang M. Nutritional status and related factors of patients with advanced lung cancer in northern China: a retrospective study. Cancer Manag Res 2019;11:2225-2231.

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Polypharmacy Frequency: The Relationship Between Polypharmacy and Mortality in COVID-19 (+) Older Adults

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Abstract

Objective: This study aims to determine the relationship between polypharmacy and Coronavirus disease-2019 (COVID-19) (+) related mortality.

Materials and Methods: All older adults >60 years old who had positive COVID-19 polymerase chain reaction tests were included in the study, designed retrospectively. Polypharmacy was defined as drug use of five or more.

Results: One hundred and ten people of >60 years old were included in the study. Fifty-nine (53.6%) of the participants were male and the mean age was 70.5+8.81. The prevalence of polypharmacy in patients diagnosed with COVID-19 infection was 31.8% (n=35). Eighty-two (78.8%) of participants had pneumonia. Mortality occurred in 24 (21.8%) of the participants. There was no relationship between polypharmacy and mortality (p=0.241). In multivariate analysis, older age was associated with mortality (odds ratio: 6.82 95% confidence interval: 2.46-18.91, p<0.001).

Conclusion: The prevalence of polypharmacy in individuals diagnosed with COVID-19 infection was like the literature. The most significant factors in death in people with COVID-19 infection were older age. There was no relationship between polypharmacy and mortality.

Keywords: Older age, COVID, polypharmacy, mortality, coronavirus

Introduction

The pandemic of Coronavirus disease-2019 (COVID-19), which started in China in December 2019, caused the death of 1.311.942 people, infecting about 54 million people worldwide by 15 November 2020 (1). COVID-19 infection can be asymptomatic-mild upper respiratory tract infection or it can present with pneumonia and, acute respiratory distress syndrome (2-5). In many studies on COVID-19, older age and comorbidity has been associated with poor outcomes (2,3,5-7). Results are worse in older adult individuals who need mechanical ventilation (3).

In Turkey, the first case was reported on 11 March 2020 - the first death was seen on 17 March 2020 (8). By 10 February 2021, total cases and deaths had reached 2.548.195 and 26.998 cases in Turkey, respectively (8).

With aging, the number of diseases increases; therefore, the number of drugs used by people increases (9). Polypharmacy is an acute geriatric syndrome (10). Polypharmacy incidence has been reported from 30% to 60% in older adults (10-12). The reason for such a difference in polypharmacy incidence is that there is no universal definition of polypharmacy (10). Some define it as drug use other than indication (12), while others define it with more drug use than a certain number of drugs (10,13). Polypharmacy has been associated with many clinical conditions such as falls, mortality, adverse drug events, impaired cognition, and frailty (10,11,14). Until now, many factors related to mortality have been revealed in patients with a diagnosis of COVID-19, but there are a limited number of studies evaluating them in terms of geriatric syndromes (3,6,15). In the studies performed, mortality with frailty was evaluated, and unlike expectedly, no relation with mortality in frail patients was

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shown (6,15). There are few studies of the relationship between polypharmacy and COVID-19 related mortality, and their results are conflicting (3,6).

This study aimed to clarify the relationship between COVID-19 and polypharmacy because the research results published so far are contradictory. This study aims to determine the prevalence of polypharmacy in patients diagnosed with COVID-19 (+), to investigate whether the presence of polypharmacy in patients with COVID-19 (+) has an impact on mortality, and to identify other causes of mortality in people diagnosed with COVID-19 (+).

Materials and Methods

All older adults >60 years old who had a positive COVID-19 polymerase chain reaction (PCR) test at Erciyes University Medical School Hospital were included in the study. Erciyes University Medical School Hospital was the reference hospital for the pandemic. This research had been designed retrospectively. For the retrospective design, we did not evaluate the comprehensive geriatric assessment and frailty status of patients.

The files of the participants included in the study were scanned retrospectively. Their socio-demographic characteristics (age, gender), comorbidities [e.g., chronic obstructive pulmonary disease, cancer, hypertension (HT), coronary artery disease, chronic kidney disease, and/or diabetes mellitus (DM)], the number of drugs, the types of drugs, the presence of pneumonia, the history of admission on intensive care unit (ICU), the history of mechanical ventilation and the presence of mortality were recorded.

COVID-19 was detected by real-time reverse transcriptase-PCR assay of samples collected by using nasopharyngeal swabs. Computed tomography (CT) was performed on all patients without contraindications (claustrophobia, etc.), who resulted in COVID-19 PCR positive. A specialist radiologist evaluated CT. Patients with infiltration on CT were considered to have COVID-19 pneumonia.

In this study, five or more drug use was defined as polypharmacy (10). When the patients admitted to the hospital, those who used five or more medications regularly for the last year were accepted as "polypharmacy". The drugs were recorded through the patients' reports during hospitalization and controlled from the medulla system (in Turkey). The drugs used by the patients were categorized as antihypertensive, antiaggregant, anticoagulant, antidepressant, antidiabetic (AD) drugs, inhaler drugs, antilipidemic drugs, immunosuppressant drugs, and proton pump inhibitors (PPIs).

This research was approved by the Erciyes University Ethics Committee (date: 10.06.2020, number: 2020/285). Consent was obtained from the participants or their relatives.

Statistics

Histogram, q-q plots are examined, and the Shapiro-Wilk's test was applied to assess the data normality. Levene test was used to test variance homogeneity. To compare the differences between groups, the Pearson chi-square test or Fisher's Exact test were applied for categorical variables to compare the differences between groups. Mann-Whitney U tests were applied for continuous variables. Binary logistic regression analysis models were built to investigate the effect of variables in estimating mortality in geriatric patients. Crude, age, and gender-adjusted, and multiple models were fitted separately. Significant variables at $p<0.25$ were included in numerous models, and backward elimination was performed to identify independent risk factors. Wald statistic was used as a model selection criterion. Hosmer-Lemeshow tests were used for the goodness of fit test. Odds ratios were calculated with 95% confidence intervals. All analyses were performed using TURCOSA (Turcosa Analytics Ltd. Co., www.turcosa.com.tr) statistical software. P-values less than 5% were considered as statistically significant.

Results

One hundred ten people of >60 years old were included in this research. Fifty-nine (53.6%) of the participants were male and the mean age was 70.5 (64.0-78.2, standard deviation 8.81). Ninety-five (86.4%) of the participants had comorbidities. The most common comorbidity was HT with 61.8% (n=68) patients, the second was DM with 28.2% (n=31) patients. Polypharmacy was recorded in 31.8% (n=35). The most widely used drugs were diuretics (hydroxychlorothiazide, spironolactone) (n=41, 37.3%), beta-blockers (n=34, 30.9%), acetyl-salicylic acid (ASA) (n=32, 29.1%), angiotensin receptor blockers (ARB) (n=31, 28.2%), calcium channel blockers (n=26, 23.6%), angiotensin-converting enzyme inhibitors (ACE-I) (n=24, 21.8%) and metformin (n=21, 19.1%). While a total of 78.8% (n=82) had COVID-19 pneumonia. Ten (9.1%) of 110 participants had a history of admission in ICU, and five (4.5%) had mechanical ventilation. Mortality occurred in 21.8% (n=24) of the participants. Table 1 shows the demographic and clinical characteristics of the participants according to mortality. The participants who had mortality were older (69 vs. 79.5, $p<0.001$). Moreover, the mortality rate was higher in hospitalized individuals (69.8% vs. 100%, $p=0.002$). Table 2 shows the relationship between drug groups and mortality. There was no relationship between any drug group and mortality. Thirteen (22.0%) of the patients with mortality were male and 21.6% (n=11) were female ($p=0.570$). Twelve (13.8%) of those with mortality were between the ages of 60-79 and 52.2% (n=12) were over 80 years old ($p<0.001$). While no mortality occurred in patients who were followed at home, mortality was observed in all hospitalized and followed up ($p=0.002$). Admission in ICU and history of mechanical ventilation were not associated with mortality ($p=0.08$ and

0.227, respectively), but the number of patients was very low for these parameters.

The Hosmer-Lemeshow test was applied for each final models resulted in X^2=0.371 p=0.831 for mortality. These results revealed the built multiple binary logistic regression model's appropriateness in predicting the clinical outcomes in geriatric patients. Table 3 shows the univariate, adjusted, and multiple logistic regression analysis results identifying the risk factors of mortality. In univariate analysis, we found that people with intubation history increased the mortality risk 48.6 times (odds ratio: 48.60 95% confidence interval 13.35-176.94, p<0.001). History of intubation was not included in the multivariate analysis since it would suppress all other multivariate analysis parameters. Gender, polypharmacy, and the presence of COVID pneumonia parameters do not affect mortality in univariate analysis. We found that age was the only parameter affecting mortality in univariate analysis. When an adjusted model was established considering the effects of age and gender, that the variables of polypharmacy and the presence of COVID pneumonia do not affect mortality. In our study, the only factor that affects mortality was age. Patients aged 80 and over had a mortality rate of 6.82 times higher than patients aged 60-79 (p<0.001). The same situation was similar in the multiple models.

Discussion

In the present study, the prevalence of polypharmacy in patients diagnosed with COVID-19 infection was 31.8%. Mortality occurred in 21.8% of the participants. There was no relationship between polypharmacy and mortality. The most important factor associated with mortality was older age.

Until now, quite a few studies have examined the relationship between polypharmacy and COVID-19. In one of them, De Smet et al. (6) reported a higher prevalence of polypharmacy than ours (64% vs. 31.8%), but the number of patients in this study was less than our study. Until now, there were very few publications on polypharmacy and COVID-19 related mortality. While no relationship was found between mortality and polypharmacy in one of these studies (6), another study found polypharmacy to increase the mortality risk (3). Polypharmacy has been shown to increase mortality in older adults in many meta-analyses (11,12). However, surprisingly, this study did not show an association between polypharmacy and mortality (41.7% vs. 29.1%, p=0.241). Therefore, some things that affect outcomes in COVID-19 infection may be thought to be different from prognostic factors (age, sex, polypharmacy, and comorbidities) described in other cases. More research is needed to clarify the relationship between polypharmacy and COVID-19.

Table 1. The characteristics of patients with COVID-19 (+) with or without mortality

Variables	Total n (%) n=110	Survivors n (%) n=86 (78.2)	Non-survivors n (%) n=24 (21.8)	p
Age	70.50 (64.0-78.2)	69.00 (63.75-76.00)	79.50 (71.00-87.00)	**<0.001**
Age 60-79 ≥80	 87 (79.1) 23 (20.9)	 75 (86.2) 11 (47.8)	 12 (13.8) 12 (52.2)	**<0.001**
Gender Male Female	 59 (53.6) 51 (46.4)	 46 (78.0) 40 (78.4)	 13 (22.0) 11 (21.6)	0.953
Comorbidity HT DM CAD COPD CKD Carcinoma	 68 (61.8) 31 (28.2) 28 (25.5) 17 (15.5) 4 (3.6) 5 (4.5)	 52 (60.50) 24 (27.90) 21 (24.40) 14 (16.30) 2 (2.30) 4 (4.7)	 16 (66.70) 7 (29.20) 7 (29.20) 3 (12.50) 2 (8.30) 1 (4.2)	 0.580 0.903 0.637 0.651 0.164
Number of comorbidity	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.572
Number of drugs	3.00 (1.00-5.20)	3.00 (1.00-5.00)	3.50 (2.00-6.00)	0.450
Polypharmacy	35 (31.80)	25 (29.10)	10 (41.70)	0.241
Presence of COVID pneumonia	82 (78.80)	67 (77.90)	15 (62.50)	0.126
Follow-up status Home Hospital	 26 (23.60) 84 (76.40)	 26 (30.20) 60 (69.80)	 0 (0.0) 24 (100)	**0.002**
Admission on ICU	34 (30.90)	10 (11.60)	24 (100)	**<0.001**
Mechanical ventilation	5 (4.50)	5 (5.80)	18 (75.00)	**<0.001**

CAD: Coronary artery disease, CKD: Chronic kidney diasease, COPD: Chronic obstructive pulmonary disease, COVID: Coronavirus, DM: Diabetes mellitus, HT: Hypertension, ICU: Intensive care unit, values are expressed as n (%) or median (1^{st}-3^{rd} quartiles). Adjusted p-values are calculated using Benjamini-Hochberg procedure and significant adjusted p-values are shown in bold

There were many studies in the literature that have examined various drug groups and the relationship of COVID-19. In some of these researches, the use of metformin (16,17), DPP4-I (16), ACE-I (18-20), ARB (18-20), statins (20,21) and chronic anticoagulants (22,23) was protective against COVID-19-related mortality. However, results in other studies were in the opposite direction. Kocayigit et al. (24), found no association between mortality and type of antihypertensive agents' use. In the study of Cheng et al. (25), no effect of metformin use on mortality was found. In research investigating the relationship between many drug groups and mortality in Iran (26), only statin group drugs decreased mortality. In contrast, non-steroidal anti-inflammatory drugs, ACE-I, and ARB use did not show any effect on death. In another study on diabetic COVID-19 patients (27), the use of AD agents (insulin, metformin, sulfonylurea, and DPP-4 inhibitors) did not have a protective effect on mortality. The factors that were effective in drugs to prevent mortality in those researches improve the immune response, reduce the inflammatory response, block renin-angiotensin-aldosterone system, and prevent the formation of thrombosis (17,19,21,22). Our study examined the relationship between nine different drug groups (antihypertensive, antiaggregant, anticoagulant, immunosuppressant, inhaler, antidepressant, antilipidemic and AD drugs, and PPI) and mortality, and we found no relationship (Table 2). Randomized controlled studies are needed to understand precisely what the effects of drugs on COVID-19 related mortality.

When the patients with mortality in COVID-19 patients were examined in the literature, it was seen that 20-80% of them were over 60 years old (2,4,28,29). In some research in Turkey (3,5), were like our research for over 60 years older patients (23.1% vs. 21.8%, 21.2% vs. 21.8%). When we divide it into groups by age, the mortality rates are similar to the literature and in Turkey (3,30,31). In our research, the mortality rate between the ages of 60-79 was 13.8%, and over 80 years old, was 52.2%, respectively. We found that the mortality risk increased approximately seven times in individuals aged 80 and over. As in our research, many studies have reported that older age was a risk factor in COVID-19 related deaths (3,6,7,15,24,28,29). Why is COVID-19 infection more mortal in older adults? Immunosenescence, or changes in the age-related immune system, primarily affects the adaptive immune system (32). Accordingly, intracellular pathogens are more frequent and/or severe infections (33). A decrease in T-cell and B-cell functions in relation to older age makes it challenging to limit viral replication (32). Both older age and increasing type 2 cytokine production impairs cell-mediated immune responses to infectious challenge (32). Also,

Table 2. Comparison types of drugs between mortality

Variables	Survivors n (%) n=86 (78.2)	Non-survivors n (%) n=24 (21.8)	p
Any antihypertensive drugs			
ACE-I	20 (23.30)	4 (16.70)	0.586
ARB	24 (27.90)	7 (29.20)	0.903
Beta blocers	23 (26.70)	11 (45.80)	0.085
Calcium channel blocers	17 (65.40)	9 (37.50)	0.101
Diuretics	32 (37.20)	9 (37.50)	0.979
Alfa blocers	1 (4.20)	1 (1.20)	0.390
Any antiaggregant drugs			
ASA	9 (37.50)	23 (26.70)	0.305
Clopidogrel	6 (25.00)	11 (12.80)	0.143
Ticagrelor	0 (0.0)	2 (2.30)	0.451
Any anticoagulant drugs			
Warfarin	1 (4.20)	1 (1.20)	0.475
Rivaroxaban	0 (0.0)	2 (2.30)	
Immunosuppressant drugs	0 (0.0)	3 (3.50)	0.474
Inhaler drugs	3 (12.50)	14 (16.30)	0.464
Antidepressant drugs	0 (0.0)	7 (8.10)	0.169
Antilipidemic drugs	5 (20.80)	15 (17.40)	0.453
Any antidiabetic drug(AD)s			
Biguanides	2 (8.30)	19 (22.10)	0.129
DPP-IV inhibitors	7 (29.20)	23 (26.70)	0.814
Other oral ADs	2 (8.30)	4 (4.70)	0.390
Insulin	5 (20.80)	11 (12.80)	0.323
Proton pump inhibitors	5 (20.80)	9 (10.50)	0.178

Blockers, ASA: Acetyl-salicylic acid, DPP: Dipeptidyl peptidase, values are expressed as n (%). Adjusted p-values are calculated using Benjamini-Hochberg procedure and significant adjusted p-values are shown in bold. ACE-I: Angiotensin-converting enzyme inhibitors, AD: Antidiabetic drug, ARB: Angiotensin receptor

Table 3. Univariate and multiple logistic regression analysis results in identifying the risk factors of mortality

	Crude model		Adjusted model		Multivariate model	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age, 60-79 ≥80	 6.82 (2.46-18.91) 1.00	 **<0.001** -	 - -	 - -	 6.82 (2.46-18.91) 1.00	 **<0.001** -
Gender Male Female	 0.97 (0.39-2.41) 1.00	 0.953 -	-	-	-	-
Polypharmacy (>5 drugs)	1.74 (0.68-4.42)	0.244	1.78 (0.65-4.93)	0.264	-	-
Presence of COVID pneumonia	0.47 (0.18-1.25)	0.130	0.48 (0.16-1.37)	0.169	-	-

CI: Confidence interval, COVID: Coronavirus, OR: Odds ratio. Adjusted models are controlled for age and gender

susceptibility to thrombosis and thromboembolism increases with older age (32,34-36). Systemic inflammation is a condition that enhances procoagulant effects (34,35). Many studies published to date have found abnormalities in coagulation-related values in laboratory tests, and these abnormalities were associated with mortality in COVID-19 patients (2,4,37). For these reasons, COVID-19 infection is more severe and mortal in older adults.

Study Limitations

There are some limitations to this study. The most important limitation was single-centered and of small sample size of the present study. Also, people with negative tests but radiologically with COVID-19 pneumonia were not included in this study. Therefore, the findings in this study, unfortunately, do not reflect all individuals with COVID-19 pneumonia. The government determines hospitalization and treatment algorithms for people diagnosed with COVID-19. So, there must be some selective bias. One of the limitations was that the presence of drug-drug interaction had not been studied. There was no information about the laboratory parameters and treatment modalities of the participants. Therefore, the effects of the treatments received by individuals on mortality have not been studied. Further studies are still needed.

Conclusion

In summary, the prevalence of polypharmacy in individuals diagnosed with COVID-19 infection is like the literature. The most significant effect on mortality in people with COVID-19 infection is older age. Further studies with more participants are needed to clarify the relationship between COVID-19 infection and polypharmacy.

Ethics

Ethics Committee Approval: This study is approved by the Erciyes University Ethics Committee (date: 10.06.2020, number: 2020/285).

Informed Consent: Consent was obtained from the participants or their relatives.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.Ş.D., S.A., Design: N.Ş.D., S.A., Data Collection or Processing: N.Ş.D., S.A., T.S., Z.T., Analysis or Interpretation: N.Ş.D., G.E.Z., S.A., Literature Search: N.Ş.D., S.A., Writing: N.Ş.D., S.A.

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References

1. https://coronavirus.jhu.edu/map.html.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
3. Esme M, Koca M, Dikmeer A, Balci C, Ata N, Dogu BB, Cankurtaran M, Yilmaz M, Celik O, Unal GG, Ulgu MM, Birinci S. Older Adults With Coronavirus Disease 2019: A Nationwide Study in Turkey. J Gerontol A Biol Sci Med Sci 2021;76:e68-e75.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.
5. Medetalibeyoglu A, Senkal N, Kose M, Catma Y, Bilge Caparali E, Erelel M, Oral Oncul M, Bahat G, Tukek T. Older Adults Hospitalized with Covid-19: Clinical Characteristics and Early Outcomes from a Single Center in Istanbul, Turkey. J Nutr Health Aging 2020;24:928-937.
6. De Smet R, Mellaerts B, Vandewinckele H, Lybeert P, Frans E, Ombelet S, Lemahieu W, Symons R, Ho E, Frans J, Smismans A, Laurent MR. Frailty and Mortality in Hospitalized Older Adults With COVID-19: Retrospective Observational Study. J Am Med Dir Assoc 2020;21:928-932.e1.
7. Li T, Lu L, Zhang W, Tao Y, Wang L, Bao J, Liu B, Duan J. Clinical characteristics of 312 hospitalized older patients with COVID-19 in Wuhan, China. Arch Gerontol Geriatr 2020;91:104185.
8. Ministry of Health - Republic of Turkey https://covid19.saglik.gov.tr/.

9. Franchi C, Tettamanti M, Pasina L, Djignefa CD, Fortino I, Bortolotti A, Merlino L, Nobili A. Changes in drug prescribing to Italian community-dwelling elderly people: the EPIFARM-Elderly Project 2000-2010. Eur J Clin Pharmacol 2014;70:437-443.
10. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017;17:230.
11. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf 2018;17:1185-1196.
12. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. J Am Acad Nurse Pract 2005;17:123-132.
13. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002;287:337-344.
14. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. Br J Clin Pharmacol 2018;84:1432-1444.
15. Knopp P, Miles A, Webb TE, Mcloughlin BC, Mannan I, Raja N, Wan B, Davis D. Presenting features of COVID-19 in older people: relationships with frailty, inflammation and mortality. Eur Geriatr Med 2020;11:1089-1094.
16. Singh AK, Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A narrative review. Diabetes Res Clin Pract 2020;165:108266.
17. Luo P, Qiu L, Liu Y, Liu XL, Zheng JL, Xue HY, Liu WH, Liu D, Li J. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. Am J Trop Med Hyg 2020;103:69-72.
18. Rodilla E, Saura A, Jiménez I, Mendizábal A, Pineda-Cantero A, Lorenzo-Hernández E, Fidalgo-Montero MDP, López-Cuervo JF, Gil-Sánchez R, Rabadán-Pejenaute E, Abella-Vázquez L, Giner-Galvañ V, Solís-Marquínez MN, Boixeda R, Peña-Fernández A, Carrasco-Sánchez FJ, González-Moraleja J, Torres-Peña JD, Guisado-Espartero ME, Escobar-Sevilla J, Guzmán-García M, Martín-Escalante MD, Martínez-González ÁL, Casas-Rojo JM, Gómez-Huelgas R. Association of Hypertension with All-Cause Mortality among Hospitalized Patients with COVID-19. J Clin Med 2020;9:3136.
19. Chen R, Yang J, Gao X, Ding X, Yang Y, Shen Y, He C, Xiang H, Ke J, Yuan F, Cheng R, Lv H, Li P, Zhang L, Liu C, Tan H, Huang L. Influence of blood pressure control and application of renin-angiotensin-aldosterone system inhibitors on the outcomes in COVID-19 patients with hypertension. J Clin Hypertens (Greenwich) 2020;22:1974-1983.
20. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tré G, Belmans L, Dobson R, Wynendaele E, Van De Wiele C, Vandaele F, Van Dijck D, Bean D, Fedson D, De Spiegeleer B. The Effects of ARBs, ACEis, and Statins on Clinical Outcomes of COVID-19 Infection Among Nursing Home Residents. J Am Med Dir Assoc 2020;21:909-914.e2.
21. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJ. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care 2020;24:429.
22. Inama G, Dodi C, Provini M, Bossoni E, Inama L, Balzarini L, Mancini C, Ramponi S, Marvisi M. Coronavirus disease 2019 infection in patients with recent cardiac surgery: does chronic anticoagulant therapy have a protective effect? J Cardiovasc Med (Hagerstown) 2020;21:765-771.
23. Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler A, Venugopal S, Makki I, Qin Q, Dharmapuri S, Jun T, Bhalla S, Berwick S, Feld J, Mascarenhas J, Troy K, Cromwell C, Dunn A, Oh WK, Naymagon L. Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. Blood 2020;136:144-147.
24. Kocayigit I, Kocayigit H, Yaylaci S, Can Y, Erdem AF, Karabay O. Impact of antihypertensive agents on clinical course and in-hospital mortality: analysis of 169 hypertensive patients hospitalized for COVID-19. Rev Assoc Med Bras (1992) 2020;66(Suppl 2):71-76.
25. Cheng X, Liu YM, Li H, Zhang X, Lei F, Qin JJ, Chen Z, Deng KQ, Lin L, Chen MM, Song X, Xia M, Huang X, Liu W, Cai J, Zhang XJ, Zhou F, Zhang P, Wang Y, Ma X, Xu Q, Yang J, Ye P, Mao W, Huang X, Xia J, Zhang BH, Guo J, Zhu L, Lu Z, Yuan Y, Wei X, She ZG, Ji YX, Li H. Metformin Is Associated with Higher Incidence of Acidosis, but Not Mortality, in Individuals with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020;32:537-547.e3.
26. Alamdari NM, Afaghi S, Rahimi FS, Tarki FE, Tavana S, Zali A, Fathi M, Besharat S, Bagheri L, Pourmotahari F, Irvani SSN, Dabbagh A, Mousavi SA. Mortality Risk Factors among Hospitalized COVID-19 Patients in a Major Referral Center in Iran. Tohoku J Exp Med 2020;252:73-84.
27. Kim MK, Jeon JH, Kim SW, Moon JS, Cho NH, Han E, You JH, Lee JY, Hyun M, Park JS, Kwon YS, Choi YK, Kwon KT, Lee SY, Jeon EJ, Kim JW, Hong HL, Kwon HH, Jung CY, Lee YY, Ha E, Chung SM, Hur J, Ahn JH, Kim NY, Kim SW, Chang HH, Lee YH, Lee J, Park KG, Kim HA, Lee JH. The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea. Diabetes Metab J 2020;44:602-613.
28. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respir Res 2020;21:74.
29. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620-2629.
30. Ministry of Health - Republic of Turkey https://saglik.gov.tr/.
31. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020;395:1225-1228.
32. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis 2005;41(Suppl 7):S504-S512.
33. Grubeck-Loebenstein B, Wick G. The aging of the immune system. Adv Immunol 2002;80:243-284.
34. Opal SM, Esmon CT. Bench-to-bedside review: functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis. Crit Care 2003;7:23-38.
35. Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. Am J Med 2003;114:180-187.
36. Yamamoto K, Takeshita K, Kojima T, Takamatsu J, Saito H. Aging and plasminogen activator inhibitor-1 (PAI-1) regulation: implication in the pathogenesis of thrombotic disorders in the elderly. Cardiovasc Res 2005;66:276-285.
37. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720.

ORIGINAL RESEARCH

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Experiences in a Palliative Care Unit for Patients with Dementia

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Abstract

Objective: Interest in the concept of palliative care is increasing in patients with advanced dementia; however, the effects of palliative care on the natural course of the disease remain unknown. Therefore, this study aimed to present the 1-year experience of an institutional palliative care unit for patients with dementia.

Materials and Methods: This is a retrospective cross-sectional before-after archive study, which included 35 patients who received palliative care for at least 6 months in the Palliative Care Unit of the Dementia-Alzheimer Disabled Care Center, operated by the Turkish Alzheimer Association's Mersin Branch. Patient data during the palliative care unit admission and the end of 6 months of care were compared.

Results: The mean age of 35 patients (14 females and 21 males) was 80.00±8.47 years. The average length of stay in the palliative care unit was 10.03±2.13 months. Patient weights increased with palliative care ($p<0.001$). Patients with pain experienced a decrease in their pain levels ($p=0.014$). Pressure ulcers in 10 (28.57%) patients during admission had improved pressure sore stage and pressure ulcer healing scale ($p=0.007$ and $p=0.005$, respectively). No new pressure ulcers occurred in any patient. There was a decrease in patients with behavioral symptoms, and no patients developed new behavioral symptoms and/or sleep disorders.

Conclusion: Our results indicate that the quality of life of patients who received multidisciplinary care in an institutional palliative care unit improved.

Keywords: Dementia, palliative care, nutrition, pressure ulcers, pain

Introduction

One of the most critical health problems in aging societies is dementia, a substantial cause of disability in the elderly. The number of people affected by dementia in the world nearly doubles every twenty years (1-3). Dementia is irreversible and shows a progressive process (4). Regardless of the type of dementia, almost all clinical features are similar in the advanced stage of the disease, and the patient cannot perform even basic daily life activities (5,6). The rate of being placed to care institutions increases parallel with the degree of dependence of the patients (7,8).

Palliative care (PC) is an approach focused on improving the quality of life of patients and their relatives who struggle with progressive and incurable diseases. In palliative care units (PCU), efforts are made to eliminate discomfort symptoms and integrate the psychological and spiritual aspects of care (9). Patients with advanced dementia have many symptoms that cause serious distress for patients and their caregivers. The main symptoms are nutritional problems, weight loss, pain, movement limitations, pressure sores, recurrent infections, sleep problems, and behavioral disorders (10,11).

Most of the PC studies in the world and Turkey have been carried out in general PC centers and often with cancer patients.

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However, the PC process in advanced-stage dementia patients is different from the PC process in cancer patients in many aspects. Life expectancy in advanced dementia patients is longer than in terminal stage cancer patients. The rate of functional decline in dementia patients may not always be predictable. Furthermore, cognitive impairments make it more challenging to assess patient symptoms. In patients with advanced dementia, there is even a further increase in the frequency of behavioral and psychological symptoms related to dementia (12-14). Additionally, managing behavioral and psychological symptoms requires a separate perspective and training.

Established within the Dementia-Alzheimer Disabled Care Center of the Mersin Branch of the Turkish Alzheimer's Association, the PCU is the first and only PCU in Turkey that serves only dementia patients. We do not yet have clear information about the direction and extent of the effect of PC on the natural course of the disease in patients with advanced dementia. This study aimed to examine the clinical characteristics of patients followed up in an institutional PCU where all patients are diagnosed with dementia and present the unit's one-year experiences.

Materials and Methods

A retrospective before-after cross-sectional study was conducted in a single center. Thirty-five dementia patients who stayed for 6 months or longer in the PCU at the Dementia-Alzheimer Disabled Care Center of the Turkish Alzheimer Association's Mersin Branch between 21.9.2019 and 21.9.2020 were included. Patients who stayed in the PCU for less than 6 months and who received PC outside of the determined study dates were excluded from the study.

Before starting the research, permission was obtained from the Turkish Alzheimer Association's Mersin Branch Dementia-Alzheimer Disabled Care Center, and ethics committee approval was taken from Mersin University Ethics Committee. The guardians of the patients were informed about the research, and their voluntary consent was obtained.

Admission criteria to the PCU have been established by the institution itself: 1- Being constantly in need of invasive or non-invasive mechanical ventilation support, 2- Continuous need for parenteral nutrition/hydration, 3- Being fully bed-bound and immobile, and 4- Having moderate or severe pain despite medical treatment. A patient who meets one or more of these criteria can be followed up in this PCU.

Data recorded in the files of the patients were used in our study. Evaluations of the patients during their admission to the PCU were recorded as the "first assessment". After staying in the PCU for at least 6 months, the health records closest to the death date or the date of the completion of the study were accepted as the "last assessment". Patient information was collected with a data collection form prepared by the researchers. Recorded were age, sex, place of stay before the PCU, the duration of stay in the PCU, the disability rate, presence of chronic diseases, drugs used, the reason for leaving the PCU, the Barthel daily living activities index, and the Norton risk assessment scale at the admission to the PCU. In addition, the presence of pressure ulcers, pressure ulcer stage, pressure ulcer scale for healing, oral care, presence of pain, pain severity, analgesic medication use, nutrition, geriatric nutritional risk index (GNRI), height, weight, and neuropsychiatric parameters (communication, behavioral symptoms, sleep) were recorded at the time of admission to the PCU and the closest date to 21.09.2020, the date of stopping data collection.

The disability rate

The public institution that implements the social security systems that Turkish citizens benefit from is called the Social Insurance Agency. Disability rates were determined by the Social Insurance Agency using the Balthazard Calculation Program (15). The Balthazard Calculation Program is used to calculate the degree of disability of people with more than one disability.

Charlson comorbidity index (CCI)

The CCI quantifies comorbidities, thus allowing to assess the impact of comorbidities on prognosis. In this study, the CCI was calculated to measure the comorbidity burden (16).

Activities of daily living

The daily living activity levels of the patients were measured with the Barthel activities of daily living index (17,18). The score of this index varies between 0-100. As the score increases, the degree of dependence of the patient decreases. In this index; 0-20 points are considered fully dependent, 21-61 points severely dependent, 62-90 points moderately dependent, 91-99 points mildly dependent, and 100 points completely independent.

Pressure ulcer

Norton risk assessment scale was used to determine the risk of pressure ulcers (19). The classification developed by the National Pressure Ulcer Advisory Panel in 2009 was used to determine the stage of the ulcers (20). In patients with more than one pressure ulcer, ulcers with the most advanced stage were recorded. Wound healing was monitored by the pressure ulcer scale for healing (21). The scale considers the area of the wound, the amount of exudate, and the GNRI tissue type. The lowest and highest possible scores are 0 and 17. A high score indicates the severity of the wound. The scale was applied once a week to monitor the evidence of wound healing.

Pain

Pain intensity was determined using the Pain Assessment in Advanced Dementia Scale, PAINAD (22,23). The patient's breathing pattern, voices produced, facial expression, body

language, and the need to be calmed are scored on this scale. The patient can get a score between 0 and 10. Scores between 1-3 are categorized as mild, between 4-6 as moderate, and between 7-10 as severe.

Nutritional risk assessment

GNRI is a scale used to determine the risk of malnutrition-related morbidity and mortality in acute, subacute, and/or long-term follow-up in hospitalized/nursing home patients (24). GNRI is calculated using the following formula: [1.89 x albumin (g/L)] + [41.7x (weight (kg)/ideal weight according to Lorent (W_{Lo})] (W_{Lo}: for males: Jeight (cm) - 100 - [(height-150)/4] and for women: height (cm) - 100- [(height-150)/2.5)]. The value calculated according to the GNRI formula is categorized in 4 degrees determining the patient's risk class. GNRI<82 is graded as a major risk, 82≤ GNRI <92 as medium risk, 92 ≤GNRI ≤98 as low risks, and GNRI >98 as no risk.

Oral care

Oral care was evaluated subjectively by the caring nurses as good, moderate, or bad. If the patient had only bad breath or mild stomatitis (painless erythema), oral hygiene was considered moderate, and if there were more problems, oral hygiene was deemed poor.

Neuropsychiatric parameters

The communication abilities of the patients were grouped as "verbal communication possible," "speech present but not meaningful-not consistent," "unable to speak but communicating with voices and gestures," and "no communication at all." Agitation, aggression, and apathy were evaluated as behavioral disorders. Parasomnia, insomnia, and hypersomnia were regarded as sleep disorders (25).

Statistics

Conformity to normal distribution was tested with the Shapiro-Wilk test. Numerical variables meeting the distribution assumption were summarized as mean ± standard deviation or otherwise as median (minimum-maximum). Categorical variables were summarized in numbers and percentages. The paired samples t-test or Wilcoxon rank-sum test was used in the comparison of two dependent groups according to the distribution assumption. The McNemar test was used to compare dependent variables with two categories. The statistical significance level p was accepted as <0.05. All analyzes were made with the Statistica 13.3.1 software (TIBCO Software Inc. CA, USA).

Results

Forty patients were admitted to the PCU within a year. Five were excluded from the study because they stayed in the PCU for less than 6 months (these patients left the institution due to death). The demographic and clinical characteristics of the 35 patients (aged between 65-95 years) included are shown in Table 1.

Of the 35 patients (31.4%) who stayed in the PCU for more than 6 months, 11 (31.4%) left the institution by death. Patients were not transferred home or to another institution. Considering that 40 patients were admitted to the PCU within a year, a total death frequency of 16 patients provided a mortality rate of 40% (16/40 patients).

At the admission to the PCU, all patients had Bartel daily living activities indexes <20 and were wholly dependent. Their mobility physical care indicators at the first and last evaluation are summarized in Table 2, while behavior and sleep disorders and communication levels are summarized in Table 3.

Table 1. Demographic and clinical characteristics of the patients (n=35)

Sex	**n (%)**
Male	14 (40)
Female	21 (60)
Age#	80.00±8.47
Social security institution disability rate#	82.49±1150
Place of stay before palliative care unit	**n (%)**
Home	8 (22.9)
Another unit of the institution	18 (51.4)
Hospital	9 (25.7)
Charlson comorbidity index*	2.0 (1.0-8.0)
Comorbid diseases	**n (%)**
Dementia	35 (100)
Parkinson's disease	3 (8.6)
Cerebrovascular accident	4 (11.4)
Cancer	1 (2.8)
Type 2 diabetes	11 (31.4)
Hypertension	14 (40.0)
Atherosclerotic heart disease	7 (20.0)
Heart failure	3 (8.6)
Chronic obstructive pulmonary disease	5 (14.3)
Chronic and/or acute renal disease	6 (17.1)
Thyroid dysfunction	4 (11.4)
Average number of drugs used#	6.09±1.884
Barthel daily living activities index#	3.14±4.382
Norton pressure scale#	9.06±2.209
Feeding route	**n (%)**
Oral + enteral nutrition	4 (11.4)
Nasogastric feeding tube	1 (2.8)
Percutaneous endoscopic gastrostomy	30 (85.7)
Mean length of stay in the palliative care unit (months) *	10.03±2.13

#These variables were summarized as mean ± standard deviation, *These variables were summarized as median (25P-75P)

Table 2. Functional parameters of the patients

Variable	First assessment	Last assessment	p
Pressure ulcer			
Presence of pressure ulcer n (%)	10 (28.6)	4 (11.4)	0.031
Pressure ulcer phase*	3.00 (2.00-3.00)	0.00 (0.00-1.25)	0.007
Scale of improvement*	10.00 (7.50-11.50)	0.00 (0.00-4.25)	0.005
Nutrition			
Weight#	54.93±11.770	57.39±10.770	<0.001
GNRI#(n=20)	90.62±10.997	100.47±7.169	<0.001
Pain			
Patient with pain n (%)	19 (54.3)	15 (42.8)	**0.469**
Pain scale*	1.00 (0.00-3.00)	0.00 (0.00-2.00)	0.014
Analgesic drug use n (%)	4 (11.4)	2 (5.7)	0.671
Oral care n (%)			
Good	18 (51.4)	29 (82.9)	0.011
Average	15 (42.9)	6 (17.1)	0.036
Bad	2 (5.7)	0 (0.0)	**0.475**
Total	35	35	-

#These variables were summarized as mean ± standard deviation, *These variables were summarized as median (25P-75P), GNRI: Geriatric nutritional risk index

Table 3. Neuropsychiatric parameters of the patients

Variable	First assessment	Last assessment	p
Behavioral symptom			
Agitation	9 (25.7)	7 (20.0)	0.777
Aggression	3 (8.6)	1 (2.8)	0.595
Apathy	0 (0.0)	0 (0.0)	-
No behavioral disorders	23 (65.7)	27 (77.2)	0.423
Total	35	35	-
Contact			
Unable to communicate at all	4 (11.4)	7 (20.0)	0.509
Communication with voice and gestures	12 (34.3)	15 (42.8)	0.627
Non-meaningful conversation	7 (20.0)	6 (17.2)	0.995
Verbal communication is established	12 (34.3)	7 (20.0)	0.282
Total	35	35	-
Sleeping disorders			
Parasomnia	4 (11.5)	4 (11.4)	0.717
Insomnia	2 (5.7)	1 (2.8)	0.993
Hypersomnia	1 (2.8)	1 (2.8)	0.469
No sleep disturbance	28 (80.0)	29 (83.0)	0.987
Total	35	35	-

Discussion

An average of 20-25% of patients followed up in PCU have dementia (26,27). However, there is no study evaluating only the PC processes of dementia patients in Turkey. In addition, most of the PCUs in Turkey serve within hospitals, and the hospitalization periods of the patients are much shorter than the PCU within the care centers. In this study, we examined the clinical characteristics of patients followed up in an institutional PCU where all patients were diagnosed with dementia and presented the unit's experience for one year. We concluded that the quality of life increased in patients receiving multidisciplinary care in the institutional PCU.

Verreault et al.'s (28) study in Canada showed that a multidimensional (staff training, pain, oral care, family communication, facilitating nurse) and interdisciplinary intervention program increased end-of-life care and quality of death in the long-term care facility and increased family satisfaction in patients with advanced dementia. The most critical parameters in evaluating institutional care in dementia patients are nutrition, sleep, struggle with behavioral disorders, preservation of patient communication and mobility, prevention of pressure ulcers, pain palliation, follow-up and treatment of chronic diseases, and approach to acute medical problems (29). In this study, evaluations were made on these parameters.

In a study by Koppitz et al. (30), the most common symptoms in the 3-months before death in dementia patients who stayed and died in a nursing home were limitations of movements (81%), pain (71%), and sleep disturbance (63%). As expected, the restriction of movements is higher in PCU. In our study, all patients had movement limitations and were entirely dependent on daily living activities. During the follow-up, only one patient (1/35, 2.8%) slipped from the bed but was not injured.

Patients staying in PCU have a very high risk in terms of pressure ulcers due to movement limitations, applied treatments, and patients' existing chronic diseases. The rate of pressure ulcers in PCU in European and North American Countries is between 58.8% and 29.9% (31). The Norton pressure scale enables the evaluation of the risk of developing pressure ulcers in patients admitted to the PCU. It is repeated at regular intervals and in case of changes in the patient's clinical condition. In our study, the Norton pressure scale was 11 in 91.4% of the patients during admission to the PCU, and these patients were at high risk for pressure ulcer development. During the stay in the PCU, no new pressure ulcers occurred in any patient. Therefore, it was concluded that pressure ulcers can be completely prevented by taking appropriate precautions, even in immobile patients. During admission to the PCU, 10 patients had pressure ulcers. Most of these patients (7/10, 70%) were coming from outside the institution. Pressure ulcer stages and pressure ulcer healing

scales of the patients were significantly reduced during the follow-up. Nutritional support is also very important in the prevention and treatment of pressure ulcers.

Nutritional problems become inevitable as dementia progresses into the terminal stage. The nutritional status, weight, and swallowing difficulties of the patient should be closely and regularly monitored. It is important for the patient with dementia to have a permanent feeding route at the most appropriate time, without the development of sarcopenia and complications such as aspiration pneumonia due to swallowing difficulty. Although it has not been shown in the literature that percutaneous endoscopic gastrostomy (PEG) tube placement in advanced stage dementia patients improves long-term survival rates, clinical observations suggest that adequate nutrition of patients with swallowing problems and aspiration risk is a comfortable method for the appropriate administration of drugs. For this reason, it has an important place in preventing malnutrition and malnutrition-related morbidity in long-term care institutions (32). In our study, the rate of patients fed through PEG is high. This is because patients who need parenteral nutrition are constantly followed up in the PCU. During admission to the PCU, it was observed that 30 patients were fed via PEG, 4 patients were fed orally, and 1 patient was fed through a nasogastric feeding tube. Since the patients who were fed orally could not meet all their protein and energy needs, these patients were given nutritional supplements with an oral-enteral nutritional product. Two patients who were fed orally over time had a regression in swallowing functions. A PEG tube was placed in one of these patients, and feeding was started through the nasogastric feeding tube in the other. None of the patients had minor or major PEG complications. In a year, only two patients pulled their PEG tubes, which were reinserted. During the follow-ups in the PCU, there was a significant increase in the weight of the patients. GNRI could be calculated in 20 patients whose albumin values were recorded (at admission and follow-up). GNRI values also decreased significantly. Oral health and oral hygiene tend to deteriorate in dementia patients due to various reasons (33). A regular oral care routine is applied in the institution. At the end of a minimum of 6 months of PC, it was observed that oral care was good in 29 (82.9%) of 35 patients and moderate in the remaining 6 (17.1%). There were no patients with bad oral care.

Pain is one of the most important factors affecting the quality of life in PC patients. Its frequency can reach up to 60% in dementia patients (34). However, patients with advanced dementia rarely express their pain spontaneously. Unexpressed pain may also be reflected in the clinic as depression and agitation. For this reason, it is most appropriate to evaluate pain in patients with advanced-stage dementia using tools such as PAINAD that use parameters such as the patient's voice, breathing style, facial expression, body language, and the need to calm down (22). In our study, according to the evaluation made with the PAINAD scale, 54.3% of the patients had pain complaints during admission to the PCU and 42.8% during follow-up. In most of the patients with pain complaints, the pain is mild. Regular physiotherapy exercises under the supervision of a physiotherapist are thought to have a role in the low pain proportions.

With the progression of dementia, an expected course is the decrease or disappearance of verbal communication (35). Not considering patients who could not communicate at the initial evaluation, the level of communication was maintained in about half of the patients during their stay in the PCU. In addition, it was observed that the communication of the two patients progressed from the level of communication with voice and gestures to the level of meaningful speech. The incidence of sleep disturbance has been found to be around 20%. A decrease in patients with behavioral symptoms was found during follow-up in the PCU. While 12 patients had behavioral symptoms in the first evaluation, 9 had behavioral symptoms in the final assessment. Although the difference was not statistically significant, it was close to the level of significance. Additionally, none of the patients developed new behavioral symptoms during the follow-up, which can be regarded as an indirect indicator that patients receive adequate care (concerning pain, infection, and nutritional management) and feel safe.

In our study, the mortality rate of patients who stayed in the PCU for at least 6 months was 31.4% (11/35). There was only one patient with chronic shortness of breath and in need of continuous oxygen support.

Study Limitations

Our study has some limitations. First, our study was conducted in a single center with a small number of patients. Therefore, it does not reflect all dementia patients undergoing PC in Turkey. Second, this is a retrospective study. Family perception could not be evaluated concerning the quality of care. Third, due to the characteristics of the patient group we studied (such as mobilization and communication limitations), patients were evaluated mostly with observational scales. Lastly, some problems frequently encountered in PCU, such as infectious diseases and delirium and factors associated with mortality were not assessed.

Conclusion

The number of patients with dementia is increasing worldwide and in Turkey. With the increase in the quality of care, the life expectancy of the chronically ill increases too. The importance of PC in patients with advanced dementia is increasingly appreciated. Our study showed that the quality of life increased in patients receiving multidisciplinary care in an institutional

PCU. Since the natural course of dementia is different from other chronic diseases, it is more appropriate to have a separate PCU for these individuals. For these reasons, there is a need to increase the number of PCUs where dementia patients are cared for. Furthermore, it is necessary to establish PC standards and guidelines for symptom management in individuals with advanced dementia.

Ethics

Ethics Committee Approval: Ethics committee approval was taken from Mersin University Ethics Committee (no: 431, date: 09/06/2021). The guardians of the patients were informed about the research.

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.C., Concept: Ö.K.C., E.T., H.E., B.G., E.Ç., A.Ö., Design: Ö.K.C., E.T., H.E., B.G., E.Ç., A.Ö., Data Collection or Processing: Ö.K.C., E.T., H.E., B.G., E.Ç., Analysis or Interpretation: Ö.K.C., D.D.Y., Literature Search: Ö.K.C., D.D.Y., A.Ö., Writing: Ö.K.C., D.D.Y., A.Ö.

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References

1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112-2117.
2. Kua EH, Ho E, Tan HH, Tsoi C, Thng C, Mahendran R. The natural history of dementia. Psychogeriatrics 2014;14:196-201.
3. Tulek Z, Baykal D, Erturk S, Bilgic B, Hanagasi H, Gurvit IH. Caregiver Burden, Quality of Life and Related Factors in Family Caregivers of Dementia Patients in Turkey. Issues Ment Health Nurs 2020;41:741-749.
4. Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther 2016;8:23.
5. Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, Volicer L, Givens JL, Hamel MB. The clinical course of advanced dementia. N Engl J Med 2009;361:1529-1538.
6. Erbas Sacar D. Association Between Dementia and Common Geriatric Syndromes. Eur J Geriatr Gerontol 2020;2:71-76.
7. Karadakovan A. Care of the Demensive Elderly. Turkiye Klinikleri J Geriatr-Special Topics 2015;1:67-71.
8. Sampson EL, Candy B, Davis S, Gola AB, Harrington J, King M, Kupeli N, Leavey G, Moore K, Nazareth I, Omar RZ, Vickerstaff V, Jones L. Living and dying with advanced dementia: A prospective cohort study of symptoms, service use and care at the end of life. Palliat Med 2018;32:668-681.
9. Stewart JT, Schultz SK. Palliative Care for Dementia. Psychiatr Clin North Am 2018;41:141-151.
10. Hanson E, Hellström A, Sandvide Å, Jackson GA, MacRae R, Waugh A, Abreu W, Tolson D. The extended palliative phase of dementia - An integrative literature review. Dementia (London) 2019;18:108-134.
11. Ellis-Smith C, Evans CJ, Bone AE, Henson LA, Dzingina M, Kane PM, Higginson IJ, Daveson BA; BuildCARE. Measures to assess commonly experienced symptoms for people with dementia in long-term care settings: a systematic review. BMC Med 2016;14:38.
12. van der Steen JT. Dying with dementia: what we know after more than a decade of research. J Alzheimers Dis 2010;22:37-55.
13. Hessler JB, Schäufele M, Hendlmeier I, Junge MN, Leonhardt S, Weber J, Bickel H. Behavioural and psychological symptoms in general hospital patients with dementia, distress for nursing staff and complications in care: results of the General Hospital Study. Epidemiol Psychiatr Sci 2018;27:278-287.
14. Erel M, Marcus EL, Dekeyser-Ganz F. Barriers to palliative care for advanced dementia: a scoping review. Ann Palliat Med 2017;6:365-379.
15. Calculation of disability in case of more than one disability. Regulation on Health Board Reports to be Given to Disabled Persons. Official Gazette dated 06.02.1998 and numbered 10746. http://www.hukuki.net/law/9810746.35.text.asp.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
17. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J 1965;14:61-65.
18. Küçükdeveci AA, Yavuzer G, Tennant A, Süldür N, Sonel B, Arasil T. Adaptation of the modified Barthel Index for use in physical medicine and rehabilitation in Turkey. Scand J Rehabil Med 2000;32:87-92.
19. Norton D, McLaren R, Exton-Smith AN. An investigation of geriatric nursing problems in hospitals. London 7 National Corporation for the Care of Old People; 1975.
20. Stausberg J, Kiefer E. Classification of pressure ulcers: a systematic literature review. Stud Health Technol Inform 2009;146:511-515.
21. Thomas DR, Rodeheaver GT, Bartolucci AA, Franz RA, Sussman C, Ferrell BA, Cuddigan J, Stotts NA, Maklebust J. Pressure ulcer scale for healing: derivation and validation of the PUSH tool. The PUSH Task Force. Adv Wound Care 1997;10:96-101.
22. Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc 2003;4:9-15.
23. Büyükturan Ö, Naharci Mİ, Büyükturan B, Kirdi N, Yetiş A. The Turkish Version of Pain Assessment in Advanced Dementia (PAINAD) Scale. Noro Psikiyatr Ars 2018;55:271-275.
24. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L, Aussel C. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005;82:777-783.
25. McCleery J, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database Syst Rev 2020;11:CD009178.
26. Harrison KL, Bull JH, Garrett SB, Bonsignore L, Bice T, Hanson LC, Ritchie CS. Community-Based Palliative Care Consultations: Comparing Dementia to Nondementia Serious Illnesses. J Palliat Med 2020;23:1021-1029.
27. Göksel F, Şenel G, Oğuz G, Özdemir T, Aksakal H, Türkkanı MH, Küçük A, Eğin ME, Gultekin M, Silbermann M. Development of palliative care services in Turkey. Eur J Cancer Care (Engl) 2020;29:e13285.
28. Verreault R, Arcand M, Misson L, Durand PJ, Kroger E, Aubin M, Savoie M, Hadjistavropoulos T, Kaasalainen S, Bédard A, Grégoire A, Carmichael PH. Quasi-experimental evaluation of a multifaceted intervention to improve quality of end-of-life care and quality of dying for patients with advanced dementia in long-term care institutions. Palliat Med 2018;32:613-621.

29. Heffels JCF, Everink IHJ, Oosterloo M, Roos RAC, Schols JMGA. Measuring the quality of care in nursing home residents with early-onset neurodegenerative diseases: a scoping review. BMC Palliat Care 2020;19:25.
30. Koppitz A, Bosshard G, Schuster DH, Hediger H, Imhof L. Type and course of symptoms demonstrated in the terminal and dying phases by people with dementia in nursing homes. Z Gerontol Geriatr 2015;48:176-183.
31. Demarré L, Van Lancker A, Van Hecke A, Verhaeghe S, Grypdonck M, Lemey J, Annemans L, Beeckman D. The cost of prevention and treatment of pressure ulcers: A systematic review. Int J Nurs Stud 2015;52:1754-1774.
32. Kurien M, Williams J, Sanders DS. Malnutrition in healthcare settings and the role of gastrostomy feeding. Proc Nutr Soc 2017;76:352-360.
33. Delwel S, Binnekade TT, Perez RSGM, Hertogh CMPM, Scherder EJA, Lobbezoo F. Oral hygiene and oral health in older people with dementia: a comprehensive review with focus on oral soft tissues. Clin Oral Investig 2018;22:93-108.
34. Moens K, Higginson IJ, Harding R; EURO IMPACT. Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. J Pain Symptom Manage 2014;48:660-677.
35. Eisenmann Y, Golla H, Schmidt H, Voltz R, Perrar KM. Palliative Care in Advanced Dementia. Front Psychiatry 2020;11:699.

ORIGINAL RESEARCH

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Attention to Osteosarcopenia in Older People! It May Cause Cognitive Impairment, Frailty, and Mortality: A Cross-sectional Study

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Abstract

Objective: Osteosarcopenia is a relatively new defined syndrome in older people, elucidated as the coexistence of osteoporosis and sarcopenia. As this syndrome is newly defined, the interaction between physical dependence, frailty and mortality in older adults is not clear. To determine whether osteosarcopenia (OSP) has a greater effect on daily living activities, frailty, mortality, comorbidities than osteoporosis (OP) and sarcopenia (SP) alone.

Materials and Methods: The study included patients aged 65 and over who underwent bone mineral densitometry (BMD) and bioelectrical impedance tests. According to World Health Organization criteria, the osteoporosis group was included as BMD femoral neck T-score of -2.5 and below. The diagnosis of sarcopenia was done according to the criteria of the, "European Working Group on Sarcopenia of Older People 2018". Mortality detection was performed using the ''TC Turkey Ministry of Health Public Health Agency of Death Reporting System''. Comprehensive geriatric assessment, comorbidities and clinical frailty scores of the patients were recorded.

Results: The mean age of 306 patients (199 women, 65%) was 76.93±7.03. The prevalence of each category (non-sarcopenic non-osteoporotic, OP, SP and OSP) was 40.8%, 17.0%, 19.0% and 23.2%, respectively. Katz, Lawton-Brody, mini-mental state exam and mini nutritional assessment scores were significantly lower in the OSP group (p=0.014; 0.005; <0.001; <0.001, respectively). The clinical frailty score was highest in OSP, consistent with frailty (p=0.001). Seventy-three (23.8%) of 306 patients died. Mortality was highest in OSP (37%, p=0.014). In the logistic analysis, presence of type 2 diabetes mellitus increased the risk of osteosarcopenia (β: 2.701, p=0.004).

Conclusion: Osteosarcopenia maybe associated with physical and cognitive dependence, frailty and mortality in older people. Osteoporosis and sarcopenia should be screened together and preventive measures should be taken before they become serious.

Keywords: Osteosarcopenia, frailty, comprehensive geriatric assesment, mortality, cognitive impairment

Introduction

The world is aging and the prevalence of chronic diseases, including osteoporosis and sarcopenia, is increasing in older adults. Recognition and treatment of geriatric syndromes and chronic diseases, which are the most common causes of morbidity and mortality in older adults, will enable them to complete their life in a healthy way. In 2009, Binkley and Buehring (1) described a new geriatric syndrome in the elderly. They named this subgroup as sarco-osteoporosis. This new syndrome eventually became known as osteosarcopenia (OSP) (2,3). The pathophysiology of OSP and the understanding of coexisting disease groups will be useful for fall and fracture prevention strategies at the beginning of the most important problems for older adults (4). Some studies have confirmed that

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sarcopenia and osteoporosis (OSP) share common risk factors and that biological pathways and OSP are associated with significant physical disability, which poses an important threat to loss of independence in later life (4).

OSP is the combination of two conditions that affect the quality of life of older people. Patients with OSP have greater risk of dependence, falls, prevalence of fractures and death (5-7). In order to provide comprehensive care for older adults, especially musculoskeletal health, clinicians should also consider OSP. This topic has been the focus of interest in many studies due to its relatively new definition compared to other geriatric syndromes and due to its importance (8-10). It should not be ignored that the combination of these two conditions may cause dependency in daily basic and instrumental life activities and should be screened.

Our aim in this study was to determine whether OSP interacts with daily living activities, frailty, mortality, comorbidities and laboratory values.

Materials and Methods

Study participants

This cross-sectional study included patients aged 65 and over who underwent bone mineral densitometry (BMD) and bioelectrical impedance (BIA) tests between 2013 and 2019. Demographic data (age, sex, comorbidities), comprehensive geriatric assesment results and laboratory values were recorded in their hospital files. Patients whose data were incomplete in the file (those who were not suitable for BIA, BMD images were not transferred to the system, laboratory values were missing, comprehensive geriatric assesment tests could not be performed or were missing) were not included in the study. Mortality detection was performed using the "TC Turkey Ministry of Health Public Health Agency of Death Reporting System" (11). Mortality screenings of the patients were performed within 1 year after their measurements. Mortality status was compared on a case-by-case basis as a percentage. Patients were divided into 4 groups according to BIA and BMD data; group 1: Non-osteoporotic, non-sarcopenicgroup; group 2: Osteoporotic group (BMD value-2.5 and below); group 3: Sarcopenic group [sarcopenia was diagnosed according to the definition of the European Working Group on Sarcopenia of Older People 2018 (EWGSOP)]; group 4: Osteosarcopenic (OSP) group (taken as a coexistence of osteoporosis and sarcopenia status).

Bone mineral density and sarcopenia measurement

Bone mineral density was measured using DXA (HologicExplorer S/N 90704). According to World Health Organization (WHO) criteria, the osteoporosis group was included as BMD femoral neck T-score of -2.5 and below (12). The diagnosis of sarcopenia was done according to the criteria of the, "European Working Group on Sarcopenia of Older People 2018" (13). For muscle mass measurement, BIA; for muscle strength measurement, handgrip strength; for physical performance evaluation, gait speed measurement (m/sn) were used. BIA was performed with a portable BIA analyzer in supine position. Quadscan 4000 (Bodystat, Douglas, Isle of Man, UK) was used to obtain the BIA resistance in ohms (Ω). The device was set for the participant's age, gender, height and body weight. Skeletal muscle mass (SMM) was calculated according to the formula suggested by Janssen et al. (14). Low muscle mass was calculated according to the values indicated in studies on Turkish populations. In this study, values less than 9.2 kg/m^2 in men and 7.4 kg/m^2 in women were taken as low muscle mass (15).

The diagnosis of sarcopenia was made according to the revised European consensus on the definition and diagnosis "EWGSOP-2" (13). Three components are used in diagnosis:

1- Muscle strength: Muscle strength was measured with the hand grip test in our study, as mentioned in the comprehensive geriatric assessment section above. Local cut-off values were used as recommended by EWGSOP-2 (grip strengths of <22 kg for females and <32 kg for males).

2- Muscle quantity: Skeletal muscle mass was evaluated by BIA. The measurement was carried out in the supine position in the morning before breakfast after all of the participant's metal items were removed. Four electrodes of the device were fixed to the right foot and right hand of the individual, two for each, with the adhesive tape of the device itself in accordance with the measurement protocol. After entering the individual's age, gender, height, and body weight into the device, the measurement was made at a frequency of 50 kHz. Resistance value in ohms, which is one of the data items obtained from the analysis, was used to calculate skeletal muscle mass. The resistance value measured during the analysis was used in the following formula to calculate skeletal muscle mass, as proposed by Janssen et al. (14): [(height^2/resistance value in BIA measurement x 0.401) + (gender x 3.825) + (age x -0.071)]+5.102 (height in meters, resistance in ohms, for gender part 1 for male and 0 for female). The value obtained by this formula was divided by the square meter of the participant's height to obtain absolute skeletal muscle mass. An absolute skeletal muscle mass value of <7.4 kg/m^2 in females and <9.2 kg/m^2 in males corresponds to reduced skeletal muscle mass (15).

3- Physical performance: Gait speed was used in this study (≤0.8 m/s for men and women).

Those with low muscle strength were defined as probable sarcopenia. If low muscle strength was supported by the measurement (low skeletal muscle mass), the diagnosis of confirmed sarcopenia was made. If low physical performance was added to these, severe sarcopenia was diagnosed.

Definition of frailty

In the assessment of frailty, clinical frailty scores were used. In this scoring, high values are associated with frailty (16). There are nine categories: 1: Very fit- robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age. 2: Fit- without active disease, but less fit than people in category 1. 3: Well, with treated comorbid disease- disease symptoms are well controlled compared with those in category 4. 4: Apparently vulnerable- although not frankly dependent, these people commonly complain of being ''slowed up'' or having disease symptoms. 5: Mildly frail- with limited dependence on others for instrumental activities of daily living. 6: Moderately frail- help is needed with both instrumental and non-instrumental activities of daily living. 7: Severely frail- completely dependent on others for activities of daily living, but not at high risk of dying within 6 months. 8: Very severely frail- completely dependent on others for activities of daily living and approaching end of life. 9: Terminally ill- approaching end of life with life expectancy <6 months. The ADL and IADL methods used in this scale were used as described above.

Laboratory values

As laboratory values (unit-normal range): Fasting blood glucose (mg/dL 74-100), calculated glomerular filtration rate (mL/min/1.73 m^2>60), calcium (mg/dL 8.8-10.6), total protein (g)/L 66-83), albumin (g/L 35-52), leukocyte (white blood cell) (x10^9/L 4.5-11), hemoglobin (g/dL 11.7-16.1), vitamin B12 (pg/mL 126.5-505), thyroid-stimulating hormone (µIU/mL 0.38-5.33), C-reactive protein (CRP) (mg/L 0.0-5.0), 25-hydroxy vitamin D (µg/L 10-60) were recorded. Biochemical parameters were studied using spectrophotometric, CRP turbidimetric, hormonal tests using ECLIA method, and vitamin D levels using HPLC method in Ankara University İbn-i Sina Hospital Laboratories.

Comprehensive geriatric assessment

Comprehensive geriatric assessment tests included the Katz activities of daily living index (ADL), Lawton instrumental activities of daily living scale (IADL), mini-mental status examination (MMSE), geriatric depression scale (short form of 15 questions) and mini-nutritional assessment-short form (MNA-SF). Daily life activities were evaluated with Katz ADL. This index evaluates the functions of dressing, bathing, going to the toilet, getting out of bed, eating and continence, over 6 points (17). Instrumental daily living activities were evaluated using the Lawton IADL. In this scale, activities such as telephone use, shopping, food preparation, household chores, laundry, urban transportation and proper use of drugs are evaluated over eight points (18,19). Cognitive functions were investigated by MMSE. Low scores on this test, which is evaluated over 30 points, indicate impairment in cognitive functions (20,21). The 15-item short form of geriatric depression was used (22). Nutritional status was investigated by MNA-SF. This test has validity and reliability in Turkey: Malnutrition between 0-7 points, malnutrition risk between 8-11 points and normal nutrition between 12-14 points (23,24). Hand grip strength measured by an electronic hand dynamometer (GRIP-D, influenza strength dynamometer, produced by Takei, made in Japan). The unit of results is kilograms. <22 kg for women and <32 kg for men were evaluated in favor of reduced muscle strength (15). Muscle performance was assessed by gait speed measured on a 4-meter course. After walking time was measured with an electronic stopwatch, the walking speed was calculated with the formula 4 meter/walking time (seconds) in m/s. The walking speed was evaluated in favor of decreased muscle performance as ≤0.8 m/sec (15).

Statistics

Statistical analyses were performed using ''Statistical Package for Social Sciences (SPSS) for Windows 24 (IBM SPSS Inc, Chicago, IL)''. The suitability of variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were performed using mean and standard deviation for normally distributed variables, and median and maximum-minimum values for non-normally distributed variables. The frequency of categorical variables was expressed as (%). Chi-square and ANOVA tests were used for evaluation between groups in Table 1. Bonferroni post hoc tests were performed. Logistic regression was performed to determine associations [odds ratio (OR) and 95% confidence interval] between osteoporosis, sarcopenia and OSP, while adjusting for potential confounders including age and sex.

Results

The mean age of the 306 patients included in the study was 76.93±7.03 years. 199 (65%) were female. The prevalence of each category (non-sarcopenic non-osteoporotic, osteoporosis only, sarcopenia only and OSP) was 40.8%, 17.0%, 19.0% and 23.2%, respectively. Probable sarcopenia was 3.92% (n=12), confirmed sarcopenia was 10.45% (n=32) and severe sarcopenia was 4.57% (n=14). In the comparison between groups, the mean age of the OSP group was significantly higher than the other groups (79.41±7.21, p<0.001). Katz ADL, Lawton-Brody IADL, MMSE score, MNA-SF scores were significantly lower in the OSP group (p-values were 0.014; 0.005; <0.001; <0.001, respectively). Interactions between groups are specified in Table 1. Handgrip strength (kg) was significantly lower in the OSP group (p<0.001). Clinical frailty scores were found to be the highest in the OSP group (p=0.001). When the mortality of the patients were examined, 73 (23.8%) of 306 patients died. Mortality rate was significantly higher in the OSP group

Table 1. Comparison of patient comorbidities, comprehensive geriatric assessment tests and laboratory tests

	Non-sarcopenic non-osteoporotic n (%)	OP n (%)	SP n (%)	OSP n (%)	All	p*
n (%)	125 (40.8)	52 (17.0)	58 (19.0)	71 (23.2)	306	
Age	75.10±7.07[d]	76.96±6.81	77.67±5.80	79.41±7.21[a]	76.9±7.27	<0.001
Comorbidities						
Hypertension	96 (44.7)[d]	38 (17.7)	40 (18.6)	41 (19.1)[a]	215	0.430
Diabetes mellitus	53 (47.3)[d]	20 (17.9)	25 (22.3)[d]	14 (12.5)[ac]	112	0.008
Congestive heart failure	18 (31)[b]	17 (29.3)[a]	10 (17.2)	13 (22.4)	58	0.042
Cancer	8 (26.7)	5 (16.7)	8 (26.7)	9 (30)	30	0.253
Dementia	11 (28.2)	5 (12.8)	9 (23.1)	14 (35.9)	39	0.127
Cerebrovascular event	9 (27.3)	9 (27.3)	7 (21.2)	8 (24.2)	33	0.126
Hypothyroidism	25 (38.5)	14 (21.5)	14 (21.5)	12 (18.5)	65	0.243
Depression	22 (28.9)[c]	15 (19.7)	23 (30.3)[a]	16 (21.1)	76	0.007
CGA						
Katz ADL	5.34±1.48[d]	4.77±2.03	4.90±2.05	4.49±2.02[a]	4.96±1.85	**0.014**
LB-IADL	6.58±2.16[d]	5.77±2.79	6.02±2.71	5.21±3.07[a]	6.02±2.65	**0.005**
MMSE	23.5±5.35[bd]	21.40±6.45	22.31±6.74[d]	18.93±8.40[ac]	21.82±6.98	**<0.001**
MNA-SF	12.13±1.66[d]	11.87±1.63[d]	11.56±2.2[d]	10.29±3.19[abc]	11.5±2.31	**<0.001**
GDS	3.92±3.85	5.90±7.41	6.04±2.85	4.07±3.57	4.67±3.21	0.163
4 m walking speed (m/sn)	0.6±0.26	0.47±0.27	0.70±0.38	0.51±0.40	0.58±0.51	0.114
Handgrip strength (kg)	20.77±7.9[d]	17.9±18.17[d]	17.61±7.16[d]	13.6±6.46[abc]	18.05±8.03	**<0.001**
Clinical frailty score	4.04±1.54[cd]	4.57±1.58	4.74±1.43[a]	4.90±1.50[a]	4.46±1.55	**0.001**
Mortality	23 (31.5)[d]	12 (16.5)	11 (15.1)	27 (37.0)[a]	73	**0.014**
Laboratory values						
Fasting blood glucose (mg/dL)	105.12 (57-345)[d]	96.50 (79-200)	97.34 (69-197)	96.12 (77-196)[a]	98.56 (51-442)	**0.013**
Calculated glomerular filtration rate (mL/min/1.73 m²)	75 (21-90)[d]	76 (25-90)[d]	69 (22-89)	67 (52-90)[ab]	70.5 (60-134)	**<0.001**
Calcium (mg/dL)	9.7 (8.90-10.6)	9.6 (9.10-10.30)	9.6 (8.30-10.9)	9.80 (8.90-11.70)	9.5 (8.2-11.7)	0.097
Total protein (g)/L	7.40 (6.30-8.20)	7.30 (6.40-8.10)	6.91 (5.56-7.84)	7.32 (6.40-8.10)	7.15 (5.2-8.2)	0.672
Albumin (g/L)	4.20 (3.40-4.80)	4.20 (3.60-4.60)	4.10 (2.50-4.80)	4.09 (2.90-4.90)	4.00 (1.80-4.90)	0.774
Leukocyte (WBC) (x10⁹/L)	7.03 (2.63-12.75)	7.09 (3.76-9.69)	6.54 (3.66-11.77)	6.16 (4.14-12.47)	6.77 (2.66-35.77)	0.060
Hemoglobin (Hb) (g/dL)	13.7 (9.10-17.20)	13.55 (7.00-16.60)	13.90 (9.30-15.10)	12.9 (11.00-16.50)	12.60 (7.00-17.70)	0.129
Vitamin B12 (pg/mL)	298 (77-1500)	343 (169-648)	501 (102-1500)	395 (50-1500)	332 (50-1500)	0.132
TSH (µIU/mL)	1.70 (0.02-6.57)	1.52 (0.55-30.59)	2.06 (0.60-1.62)	1.15 (0.02-6.76)	1.48 (0.01-40.72)	0.461
CRP (mg/L)	3.67 (0.20-17.60)	2.70 (0.90-16.60)	4.90 (0.10-79.30)	2.20 (0.10-77.30)	4.80 (0.10-147.12)	0.998
25-hydroxy vitamin D (µg/L)	19.1 (5.7-65.2)	21.6 (5.2-33.3)	19.9 (4.9-47.4)	21.4 (5.3-51.4)	18.2 (4.50-75.2)	0.562

Bold values are p<0.05 and are statistically significant. -value *: Comparison between groups; p-value, [abcd]: Intragroup post hoc value (Bonferroni post hoc tests) [a]: Significant difference to non-sarcopenic non-osteoporotic, [b]: Significant difference to OP, [c]: Significant difference to SP, [d]: Significant difference to OSP, OP: Only osteoporosis group, SP: Only sarcopenic group, OSP: Osteosarcopenic group, CGA: Comprehensive geriatric assesment, Katz ADL: Katz index of activities of daily living, LB-IADL: Lawton-Brody instrumental activities of daily living scale, MMSE: Mini-mental state exam, MNA-SF: Mini-nutritional assessment-short-form, GDS: Geriatric depression scale, CRP: C-reactive protein, WBC: White blood cell

(37%, p=0.014). The comparison of patient comorbidities, comprehensive geriatric assessment tests and laboratory tests are summarized in Table 1.

Logistic regression analysis was performed to determine the factors that may affect osteoporosis, sarcopenia and OSP. Factors that were significant in Table 1 between groups were analyzed further. Adjusted for age and gender, it was determined that diabetes mellitus increases the risk of osteoporosis and OSP. It was observed that the presence of type 2 diabetes mellitus (T2DM) increased the risk of OSP by 2.7 times. No such relationship was found for sarcopenia. Variables that were significant in the previous comparison and were previously known to contribute to the formation of sarcopenia, obesity, and sarcopenic obesity were included in the multiple analysis in the logistic regression analysis. Each group was studied separately to determine the variable that could increase the risk in all three groups. In the osteoporosis and OSP group, diabetes mellitus was found to be a risk-increasing factor. These findings are summarized in Table 2.

Discussion

In our study, OSP patients (prevalence was 23.2%) showed a significant reduction in Katz (ADL), Lawton-Brody (IADL), MMSE and MNA scores for components of comprehensive geriatric assesment. Furthermore, the Clinical Frailty Score was higher in the OSP group, indicating a high frailty rate. Supported by all these scores, the OSP group was at greater risk of physical and cognitive dependence in daily functions than the osteoporotic and sarcopenic groups alone. In addition, the mortality rate was significantly higher in the OSP group compared to the only osteoporosis (OP) and only sarcopenic (SP) groups. Adjusted for age and gender, it was determined that diabetes mellitus increases the risk of osteoporosis and OSP.

Table 2. Logistic regression shows the odds ratio for osteoporosis, sarcopenia and osteosarcopenia

Odds ratio for osteoporosis			
	Odds ratio	**(95% CI)**	**p**
Age	1.047	(1.011-1.084)	**0.001***
Sex (female)	0.826	(0.492-1.388)	0.471
Diabetes mellitus	1.785	(1.071-2.974)	**0.025***
Congestive heart failure	1.564	(0.835-2.931)	0.162
Depression	0.958	(0.544-1.685)	0.881
Odds ratio for sarcopenia			
	Odds ratio	**(95%)**	**p**
Age	1.066	(1.029-1.105)	**<0.001***
Sex (female)	0.537	(0.315-0.916)	**0.022***
Diabetes mellitus	0.618	(0.369-1.034)	0.067
Congestive heart failure	0.709	(0.366-1.374)	0.059
Depression	1.668	(0.951-2.926)	0.074
Odds ratio for osteosarcopenia			
	Odds ratio	**(95%)**	**p**
Age	1.078	(1.033-1.124)	**0.001***
Sex (female)	2.235	(1.140-4.383)	**0.019***
Diabetes mellitus	2.701	(1.366-5.344)	**0.004***
Congestive heart failure	1.308	(0.590-2.878)	0.059
Depression	1.245	(0.628-2.471)	0.530

Bold values indicate signifcant p-value, CI: Confidence interval

The prevalence of OSP in our study was similar to that of other studies (5,25-28). The mean age was significantly higher in the OSP group. There are many reasons for OSP, OP and SP formation. However, as emphasized in previous studies (5,29), the higher mean age in the OSP group suggests that there may be a chronological relationship. When the nutritional status of patients was examined, in many studies poor nutritional status was associated with low MNA score and BMI (5,28). In our study, the MNA score was found to be low in the OSP group.

Many of the previous studies have been specifically focused on physical performance (27,30). Drey et al. (26) showed that some parameters, especially indicative of muscle strength (such as hand grip strength and chair rise time), decreased in the OSP group and they found that balance and coordination tests (such as walking speed) did not affect the OSP group (27). Similarly, Yoshimura et al. (31) reported that hand grip strength and walking speed used in the diagnosis of frailty and sarcopenia was not a risk factor for osteoporosis. In another study, it was found that physical performance and balance were more impaired in those with OSP compared to the non-OSP group (32). In our study, hand grip strength was significantly different between the groups. Although the 4 m walking test was one of the criterias for sarcopenia, it was not statistically significant between the groups. Further studies of coordination, balance and power [and as Yoshimura et al. (31) stated, with many years of follow-up] can give us more insight into this issue.

When muscles and bones are involved, physical performance and risk of fracture come to mind. Cognitive functions and OSP have not been widely studied in literature. However, there are studies showing that muscle and bone health affect cognitive health (33,34). It is difficult to involve dementia patients with very low cognition in studies related to this type of force and to perform tests. However, involving patients who are able to perform the tests, who do not have dementia or who are under follow-up, will make the studies more valuable. There are studies examining the relationship between sarcopenia and cognition. They have shown that low physical performance can lead to low mental performance (35). In our study, MMSE scores of the OSP group were lower than the other groups. However, there was no difference between the groups in terms of dementia rates. In other words, the decrease in MMSE scores were significant but the dementia rate was not. In a study of OSP obesity, cognitive

decline of patients was examined and no significant relationship was found between the two groups (36). It is an expected and demonstrated condition that the physical performance of patients with cognitive decline (but not dementia) is affected. There are studies showing that cognitive status is affected in both osteoporosis and in sarcopenia and with treatments (33,35,37,38). The main hypothesis of these studies summarizes that "Interventions to prevent sarcopenia and osteoporosis and increase bone-muscle strength can also help the cognitive dimension of functionality in the elderly community". Specific prospective studies will be valuable for OSP cases.

When we look at the relationship between comorbidities of patients and OSP, interestingly, in our study the percentage of chronic diseases such as HT, T2DM and CHF was higher in the non-sarcopenic non-osteoporotic group. When a similar study was examined, especially gout, osteoarthritis and other inflammatory diseases were found to be risk factors for OSP (5). One of the main reasons for this may be that people with a chronic illness come for periodic exams because of their illness. Thus, they enter screening programs for osteoporosis and malnutrition and can be diagnosed and treated before their disease progresses.

In the logistic analysis performed in our study, it was found that the presence of T2DM increases the risk of OSP. Even though incidences of chronic diseases such as T2DM and HT was higher in the non-sarcopenic non-osteoporotic group, it was found that the risk of OSP increased 2.7 times in those with T2DM in logistic regression. Diabetes mellius is considered among the secondary causes of OSP (39,40). T2DM is characterized by insulin resistance, inflammation, advanced glycation end product accumulation and increased oxidative stress. These properties can negatively affect various aspects of muscle health, including muscle mass, strength, quality, and function, by leading to disruptions in protein metabolism, vascular and mitochondrial dysfunction, and cell death (40). In the analysis in our study, while risk increased in the osteoporosis and OSP groups, the high OR in the OSP group draws attention.

In this study, glucose and GFR values were significantly lower in the OSP group. In many studies on OSP, GFR related to muscle structure was found to be low, as expected. Glucose may be related to the nutritional status of the patients. Considering that the percentage of T2DM was low in the OSP group, it would not be meaningful to evaluate this result as a treatment complication. It may be reasonable to detect low glucose levels in this group with poor nutrition and low MNA score. Contrary to expectations, the ratio of albumin and total protein used as other nutrient markers, did not differ between the groups. In our study, the vitamin D level, which is implicated in the pathophysiology of sarcopenia and osteoporosis, was found to be insignificant. In some studies in literature, low vitamin D was found to be associated with OSP. In other studies, (as in our study) no relationship was found between them. This heterogeneity was indicated in a review and larger studies have been recommended (41).

In a study of 1.083 patients followed for 4 years to investigate the relationship between OSP and frailty, it was found that OSP caused more frailty than OP alone or SP alone (31). In another study, OSP obesity and frailty were examined and a significant correlation was found with all three tests [frailty phenotype (Fried criteria), gerontopole frailty screening tool and the FRAIL scale]. The weaknesses of this study were that it included people younger than 65 years old and it was done with just women. In another study conducted in our country, the frailty score determined by Fried criteria was found to be high in the OSP group (42). Another study provided information about the relationship between individual OS, SP and OSP groups and frailty. The presence of OS and OSP increased the risk of frailty, but was not associated with SP. They reported that OSP had more frailty than OS and SP alone (31). In our study, the mean clinical frailty score was found to be high in the OSP group, consistent with frailty.

OSP is a condition that increases the morbidity affecting elderly people. Mortality was found to be correlated with OSP, as expected. In the study performed by Balogun et al. (6) 10-year mortality was found to be higher in the OSP group compared to the SP group alone and the OP group alone. The lower mortality rates of the alone groups indicate that the combination of these conditions increases mortality. In a study of 314 patients with hip fractures, 1-year mortality was found to be 15.1%. This was higher than the individual OP and SP groups (7). In another study, poor musculoskeletal health was found to increase the risk of death regardless of age (43). In another study conducted with a good number of patient populations, when all three groups were compared, similar to our study, after a Cox regression analysis, OSP individuals had a 2.48-fold risk of death. Also in this study, falls, fractures, and functional impairments were found more frequently in OSP patients. In our study, patient mortality was determined retrospectively and 37% of the patients in the OSP group died. This rate was higher than the other groups. In this study, causes of death were not considered as subgroups.

Treatment of OSP is as important as its screening and definition. Studies have found that adequate amounts of protein (1.2-1.5 g/kg/day), vitamin D (800 IU/day) and calcium (1.000-1.200 mg/day) supplements can be tolerated. It has been shown that some components such as lean mass, bone density and fracture risk can be alleviated with these supports (4).

Study Limitations

There are limitations to our study. First, this was a retrospective cross-sectional study that did not allow the establishment of

chronological or causal relationships leading to OSP. Second, a score such as the more commonly used Fried score could have been used instead of the clinical frailty score used to define frailty. In further studies, it may be planned to use more objective methods with frailty score and mortality status as sub-groups.

Strengths of our study: This study presents data from a geriatric clinic that gives the clinician insight into the prevalence, degree of overlap and the geriatric functions affected by the two major pathologies of the locomotor and skeletal system. It is a study that gives information about OSP in our country from the whole geriatric society. It is also the first data in our country with both frailty and mortality related to OSP. In our study, the diagnosis of sarcopenia was done by BIA and according to revised EWOGS2 criteria. Osteoporosis was diagnosed using femoral neck or total in accordance with WHO standards.

Conclusion

In our study we showed that OSP, which is the most serious and last stage of bone and muscle loss combination, is closely related to physical and cognitive dependence, frailty and death, which are the most feared conditions in older adults. Osteoporosis and sarcopenia should be screened together, preventive measures should be taken before they become serious, and treatments such as osteoporosis treatment, exercise and nutrition therapy should be given and followed.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of Ankara University Faculty of Medicine with document number: 10-806-19.

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S.Ö., R.B., T.T., D.M.S., Ç.C., V.A., A.Y., Concept: S.A., M.V., Design: S.A., M.V., Data Collection or Processing: H.S.Ö., R.B., T.T., D.M.S., Ç.C., V.A., A.Y., Analysis or Interpretation: H.S.Ö., R.B., S.A., Literature Search: H.S.Ö., D.M.S., Ç.C., V.A., A.Y., Writing: H.S.Ö., M.V.

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References

1. Binkley N, Buehring B. Beyond FRAX: it's time to consider "sarco-osteopenia". J Clin Densitom 2009;12:413-416.
2. Kirk B, Miller S, Zanker J, Duque G. A clinical guide to the pathophysiology, diagnosis and treatment of osteosarcopenia. Maturitas 2020;140:27-33.
3. Fagundes Belchior G, Kirk B, Pereira da Silva EA, Duque G. Osteosarcopenia: beyond age-related muscle and bone loss. Eur Geriatr Med 2020;11:715-724.
4. Zanker J, Duque G. Osteosarcopenia: the Path Beyond Controversy. Curr Osteoporos Rep 2020;18:81-84.
5. Huo YR, Suriyaarachchi P, Gomez F, Curcio CL, Boersma D, Muir SW, Montero-Odasso M, Gunawardene P, Demontiero O, Duque G. Phenotype of osteosarcopenia in older individuals with a history of falling. J Am Med Dir Assoc 2015;16:290-295.
6. Balogun S, Winzenberg T, Wills K, Scott D, Callisaya M, Cicuttini F, Jones G, Aitken D. Prospective associations of osteosarcopenia and osteodynapenia with incident fracture and mortality over 10 years in community-dwelling older adults. Arch Gerontol Geriatr 2019;82:67-73.
7. Yoo JI, Kim H, Ha YC, Kwon HB, Koo KH. Osteosarcopenia in Patients with Hip Fracture Is Related with High Mortality. J Korean Med Sci 2018;33:e27.
8. Hassan EB, Duque G. Osteosarcopenia: A new geriatric syndrome. Aust Fam Physician 2017;46:849-853.
9. Crepaldi G, Maggi S. Sarcopenia and osteoporosis: A hazardous duet. J Endocrinol Invest 2005;28(10 Suppl):66-68.
10. Hirschfeld HP, Kinsella R, Duque G. Osteosarcopenia: where bone, muscle, and fat collide. Osteoporos Int 2017;28:2781-2790.
11. https://obs.saglik.gov.tr.
12. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929-1936.
13. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
14. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985) 2000;89:465-471.
15. Bahat G, Tufan A, Tufan F, Kilic C, Akpinar TS, Kose M, Erten N, Karan MA, Cruz-Jentoft AJ. Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. Clin Nutr 2016;35:1557-1563.
16. Özsürekci C, Balcı C, Kızılarslanoğlu MC, Çalışkan H, Tuna Doğrul R, Ayçiçek GŞ, Sümer F, Karabulut E, Yavuz BB, Cankurtaran M, Halil MG. An important problem in an aging country: identifying the frailty via 9 Point Clinical Frailty Scale. Acta Clin Belg 2020;75:200-204.
17. Arik G, Varan HD, Yavuz BB, Karabulut E, Kara O, Kilic MK, Kizilarslanoglu MC, Sumer F, Kuyumcu ME, Yesil Y, Halil M, Cankurtaran M. Validation of Katz index of independence in activities of daily living in Turkish older adults. Arch Gerontol Geriatr 2015;61:344-350.
18. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-86.
19. Isik EI, Yilmaz S, Uysal I, Basar S. Adaptation of the Lawton Instrumental Activities of Daily Living Scale to Turkish: Validity and Reliability Study. Ann Geriatr Med Res 2020;24:35-40.
20. Thal LJ, Grundman M, Golden R. Alzheimer's disease: a correlational analysis of the Blessed Information-Memory-Concentration Test and the Mini-Mental State Exam. Neurology 1986;36:262-264.
21. Babacan-Yıldız G, Ur-Özçelik E, Kolukısa M, Işık AT, Gürsoy E, Kocaman G, et al. Eğitimsizler İçin Modifiye Edilen Mini Mental Testin (MMSE-E) Türk Toplumunda Alzheimer Hastalığı Tanısında Geçerlik ve Güvenilirlik Çalışması. 2015.
22. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983;17:37-49.

23. Guigoz Y, Vellas B. The Mini Nutritional Assessment (MNA) for grading the nutritional state of elderly patients: presentation of the MNA, history and validation. Nestle Nutr Workshop Ser Clin Perform Programme 1999;1:3-11; discussion 11-2.

24. Sarikaya D, Halil M, Kuyumcu ME, Kilic MK, Yesil Y, Kara O, Ozturk S, Gungor E, Karabulut E, Balam Yavuz B, Cankurtaran M, Ariogul S. Mini nutritional assessment test long and short form are valid screening tools in Turkish older adults. Arch Gerontol Geriatr 2015;61:56-60.

25. Wang JH, Joslin J, Jenkins R, Sharpe CC, Jayawardene S, Shah S. Outcomes of elderly patients with acute kidney injury on a renal high dependency unit. Int J Clin Pract 2015;69:1209-1210.

26. Drey M, Sieber CC, Bertsch T, Bauer JM, Schmidmaier R; FiAT intervention group. Osteosarcopenia is more than sarcopenia and osteopenia alone. Aging Clin Exp Res 2016;28:895-899.

27. Kobayashi K, Imagama S, Ando K, Machino M, Ota K, Tanaka S, Morozumi M, Kanbara S, Ito S, Ishiguro N, Hasegawa Y. Epidemiology and effect on physical function of osteosarcopenia in community-dwelling elderly people in Japan. Mod Rheumatol 2020;30:592-597.

28. Reiss J, Iglseder B, Alzner R, Mayr-Pirker B, Pirich C, Kässmann H, Kreutzer M, Dovjak P, Reiter R. Sarcopenia and osteoporosis are interrelated in geriatric inpatients. Z Gerontol Geriatr 2019;52:688-693.

29. Lima RM, de Oliveira RJ, Raposo R, Neri SGR, Gadelha AB. Stages of sarcopenia, bone mineral density, and the prevalence of osteoporosis in older women. Arch Osteoporos 2019;14:38.

30. Frisoli A, Chaves P, Inghan S, Carvalho A. Osteosarcopenia Has Stronger Association With Impaired Physical Function Than Sarcopenia Only. Innovation in Aging. 2018;2(Suppl 1):304.

31. Yoshimura N, Muraki S, Oka H, Iidaka T, Kodama R, Horii C, Kawaguchi H, Nakamura K, Akune T, Tanaka S. Do sarcopenia and/or osteoporosis increase the risk of frailty? A 4-year observation of the second and third ROAD study surveys. Osteoporos Int 2018;29:2181-2190.

32. Sepúlveda-Loyola W, Phu S, Bani Hassan E, Brennan-Olsen SL, Zanker J, Vogrin S, Conzade R, Kirk B, Al Saedi A, Probst V, Duque G. The Joint Occurrence of Osteoporosis and Sarcopenia (Osteosarcopenia): Definitions and Characteristics. Journal of the American Medical Directors Association 2020;21:220-225.

33. Daly R, Duque G. Improving Muscle, Mind And Mobility Through Exercise And Nutrition In Old Age. Innovation in Aging 2017;1(Suppl 1):1308-1309.

34. Peng W, Li Z, Guan Y, Wang D, Huang S. A study of cognitive functions in female elderly patients with osteoporosis: a multi-center cross-sectional study. Aging Ment Health 2016;20:647-654.

35. Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association Between Sarcopenia and Cognitive Impairment: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc 2016;17:1164.e7-1164.e15.

36. Szlejf C, Parra-Rodríguez L, Rosas-Carrasco O. Osteosarcopenic Obesity: Prevalence and Relation With Frailty and Physical Performance in Middle-Aged and Older Women. J Am Med Dir Assoc 2017;18:733.e1-733.e5.

37. Tolea MI, Galvin JE. Sarcopenia and impairment in cognitive and physical performance. Clin Interv Aging 2015;10:663-671.

38. Safer U, Safer VB, Demir SO, Yanikoglu I. Effects of Bisphosphonates and Calcium plus Vitamin-D Supplements on Cognitive Function in Postmenopausal Osteoporosis§. Endocr Metab Immune Disord Drug Targets 2016;16:56-60.

39. Wang T, Feng X, Zhou J, Gong H, Xia S, Wei Q, Hu X, Tao R, Li L, Qian F, Yu L. Type 2 diabetes mellitus is associated with increased risks of sarcopenia and pre-sarcopenia in Chinese elderly. Sci Rep 2016;6:38937.

40. Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes Metab Syndr Obes 2019;12:1057-1072.

41. Bruyère O, Cavalier E, Reginster JY. Vitamin D and osteosarcopenia: an update from epidemiological studies. Curr Opin Clin Nutr Metab Care 2017;20:498-503.

42. Kaya S, Deniz O, Varan HD, Kizilarslanoğlu M, Goker B. MON-P042: The Relationship between Frailty and Osteosarcopenia in Geriatric Patients. Clinical nutrition 2017;36:S195.

43. Pasco JA, Mohebbi M, Holloway KL, Brennan-Olsen SL, Hyde NK, Kotowicz MA. Musculoskeletal decline and mortality: prospective data from the Geelong Osteoporosis Study. J Cachexia Sarcopenia Muscle 2017;8:482-489.

ORIGINAL RESEARCH

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Sicca Symptoms and Its Relationship with Primary Sjögren's Syndrome in Geriatric Patients

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Abstract

Objective: Sicca symptoms are frequently observed in geriatric patients, and Sjögren's syndrome is a prototypic disease associated with sicca symptoms. This study aimed to determine the frequency of sicca symptoms and its relationship with primary Sjögren's syndrome (pSS) in geriatric patients in comparison with young patients.

Materials and Methods: This study included 477 patients, with the geriatric group comprising 277 patients aged ≥65 years who were compared to the 200 young patients in the control group. All the subjects were asked questions for the evaluation of sicca symptoms. The Schirmer's and unstimulated whole salivary flow tests were conducted on all the subjects. The diagnosis of pSS was based on the American-European Consensus Group criteria.

Results: The symptoms of dry mouth (33.9% vs. 2%) (p<0.001) and eyes (20.9% vs. 2.5%) (p<0.001) were significantly higher in the geriatric group. Thirteen patients in the geriatric group (13/277, 4.69%) and one patient in the control group (1/200, 0.5%) were diagnosed with pSS (p=0.010). The rate of pSS was 6.89% (12/174) for elderly females and 0.97% (1/103) for males (p=0.036).

Conclusion: The prevalence of pSS is considerably higher in geriatric patients. Every geriatric patient, especially elderly women, should be routinely assessed for sicca symptoms and objective tests should be performed in the presence of sicca symptoms.

Keywords: Dry eyes, dry mouth, geriatric, primary Sjögren's syndrome, sicca symptoms

Introduction

Sicca symptoms are frequent complaints in geriatric patients. Often, both the patients and their attending physicians consider these complaints as a component of aging or as a side-effect of medications. Therefore, these symptoms are mostly ignored and eventually causing the patients to stop mentioning about them (1,2). Also, age-related cognitive deterioration prevents many symptoms such as dry mouth and dry eye from being noticed. Besides medications, acute or chronic parotitis, graft-versus-host disease, hepatitis C, head and neck radiotherapy, SS and sarcoidosis are among the causes of sicca symptoms (3). In large studies focusing on the sicca symptoms in geriatric patients, affirmation with objective tests was only made when subjective complaints of dry mouth and dry eye were present. Thus, the sensitivity of the tests decreased with cognitive impairment.

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease, where the exocrine glands are mainly affected. Permanent dry mouth and dry eye occur due to functional and structural impairment of salivary and tear glands. According to the European League Against Rheumatism (EULAR)- SS task force, sicca symptoms are the most common manifestation of SS, with up to 98% of cases (4). The frequency of dry mouth

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and dry eye increases with age (5). pSS can occur in patients of all ages, it mainly manifests in the fourth and fifth decade of life. The prevalence of pSS ranges between 0.01-5% (6). The difference in the prevalence ratios is generally due to the age of the studied population, the differences in sample sizes, and the use of different classification criteria for pSS. Precise data could not be obtained both because of the small number of prevalence studies in geriatric population and the implementation of different classification criteria. However, the prevalence in the geriatric population is higher than the young (7,8). There are no previous studies concerning the prevalence of pSS in the geriatric population of Turkey.

This study aims to investigate the rate of sicca symptoms and its relation to pSS in geriatric patients and compare with the young patients. pSS diagnosis was based on the AECG criteria. The most widely accepted current classification criteria for pSS are the AECG criteria (9). The American College of Rheumatology (ACR)/EULAR classification criteria have been published in 2016 (10). The population described by both criteria is very similar (11). The diagnosis of pSS was also evaluated according to the 2016 ACR/EULAR classification criteria in this study.

Materials and Methods

This study was designed as an observational cross-sectional study.

Study population

A total of 477 patients were included in this study. 277 patients ≥65 years who received outpatient treatment in the Geriatrics Clinic of Ankara University Faculty of Medicine within 6-months period constituted the study group. Two hundred patients ≥18 years who received outpatient treatment in the General Internal Medicine Clinic of Ankara University Faculty of Medicine between the same dates constituted the control group.

Ethic

The protocol of this study was approved by the Ankara University Faculty of Medicine Medical Research Ethics Committee as dated 24.9.2012 and numbered 13-247. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki. All of the patients signed the informed consent forms.

Exclusion criteria

The patients who were previously diagnosed with a systemic autoimmune disease, acute or chronic parotitis, graft-versus-host disease, hepatitis C, acquired immunodeficiency disease, lymphoma, sarcoidosis, who had a medical history of head and neck radiotherapy, who had uncontrolled diabetes mellitus, who used anticholinergic drugs, who had a general condition disorders that impair their ability to make the Schirmer's test or the unstimulated whole salivary flow test, who refused to participate in the study were excluded from the study.

Investigation of sicca symptoms

All patients were asked questions evaluating sicca symptoms. Patients who gave a positive answer to at least one of the following questions were considered to have dry eye symptom; 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have a recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day? Patients who gave a positive answer to at least one of the following questions were considered to have dry mouth symptom; 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrently or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry food? These questions are those used in revised version of the European criteria proposed by the AECG to detect sicca symptoms (9).

Demonstration of dry mouth and dry eye with objective tests

All participants in the study, no matter whether they had dry mouth and dry eye or not, were subjected to the unstimulated whole salivary flow test and the Schirmer's test.

In the Schirmer test, sterilized standard Schirmer strips were carefully placed on the lower lid margins of both eyes. The strips remained in position for 5 min. After 5 min, the wetting levels of the strips were recorded in units of millimetres. If the Schirmer test result was ≤5 mm in at least one eye, the test was considered positive (12).

The unstimulated whole salivary flow test was used for the evaluation of salivary hypofunction. The volume of saliva that the participant accumulated within 15 min was measured and the result of the test was considered to be positive in the presence of a collection ≤1.5 mL (the unstimulated whole saliva flow rate ≤0.1 mL/minute) (13).

Diagnosis of pSS

The pSS diagnosis was based on the American-European Consensus Group (AECG) criteria. All patients who had objective dry mouth and/or dry eye were reevaluated for pSS by a rheumatology specialist. The blood samples were collected from these patients to test for anti-Ro [Sjögren's syndrome antigen A (SSA)] and anti-La [Sjögren's syndrome antigen B (SSB)] autoantibodies (by enzyme-linked immunosorbent assay test). The patients with objective dry mouth and/or dry eye and having either anti-SSA/Ro or anti-SSB/La antibody positivity were diagnosed as pSS. A minor salivary gland biopsy was performed to the patients who had dry mouth and/or dry eye but negative anti-SSA/Ro or anti-SSB/La antibodies by the rheumatology specialist. The patients who were found to have a focus score of ≥1 were diagnosed with pSS. Additionally, the diagnosis of pSS was evaluated according to the 2016 ACR/EULAR classification

criteria. The compatibility between the two diagnostic criteria was checked.

Histological examination of minor salivary gland biopsy

Salivary gland samples were obtained from the mucosa of the lower lip that appeared normal. The biopsy was evaluated using focus scoring according to the American-European criteria by an expert histopathologist. Focus is defined as an aggregate of 50 or more mononuclear cells per 4 mm^2. The biopsy was accepted as positive when the focus score was ≥1 (14).

Statistics

SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used to statistically analyse all data. Variables are presented as mean ± standard deviation or frequency. The data had previously been subjected to a normal distribution test (Kolmogorov-Smirnov). To compare quantitative variables, Student's t-test was used for the normally distributed variables, and Mann-Whitney U test was used for variables that were not normally distributed. For the comparison of qualitative data, the chi-squared test was used. Fisher's Exact test was used where cell values are expected to be smaller than 5 exceeded 20% percentage. All tests were two tailed, and p-values <0.05 were considered to indicate statistical significance.

Results

The geriatric group and the control group are compared terms of sicca symptoms and clinical features (Table 1). According to the revised AECG criteria, 13 patients in the geriatric group (13/277, 4.69%) and 1 patient in the control group (1/200, 0.5%) received a pSS diagnosis (p=0.010). Twelve of geriatric cases and the young case were females (F/M=13/1). The rate of pSS according to gender is shown in Table 2. Considering all patients included in the study, the rate of pSS was determined as 2.93% (14/477). When evaluated with the 2016 ACR/EULAR classification criteria, the same patients were diagnosed with pSS.

From the patients with objective dry mouth and/or dry eye and having either anti-SSA/Ro or anti-SSB/La antibody positivity, 4 patients (3 patients from the geriatric group and 1 patient from the control group) were diagnosed as pSS. Four cases had only anti-SSA/Ro positivity. Minor salivary gland biopsy was performed to 14 patients who did not have positive antibodies. Ten patients were found to have a focus score of ≥1 and these patients were diagnosed with pSS.

Although there were no complaints of dry mouth or dry eye, dryness was detected by objective tests in two geriatric patients. One of these patients was diagnosed with anti-SSA/Ro autoantibody positivity and the other was diagnosed with pSS by salivary gland biopsy.

The patients diagnosed with pSS and not diagnosed with pSS in the study group compared in terms of dry mouth and dry eye symptoms and clinical features (Table 3).

Discussion

In our study to determine the rate of sicca symptoms and its relation to pSS in geriatric individuals and compare with the young patients, both sicca symptoms and pSS were found to be significantly more common in geriatric individuals.

The prevalence of sicca symptoms in people ≥65 years of age is reported by up to 30% (2,15). In a population-based study with 2481 subjects aged between 65-84 years, dry mouth or dry eye was present in approximately 27% of the community, and they

Table 1. Comparison of the groups in terms of sicca symptoms and clinical features

Parameters	Study group (n=277)	Control group (n=200)	p
Age (mean)	74.08±6.52	39.25±10.69	**<0.001**
Gender (female/male)	174/103	126/74	0.956
Number of chronic diseases	2.76±1.65	1.17±0.87	**<0.001**
Number of drugs used	3.35±1.38	1.60±1.08	**<0.001**
Presence of dry mouth symptom (%)	122 (44.0)	13 (6.5)	**<0.001**
Presence of objective dry mouth (%)	94 (33.9)	4 (2)	**<0.001**
Swollen salivary glands (parotid or submandibular) (%)	14 (5.1)	0	**<0.001**
Presence dry eye symptom (%)	85 (30.7)	8 (4)	**<0.001**
Presence of objective dry eye (%)	58 (20.9)	5 (2.5)	**<0.001**
Presence of both dry mouth and dry eye symptom (%)	51 (18.4)	1 (0.5)	**<0.001**
Simultaneous positivity of saliva test and Schirmer's test (%)	17 (6.1)	0	**<0.001**
Use of artificial eye drops (%)	37 (13.4)	2 (1)	**<0.001**
Diagnosis of pSS	13 (4.69)	1 (0.50)	**0.010**

pSS: Primer Sjögren's syndrome

Table 2. The rate of primary Sjögren's syndrome according to gender

Group	Patient with primary Sjögren's syndrome		
	Female	Male	p
Geriatric (%)	12 (12/174-6.89%)	1 (1/103-0.97%)	**0.036**
Control (%)	1 (1/126-0.8%)	0 (0/74-0%)	1.000
Total (%)	13 (13/301-4.32%)	1 (1/176-0.56%)	**0.023**

Table 3. Comparison of patients diagnosed with pSS and not diagnosed with pSS in the study group in terms of sicca symptoms

Parameters	pSS (n=13)	No pSS (n=264)	p
Age (mean)	72.85±6.29	74.14±6.53	0.486
Presence of dry mouth symptom (%)	8 (61.5)	114 (43.2)	0.309
Presence of objective dry mouth (%)	10 (76.9)	84 (31.8)	**0.002**
Presence dry eye symptom (%)	7 (53.8)	78 (29.5)	0.122
Presence of objective dry eye (%)	8 (61.5)	50 (18.9)	**<0.001**
Presence of both dry mouth and dry eye symptom (%)	6 (46.1)	45 (17.0)	**0.022**
Simultaneous positivity of saliva test and Schirmer's test (%)	6 (46.1)	19 (7.2)	<0.001

pSS: Primer Sjögren's syndrome

were simultaneously present in 4.4% of the population (16). However, the patients with sicca symptoms were not examined by a rheumatologist for the presence of SS. In our study, the complaints of dry mouth and dry eye in geriatric patients were 44% and 30.7%, respectively. These rates were higher than the literature. This result may be related to the fact that the patients included in the study were selected from the patients who were admitted to the hospital, not from the society. In our study, all subjects, whether or not they had the complaints of dry mouth and/or dry eye, were evaluated by objective tests (the unstimulated whole salivary flow test and the Schirmer's test). Thus, the patients who do not feel dry mouth or dry eye or who could not report dry mouth and dry eye due to cognitive deficiency were also identified. By the objective tests, dry mouth rate as 33.9%, and dry eye rate as 20.9% was determined in geriatric patients. Cases that were positive for one or both objective tests were further evaluated by a rheumatologist for the presence of pSS according to the AECG and ACR/EULAR classification criteria.

Estimates of the prevalence of pSS vary widely, depending upon the specific classification criteria, study design, and the population examined (17,18). By Kabasakal et al. (19) in a study of women in Turkey have investigated the prevalence of pSS. According to the revised European criteria and AECG criteria, the prevalence of pSS was found to be 1.56% and 0.72%, respectively. In a prevalence study conducted by Birlik et al. (20) on both male and female subjects, the prevalence of pSS was reported as 0.21% according to the AECG criteria, which is actually surprisingly lower than the predicted mean value for the general population. There are no previous studies concerning the prevalence of pSS in the older adults of Turkey. In our study, considering all patients included in the study, the rate of pSS was determined as 2.72%. A small group of patients diagnosed with pSS could have primarily extraglandular manifestations without significantly demonstrating dry mouth or dry eye (21). Since the rate of such patients is quite low, we did not evaluate our patients in this respect, considering that it would not affect our study results.

According to the "1993 European Community criteria," Thomas et al. (22) predicted the prevalence of pSS in geriatrics as 3-4%. Botsios et al. (23) reported the pSS prevalence as 6% by using "1996 Revised European Classification Criteria". These studies were conducted according to the European study criteria identified in 1993 and 1996, which are less strict than the 2002 "AECG Criteria". Haugen et al. (24) have evaluated two different populations with an age range of 40-44 and 70-74, according to the 1993 European criteria and 1996 revised European criteria. In the group aged between 40-44, the prevalence of pSS according to the 1993 and 1996 rules was found to be 0.44% and 0.22% respectively; whereas in the second group aged between 71-74, it was reported as 3.39% and 1.4%, respectively. Drosos et al. (25) have diagnosed 8 out of 62 elderlies from a public nursing home with pSS through biopsy, all of whom were asymptomatic. Among 103 older adults women, Strickland et al. (26) have identified dry mouth in 39% and dry eye (with the Schirmer's test) in 24% of the patients. Two of these 103 women were diagnosed with pSS, and 12% were evaluated as possible pSS. In our study, the rate of pSS in older adults subjects was 4.7% (6.9% for older adults females and 0.9% for males). SS affects primarily middle-aged women. The female/male ratio ranges from 9/1 to 14/1 (27,28). Our results are also compatible with the literature (female/male ratio: 12/1).

Unlike the 2002 AECG criteria, in the ACR/EULAR classification criteria, positive serology for anti-SSB/La in the absence of anti-SSA/Ro is no longer considered a criteria item. Nevertheless, in this study, all patients diagnosed with pSS according to 2002 AECG Criteria were anti-SSA/Ro antibody positive while anti-SSB/La negative. Therefore, when the patients were evaluated with the 2016 ACR/EULAR classification criteria, the same patients who were diagnosed with pSS according to the AECG criteria were diagnosed with pSS. We found that both sets of criteria were compatible with each other and we think that any of them could be used in geriatric patients, depending on the clinician's preference. In our study, only 4 (1 young and

3 geriatric patients) patients having dry mouth and/or dry eye were diagnosed through anti-SSA/Ro antibody positivity. Older patients with SS have lower frequency of serologic abnormalities, such as anti-SSA, anti-SSB, rheumatoid factor, and hyperglobulinemia, than a young one (29-31). In addition, biopsy was positive in 10 of 14 patients who underwent salivary gland biopsy.

In our study, two geriatric patients who did not complain of dry mouth or dry eye were diagnosed with pSS. This is a remarkable finding and it demonstrates that the presence of dry mouth and dry eye could be detected through objective tests, even though the patients do not mention them as a result of possible cognitive impairment or other reasons (32,33).

Study Limitations

The study has some limitations. Firstly, this study was conducted with outpatients. This is not a community survey. Therefore, only the pSS ratio was determined. pSS prevalence information was not available. Secondly, because our study aimed not only to determine the rate of sicca symptoms, but also to determine the relationship between sicca symptoms and pSS, patients with a condition other than pSS that would cause sicca symptoms were excluded from the study. Therefore, the rate of sicca symptoms in geriatric patients may be higher than that shown in our study. However, our study is the only study in Turkey to determine the rate of sicca symptoms and pSS in geriatric patients. Finally, the control group in the study consisted of young patients. Considering that comparisons with young patients would not be made, the results of the comprehensive geriatric evaluation of the geriatric patients were not recorded during the study. For this reason, comprehensive geriatric evaluation results of geriatric patients could not be given.

Conclusion

In our study, the rate of pSS in the older adults was found 4.69%, despite the use of the revised AECG and ACR/EULAR Classification Criteria, which are much conservative than the previous measures. This ratio quite high and is worth attention. Sicca symptoms are the cardinal symptoms in pSS. These symptoms are non-specific and can occur with many other conditions. Also, these have a profound effect on the quality of life of patients with pSS. In the geriatric age group, sicca symptoms are not commonly mentioned complaints in doctor visits. On the other hand, most of the patients with sicca symptoms do not have Sjögren syndrome. In our study, especially in geriatric patients with dry mouth and dry eye symptoms, pSS detection rate was significantly higher. Therefore, patients with sicca symptoms should be carefully interviewed by geriatrics, and objective tests should be conducted in order not to miss pSS. Early diagnosis and treatment will have a positive effect on the quality of life of patients with pSS. Awareness should be raised for morbidity in these patients and the possible lymphoproliferative diseases that can develop in further years.

Ethics

Ethics Committee Approval: The protocol of this study was approved by the Ankara University Faculty of Medicine Medical Research Ethics Committee as dated 24.9.2012 and numbered 13-247. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki.

Informed Consent: All of the patients signed the informed consent forms.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.C., O.K., A.Ş., Concept: Ö.K.C., O.K., A.Ş., N.T., T.A., Design: Ö.K.C., O.K., A.Ş., N.T., T.A., Data Collection or Processing: Ö.K.C., O.K., A.Ş., Analysis or Interpretation: Ö.K.C., O.K., A.Ş., Literature Search: Ö.K.C., O.K., A.Ş., N.T., T.A., Writing: Ö.K.C., O.K., A.Ş., N.T., T.A.

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References

1. Su Y, Yang C. Keratoconjunctivitis Sicca in Sjögren's Syndrome. N Engl J Med. 2020;383:1663.
2. Baer AN, Walitt B. Update on Sjögren Syndrome and Other Causes of Sicca in Older Adults. Rheum Dis Clin North Am 2018;44:419-436.
3. Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjögren's syndrome: beyond the dryness - From pathophysiology to diagnosis and treatment. Int J Med Sci 2017;14:191-200.
4. Brito-Zerón P, Theander E, Baldini C, Seror R, Retamozo S, Quartuccio L, Bootsma H, Bowman SJ, Dörner T, Gottenberg JE, Mariette X, Bombardieri S, de Vita S, Mandl T, Ng WF, Kruize AA, Tzioufas A, Vitali C, Buyon J, Izmirly P, Fox R, Ramos-Casals M; Eular Sjögren Syndrome Task Force. Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations. Expert Rev Clin Immunol 2016;12:137-156.
5. Witte T. Sjögren-Syndrom [Sjögren's syndrome]. Z Rheumatol 2019;78:511-517.
6. Bowman SJ. Primary Sjögren's syndrome. Lupus 2018;27(Suppl 1):32-35.
7. Moerman RV, Bootsma H, Kroese FG, Vissink A. Sjögren's syndrome in older patients: aetiology, diagnosis and management. Drugs Aging 2013;30:137-153.
8. Ramos-Casals M, García-Carrasco M, Brito MP, López-Soto A, Font J. Autoimmunity and geriatrics: clinical significance of autoimmune manifestations in the elderly. Lupus 2003;12:341-355.
9. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-558.

10. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ, Mariette X; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol 2017;69:35-45.
11. Mariette X, Criswell LA. Primary Sjögren's Syndrome. N Engl J Med 2018;378:931-939.
12. Navazesh M, Kumar SK; University of Southern California School of Dentistry. Measuring salivary flow: challenges and opportunities. J Am Dent Assoc 2008;139(Suppl 3):5S-40S.
13. Negrini S, Emmi G, Greco M, Borro M, Sardanelli F, Murdaca G, Indiveri F, Puppo F. Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med 2021.
14. Greenspan JS, Daniels TE, Talal N, Sylvester RA. The histopathology of Sjögren's syndrome in labial salivary gland biopsies. Oral Surg Oral Med Oral Pathol 1974;37:217-229.
15. Diep JT, Gorevic PD. Geriatric autoimmune diseases: systemic lupus erythematosus, Sjogren's syndrome, and myositis. Geriatrics 2005;60:32-38.
16. Schein OD, Hochberg MC, Muñoz B, Tielsch JM, Bandeen-Roche K, Provost T, Anhalt GJ, West S. Dry eye and dry mouth in the elderly: a population-based assessment. Arch Intern Med 1999;159:1359-1363.
17. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, Zhong R. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:1983-1989.
18. Ayar K, Tunç R, Pekel H, Esen HH, Küçük A, Çifçi S, Ataseven H, Özdemir M. Prevalence of sicca symptoms and Sjögren's syndrome in coeliac patients and healthy controls. Scand J Rheumatol 2020;49:233-238.
19. Kabasakal Y, Kitapcioglu G, Turk T, Oder G, Durusoy R, Mete N, Egrilmez S, Akalin T. The prevalence of Sjögren's syndrome in adult women. Scand J Rheumatol 2006;35:379-383.
20. Birlik M, Akar S, Gurler O, Sari I, Birlik B, Sarioglu S, Oktem MA, Saglam F, Can G, Kayahan H, Akkoc N, Onen F. Prevalence of primary Sjogren's syndrome in Turkey: a population-based epidemiological study. Int J Clin Pract 2009;63:954-961.
21. Manfrè V, Cafaro G, Riccucci I, Zabotti A, Perricone C, Bootsma H, De Vita S, Bartoloni E. One year in review 2020: comorbidities, diagnosis and treatment of primary Sjögren's syndrome. Clin Exp Rheumatol 2020;38 (Suppl 126):10-22.
22. Thomas E, Hay EM, Hajeer A, Silman AJ. Sjögren's syndrome: a community-based study of prevalence and impact. Br J Rheumatol 1998;37:1069-1076.
23. Botsios C, Furlan A, Ostuni P, Sfriso P, Andretta M, Ometto F, Raffeiner B, Todesco S, Punzi L. Elderly onset of primary Sjögren's syndrome: clinical manifestations, serological features and oral/ocular diagnostic tests. Comparison with adult and young onset of the disease in a cohort of 336 Italian patients. Joint Bone Spine 2011;78:171-174.
24. Haugen AJ, Peen E, Hultén B, Johannessen AC, Brun JG, Halse AK, Haga HJ. Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scand J Rheumatol 2008;37:30-34.
25. Drosos AA, Andonopoulos AP, Costopoulos JS, Papadimitriou CS, Moutsopoulos HM. Prevalence of primary Sjögren's syndrome in an elderly population. Br J Rheumatol 1988;27:123-127.
26. Strickland RW, Tesar JT, Berne BH, Hobbs BR, Lewis DM, Welton RC. The frequency of sicca syndrome in an elderly female population. J Rheumatol 1987;14:766-771.
27. Parisis D, Chivasso C, Perret J, Soyfoo MS, Delporte C. Current State of Knowledge on Primary Sjögren's Syndrome, an Autoimmune Exocrinopathy. J Clin Med 2020;9:2299.
28. Al-Hashimi I. Xerostomia secondary to Sjögren's syndrome in the elderly: recognition and management. Drugs Aging 2005;22:887-899.
29. Haga HJ, Jonsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. Scand J Rheumatol 1999;28:227-232.
30. Manzo C, Maslinska M. Primary Sjögren's Syndrome in the Elderly: Does Age of Onset Make a Difference? EMJ Rheumatol 2018;5:75-82.
31. Yao Y, Ma JF, Chang C, Xu T, Gao CY, Gershwin ME, Lian ZX. Immunobiology of T Cells in Sjögren's Syndrome. Clin Rev Allergy Immunol 2021;60:111-131.
32. Pego-Reigosa JM, Restrepo Vélez J, Baldini C, Rúa-Figueroa Fernández de Larrinoa Í. Comorbidities (excluding lymphoma) in Sjögren's syndrome. Rheumatology (Oxford) 2021;60:2075-2084.
33. Cornec D, Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puéchal X, Le Guern V, Sibilia J, Gottenberg JE, Chiche L, Hachulla E, Yves Hatron P, Goeb V, Hayem G, Morel J, Zarnitsky C, Dubost JJ, Saliou P, Pers JO, Seror R, Saraux A. Severe Health-Related Quality of Life Impairment in Active Primary Sjögren's Syndrome and Patient-Reported Outcomes: Data From a Large Therapeutic Trial. Arthritis Care Res (Hoboken) 2017;69:528-535.

ORIGINAL RESEARCH

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Perceived Stigma Against Alzheimer's Disease in the Turkish Population

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Abstract

Objective: Cognitive, behavioral, and psychiatric disorders that are associated with dementia cause stigma against Alzheimer's disease (AD) in patients and caregivers as well as in healthy individuals in public. To the best of our knowledge, stigma against AD is not investigated in the Turkish population; therefore, this study aimed to evaluate the stigma of healthy Turkish people according to their demographic characteristics.

Materials and Methods: This cross-sectional observational study included a total of 439 healthy participants without any history of neurological and/or systemic disease. Demographic characteristics and AD-related knowledge of participants were recorded. A 10-item questionnaire survey was applied to the participants to assess the stigmatization against AD. Factors associated with the stigma score were evaluated in regression analysis.

Results: This study included 253 males and 186 females (mean age: 35.7±9.8 years). Most of them had knowledge about AD (94.3%). Only 18.5% had a family history of AD, and 65% were married. Of 439 persons, 95 (21.6%) worked in healthcare fields. Of the healthy participants, 60.6% had a moderate-high stigma against AD. The mean stigma score was 8.95±4.79. The total stigma scores were higher in females and singles ($p=0.001$ and $p<0.001$, respectively). Healthcare workers expressed the highest levels of stigma ($p<0.001$). Age, knowledge, and family history of AD did not influence the stigma. Shame, loss of self-esteem, and fear of exclusion were most expressed stigmas.

Conclusion: To the best of our knowledge, this is the first study that evaluated perceived stigma against AD in the healthy Turkish population. The higher incidence of stigma among females and singles can be explained by cultural reasons. Stigma in health professionals may lead to delay in the early diagnosis and management of AD.

Keywords: Alzheimer's disease, stigma, healthcare workers, healthy population

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that presents with episodic memory impairment and gradually decreases other cognitive functions (1). The global prevalence of the disease, which increases twice every 5.5 years, is expected to be 114.5 million in 2050 (2,3). Early recognition of this disease, which has a tremendous socio-economic impact worldwide, is important for increasing appropriate treatment of dementia and managing its psychological, emotional, familial, economic terms. However, the perceived stigma against AD is seen as a huge factor in preventing effective strategies for the disease (4).

Stigma is defined as the negative attitude of the public towards people who are thought to be different in terms of physical, mental, and lifestyle. People who carry this label are less desired (5). Patients with memory impairment are known to judge themselves due to their illness and symptoms and experience both social and internalized stigmatization (6). In addition, family members and caregivers have stigmatization also (7). Moreover, some people believe that AD patients are less fortunate than those with treatable diseases (8). Understanding

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the perception of stigma in healthy individuals and educating society with accessible and effective methods helps to increase disease-related awareness and improve disease management (9).

To the best of our knowledge, there is no study evaluating the perceived stigma against AD in healthy people in Turkey. Therefore, this study aims to investigate the perceived stigma level against AD in healthy people. Its second aim is to reveal the demographic characteristics and related factors of people with high stigmatization.

Materials and Methods

Study population

Four hundred thirty-nine healthy participants (253 men, 186 women) living in Turkey's capital Ankara were included in this cross-sectional observational study. Participants in the study had no known cognitive and/or systemic disorders. Participants' age, gender, marital status, educational status, and occupation were recorded. Participants were asked about knowledge and family history of AD.

Survey

A ten-question survey (Table 1) was applied to the participants to assess the perceived stigma against AD. This questionnaire is the adaptation of the "STIG-MA" survey developed by Piver et al. (10) in 2012, with the author's permission. Participants were asked to pretend that they had AD and rate what they would felt. The questions were answered as "yes, maybe, I don't know, no" and scored between 0-3. The score 3 corresponded to the greatest stigma, either "yes" if the question was positive (questions 1, 3, 4, 5, 6, 7, and 9) or "no" if the question was negative (questions 2, 8 and, 10). Other answers were scored respectively. The total score indicated the stigma severity. The highest score was 30. Zero-seven was graded as mild, 8-11 as moderate, and 12 and above the high stigma.

The questions were also grouped to explore several dimensions of perceived stigma: Reluctance to disclose the illness (questions 1 and 2), emotional impact (questions 3 and 4), fear of exclusion (questions 5, 6, and 9), courtesy stigma (question 7) and fear of loss of family support (questions 8 and 10).

Table 1. Ten questions about perceived stigma in the stigma survey

If you were suffering from Alzheimer's disease
1. Would you rather people did not know about your disease?
2. Would you tell the person you are closest to?
3. Would you lose self-esteem because of the disease?
4. Would this disease cause you shame or embarrassment?
5. Would your neighbors, your colleagues have less respect for you?
6. Do you think others would avoid you because of the disease?
7. Would your neighbors, your colleagues have less esteem for your family?
8. Do you think your wife/husband would stay with you and support you?
9. Do you think people you know at work or friends would ask you to stay away, even if you were taking medication for the disease?
10. Would your family give you their support right from the start?

The study's ethics committee approval for the research and permissions for data sharing for scientific purposes was obtained (23.12.2020/96537014). The Helsinki Declaration 2008 principles were conducted the study.

Statistics

Descriptive statistics were expressed as mean, standard deviation, median, minimum, and maximum for continuous data; and as count and proportion for categorical data. Categorical data were analysed with the chi-square or Fisher's Exact tests. The distribution normality of the continuous variables was calculated with the Shapiro-Wilk test. We analysed the two groups with independent samples t-test for the normally distributed variables and with the Mann-Whitney U test for the non-normally distributed variables. We compared the more than two groups with One-Way ANOVA for the normally distributed variables and with the Kruskal-Wallis test for the non-normally distributed variables; post-hoc multiple comparison analysis was performed with significant values that have been adjusted by the Bonferroni correction. Pearson's or Spearman's correlation analysis was used to find the relationship between continuous variables, depending on the distribution.

Statistical analyses were performed using the IBM SPSS v.24 for Windows software and was reported with 95% confidence intervals. Values of $p<0.05$ were considered significant.

Results

Four hundred thirty-nine healthy participants (186 females (42.4%), 253 males (57.6%), mean age 35.7 years $\pm$9.8) without neurological and/or systemic diseases were included in this study. 94.3% (n=414) of the participants stated that they have knowledge about AD. But only 18.5% (n=81) had a family history of AD. 95 (21.6%) of the participants were healthcare workers. Also, 152 (34.6%) participants were singles.

According to the STIG-MA survey, the mean stigma score of the participants against AD was 8.95$\pm$4.79. 60.6% of healthy participants have a moderate-high stigma against AD. Mean scores of the dimensions of perceived stigma are summarized in Table 2.

Participants were divided into three groups according to their scores from this questionnaire: mild stigma (n=173, 39.4%), moderate stigma (n=133, 30.3%), and severe stigma (n=133, 30.3%). 31.8% of the participants in the mild stigma group, 50.4% of those in the moderate stigma group, and 48.1% of those in the severe stigma group were women. Moderate and severe stigma scores were significantly higher in women than in men (p=0.001). The mean stigma score was higher in singles

Table 2. Global stigma score and five dimensions of perceived stigma	
Global stigma score (M ± SD)	8.95 (±4.79)
Reluctance to disclose the illness (M ± SD)	0.93 (±1.44)
Emotional impact (M ± SD) Fear of exclusion (M ± SD) Courtesy stigma (M ± SD) Fear of loss of family support (M ± SD)	3.00 (±2.18) 3.67 (±2.49) 0.72 (±1.01) 0.60 (±1.01)
M: Mean, SD: Standart deviation	

(p<0.001). Moderate-severe stigma was detected in 72 (75.8%) of 95 healthcare workers participating in the study, and the stigma in healthcare workers was found to be statistically significant compared to non-healthcare workers (p<0.001). Healthcare workers had higher stigma scores than non-healthcare workers. The three groups were similar in terms of age, knowledge about AD, family history of AD, and occupation (Table 3).

Correlation analysis was applied to investigate the relationship between dimensions of perceived stigma against AD and age, gender, AD awareness, marital status and occupation. The stigma scores of healthcare workers in all dimensions were higher than those without, and this result was statistically significant (respectively; p=0.006, p=0.034, p<0.001, p=0.021, p=0.009). It was observed that women got higher scores in the dimensions of "reluctance to declare the illness", "emotional impact" and "loss of family support" (p=0.018, p<0.001, p<0.001, respectively). In singles, stigma scores were higher in the dimensions of "emotional impact" and "loss of family support" (p=0.006, p<0.001). Other factors did not have a significant effect on the dimensions of the perceived stigma.

Discussion

Our study has shown that 60.6% of healthy participants have a moderate-high stigma against AD. Stigma levels were higher in women, singles, and healthcare workers.

Older people with cognitive impairment encounter stigmatization in many cultures. Stigmatization causes a delay of 1.5-1.8 years in the diagnosis of cognitive impairment (11). It has been reported that older people are stigmatized due to their age, and additional cognitive impairment increases the risk of stigmatization threefold (12). Cognitive, behavioral, and psychiatric disorders associated with dementia cause some issues such as denial, embarrassment, and irritability associated with AD in both patients, caregivers, and healthy individuals in the community. In Western societies, dementia is seen as a loss of youth, functionality, and independence. This, in turn, is associated with reduced tolerance and increased risk of stigma for dementia patients (13). In Eastern countries such as Japan, China, and India, dementia is perceived not as a disease but as a part of aging. Therefore, unlike in Western societies, the fear of having AD and the frequency of stigma associated with it are less common in these countries (14-16). While some African-Americans think of dementia as the inevitable consequence of aging, others define it as a mental illness because of their spiritual and religious beliefs. Therefore, these populations experience less stigma, caregiver burden, and caring problems against AD (17,18). In Arabic countries, because of prohibitions on disclosing personal and family issues to foreigners, Alzheimer's patients' access to hospitals has decreased, resulting in criticism and ridicule (19).

On the other hand, solid religious beliefs increase compassion and the willingness to help patients with AD and reduce aggression towards patients (13). In a study conducted with a population of AD and caregivers, approximately two-thirds of the participants stated that they were not understood by others and were exposed to negative associations in society (20). In our study, the perceived stigma against AD was high in more than half of the healthy Turkish participants. While this rate is similar to some studies reported in Western societies, it is higher than the stigma in Eastern cultures. This difference may be due to the cultural factors and demographic characteristics of the participants.

Some factors affect people's perception of stigma, such as gender, age, education level, cultural beliefs, knowledge about AD, or being an AD caregiver. The most important factor associated with the perceived stigma against AD is gender (21). In a study from Australia, stigmatization against AD was found to be higher in men. However, women have three times more risk in elderly societies with a higher male population and gender

Table 3. Stigma levels of the participants according to their demographic characteristics

	Mild stigma (n=173)	Moderate stigma (n=133)	High stigma (n=133)	p
Age** (year), (M ± SD)	36.8 (±10.3)	35.3 (±10.3)	34.7 (±8.6)	0.242
Gender***, female n, (%)	55 (31.8)	67 (50.4)	64 (48.1)	**0.001***
Knowledge about AD***, n, (%) Family history with AD***, n, (%) Marital status***, single n, (%) Occupation***, worker n, (%) Heathcare worker***, n, (%)	14 (8.1) 35 (20.2) 40 (23.1) 156 (90.2) 23 (13.3)	5 (3.8) 27 (20.3) 52 (39.1) 115 (86.5) 28 (21.1)	6 (4.5) 19 (14.3) 60 (45.1) 126 (94.7) 44 (33.1)	0.062 0.903 **0.000*** 0.071 **0.000***
N: Number, M: Mean, SD: Standart deviation, AD: Alzheimer's disease, *p-value <0.05 **independent samples Kruskal-Wallis test, ***chi-square test				

discrimination (22,23). In our study, perceived stigma against AD was found to be higher in women than in men. This result was thought to be related to the fact that women are more interested in the care of AD patients in our country, and therefore women are more exposed to the behavioral effects of the disease.

Studies have shown that the perception of stigma in young people is higher than in the elderly (22,24). Different from previous studies, although most of our participants were young, age did not have any effect on stigmatization in our study.

The socio-economic factors and education level affect stigmatization (25). In high educated and income countries, cognitive impairments are known as an unavoidable part of normal aging. This increases fear and anxiety in individuals, feelings of hopelessness, and stigmatization (26). In the low income countries, people accept patients with AD more easily and stigmatize them less (25). In some studies, it has been shown that education level does not affect stigma (21,27). Similarly, no relationship was found between marital status and stigmatization (28). In our study, the stigma level was not affected by the education level and the occupation. However, in contrast to the literature, it was observed that single participants got higher scores in the "Fear of loss of family support" and "Emotional impact" dimensions. The high stigmatization in these dimensions is thought to be due to people not having any idea about their future partners and their behavior.

Although the vast majority of the participants (94.3%) included in our study have knowledge about AD, they had a high stigma against the disease. This result is different from other studies reporting the relationship between having less knowledge about the disease and an increased risk of stigma. People who have more information about AD have less stigma (29). In a study conducted in 155 countries with more than 70.000 participants, it was found that two-thirds of the participants accepted AD as a part of the aging process, not as a neurodegenerative disease. This indicates the lack of knowledge about AD that may result in stigma (30).

There was no difference in stigma between those who had a family member with dementia and those who did not (21,24,31). Only about one-fifth of our participants had a family history of AD, which was not associated with stigma, consistent with previous studies.

It has been demonstrated that approximately 62% of healthcare workers know dementia as a part of normal aging in a large study (32). Education of healthcare professionals about AD and increasing their awareness about the disease is necessary for early diagnosis of AD and developing effective strategies to manage it. Thus, national dementia outcomes could be improved (33). A few studies have shown that the perception of stigma against AD is high among healthcare professionals (10,32). Our study also revealed a high stigma against AD in most healthcare workers.

To the best of our knowledge, our study is the first to investigate the perceived stigma prevalence against AD in the healthy Turkish population. However, the study has some limitations. Participants are generally young people, so stigmatization in older individuals is not clear. Besides, since AD caregivers were not included in this study, their stigmatization could not be evaluated.

Conclusion

Perceived stigma against AD is frequent in healthy Turkish individuals and is higher in women, singles, and healthcare workers. The prevalence of stigma may vary between different cultures. Stigma not only delays the diagnosis of AD, but also prevents patients from accessing medical and surgical interventions, making decisions about their own care and legal processes, and also expressing opinions on AD treatment and support. It is important to provide national strategies for eliminating the perception of stigma. Similar evaluations have been made before, especially in high- and low-income societies. Still, such an evaluation has never been made before in a middle income country such as Turkey. Therefore, our study is valuable because it shows the levels of stigma against AD in Turkish society, especially according to occupational groups, and such an evaluation has not been made before. Nevertheless, there is a need for large-scale studies investigating the frequency of stigma and related factors in the general population.

Information

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Ethics

Ethics Committee Approval: The study's ethics committee approval for the research and permissions for data sharing for scientific purposes was obtained (23.12.2020/96537014). The Helsinki Declaration 2008 principles were conducted the study.

Informed Consent: All volunteers participating in the survey were informed about the study and agreed to participate. Since there was no patient group, an extra voluntary consent form was not obtained.

Peer-review: Externally peer-reviewed

Authorship Contributions

Surgical and Medical Practices: M.T., Concept: N.K., B.S.A.P., Design: N.K., B.S.A.P., Data Collection or Processing: M.T., N.T.B., B.S.A.P., Analysis or Interpretation: M.T., N.K., N.T.B., B.S.A.P., Literature Search: M.T., N.T.B., B.S.A.P., Writing: M.T., B.S.A.P.

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References

1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263-269.
2. Fiest KM, Roberts JI, Maxwell CJ, Hogan DB, Smith EE, Frolkis A, Cohen A, Kirk A, Pearson D, Pringsheim T, Venegas-Torres A, Jetté N. The Prevalence and Incidence of Dementia Due to Alzheimer's Disease: a Systematic Review and Meta-Analysis. Can J Neurol Sci 2016;43(Suppl 1):S51-82.
3. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013;9:63-75.e2.
4. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54(11 Suppl 5):S4-9.
5. Jolley DJ, Benbow SM. Stigma and Alzheimer's disease: causes, consequences and a constructive approach. Int J Clin Pract 2000;54:117-119.
6. Stites SD, Milne R, Karlawish J. Advances in Alzheimer's imaging are changing the experience of Alzheimer's disease. Alzheimers Dement (Amst) 2018;10:285-300.
7. Cavayas M, Raffard S, Gély-Nargeot MC. Stigmatisation dans la maladie d'Alzheimer, une revue de la question [Stigmatization in Alzheimer's disease, a review]. Geriatr Psychol Neuropsychiatr Vieil 2012;10:297-305.
8. Alzheimer's Disease International (ADI) & In The Moment (ITM) Productions. (2018). [The Global Voice on Dementia]. Every three seconds. [Video file]. Retrieved from https://www.alz.co.uk/everythreeseconds.
9. The World Health Organization (WHO). (2017). 10 facts on dementia. From https://www.who.int/features/factfiles/dementia/en/
10. Piver LC, Nubukpo P, Faure A, Dumoitier N, Couratier P, Clément JP. Describing perceived stigma against Alzheimer's disease in a general population in France: the STIG-MA survey. Int J Geriatr Psychiatry 2013;28:933-938.
11. de Miranda LFJR, Matoso RO, Rodrigues MV, de Lima TOL, Nascimento AF, Carvalho FC, Moreira DRM, Fernandes JC, de Paula JJ, Magno LAV, Caramelli P, de Moraes EN. Factors influencing possible delay in the diagnosis of Alzheimer's disease: Findings from a tertiary Public University Hospital. Dement Neuropsychol 2011;5:328-331.
12. Benbow SM, Reynolds D. Challenging the stigma of Alzheimer's disease. Hosp Med 2000;61:174-177.
13. Cipriani G, Borin G. Understanding dementia in the sociocultural context: a review. Int J Soc Psychiatry 2015;61:198-204.
14. Traphagan JW. Senility as disintegrated person in Japan. J Cross Cult Gerontol 2002;17:253-267.
15. Sun F, Ong R, Burnette D. The influence of ethnicity and culture on dementia caregiving: a review of empirical studies on Chinese Americans. Am J Alzheimers Dis Other Demen 2012;27:13-22.
16. Dias A, Dewey ME, D'Souza J, Dhume R, Motghare DD, Shaji KS, Menon R, Prince M, Patel V. The effectiveness of a home care program for supporting caregivers of persons with dementia in developing countries: a randomised controlled trial from Goa, India. PLoS One 2008;3:e2333.
17. Mahoney DF, Cloutterbuck J, Neary S, Zhan L. African American, Chinese, and Latino family caregivers' impressions of the onset and diagnosis of dementia: cross-cultural similarities and differences. Gerontologist 2005;45:783-792.
18. Roberts JS, Connell CM, Cisewski D, Hipps YG, Demissie S, Green RC. Differences between African Americans and whites in their perceptions of Alzheimer disease. Alzheimer Dis Assoc Disord 2003;17:19-26.
19. Youssef J, Deane FP. Factors influencing mentalhealth help-seeking in Arabic-speaking communities in Sydney, Australia. Mental Health Religion & Culture 2006;9:43-66.
20. Batch ML, Mittelman, MS. World Alzheimer Report 2012: Executive Summary. 2012.
21. Rewerska-Juśko M, Rejdak K. Social Stigma of People with Dementia. J Alzheimers Dis 2020;78:1339-1343.
22. Kim S, Mortby M. Dementia-related stigma, cultural diversity and help-seeking intentions: Findings from a population survey. Innov Aging 2017;1(Suppl 1):693.
23. Graham N, Lindesay J, Katona C, Bertolote JM, Camus V, Copeland JR, de Mendonça Lima CA, Gaillard M, Gély Nargeot MC, Gray J, Jacobsson L, Kingma M, Kühne N, O'Loughlin A, Rutz W, Saraceno B, Taintor Z, Wancata J; Old Age Psychiatry section, World Psychiatric Association; World Health Organization. Reducing stigma and discrimination against older people with mental disorders: a technical consensus statement. Int J Geriatr Psychiatry 2003;18:670-678.
24. Mazurek M, Papuć E. [Stigmatisation of people with dementi]. Wiad Lek 2018;71:1275-1278.
25. Pelegrini LNC, Hall A, Hooper E, Oliveira D, Guerra F, Casemiro FG, Bonfadini J, Yong K, Pereira N, Costa R, Barbosa MT, Mioshi E. Challenges in public perception: highlights from the United Kingdom-Brazil Dementia Workshop. Dement Neuropsychol 2020;14:209-215.
26. Rosenberg A, Coley N, Soulier A, Kulmala J, Soininen H, Andrieu S, Kivipelto M, Barbera M; MIND-AD and HATICE groups. Experiences of dementia and attitude towards prevention: a qualitative study among older adults participating in a prevention trial. BMC Geriatr 2020;20:99.
27. Werner P, Davidson M. Emotional reactions of lay persons to someone with Alzheimer's disease. Int J Geriatr Psychiatry 2004;19:391-397.
28. Liang J, Jang Y, Aranda MP. Stigmatising beliefs about Alzheimer's disease: Findings from the Asian American Quality of Life Survey. Health Soc Care Community 2021;29:1483-1490.
29. Stites SD, Largent EA, Johnson R, Harkins K, Karlawish J. Effects of Self-Identification as a Caregiver on Expectations of Public Stigma of Alzheimer's Disease. J Alzheimers Dis Rep 2021;5:31-39.
30. Perel-Levin S. Stigma, dementia and age. World Alzheimer Report 2019: Attitudes to dementia 3.2, 2019;90-92.
31. Woo BK. Family history and its relationship with dementia stigma beliefs among Chinese Americans. Geriatr Gerontol Int 2017;17:122-125.
32. World Alzheimer Report 2019, Attitudes to dementia https://www.alzheimer-waw.pl/wp-content/uploads/2019/09/World-Alzheimer-Report-2019-
33. Ibanez A, Flichtentrei D, Hesse E, Dottori M, Tomio A, Slachevsky A, Serrano CM, Gonzalez-Billaut C, Custodio N, Miranda C, Bustin J, Cetckovitch M, Torrente F, Olavarria L, Leon T, Beber BC, Bruki S, Suemoto CK, Nitrini R, Miller BL, Yokoyama JS. The power of knowledge about dementia in Latin America across health professionals working on aging. Alzheimers Dement (Amst) 2020;12:e12117.

ORIGINAL RESEARCH

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Evaluation of Polypharmacy and Potentially Inappropriate Medication Use in Older Adults with Dementia Using the TIME Criteria

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Abstract

Objective: Polypharmacy and potentially inappropriate medication (PIM) are well-known risk factors for several negative health outcomes. However, polypharmacy, undertreatment, and PIMs in Turkish patients with dementia are not well-described. This study aimed to examine and compare the prevalence of polypharmacy, potential prescription omissions (PPOs), and PIMs in older adults with and without dementia in a nationwide population.

Materials and Methods: This study retrospectively evaluated the older patients (aged ≥65 years) who were admitted to the outpatient clinic of a university hospital. Patients were classified as dementia and no-dementia according to the International Classification of Diseases codes, mini-mental state examination score, clinical dementia rating scores, and clinical history. Polypharmacy, PIM, and PPO rates were compared among patients with and without dementia. The Turkish Inappropriate Medication Use in the Elderly criteria was used to define PIMs and PPOs.

Results: This study analyzed a total of 265 patients, wherein 21.5% of patients had at least one PIM and 20% had at least one PPO. Patients with dementia were more frequently exposed to polypharmacy (dementia: 51.9% vs. no-dementia: 48.1%, p<0.001) and likewise PPOs (dementia: 34.3% vs. no-dementia: 12.1%, p<0.001). Additionally, PPO prevalence increased with the severity of dementia. However, PIM prevalence was similar between patients with and without dementia (p=0.52).

Conclusion: Polypharmacy and PPOs were widespread in the older population and more in people with dementia.

Keywords: Dementia, inappropriate prescribing, older adults, polypharmacy, potentially inappropriate medication, Turkish, TIME criteria

Introduction

It is estimated that 55 million people are living with dementia, and there are nearly 10 million new cases worldwide every year (1). Dementia patients experience higher levels of comorbidities and may receive more medications than their cognitively intact counterparts (2). Prescribing for older people is a complex process where benefits of treatment must be weighed against the risks. In people with dementia, prescribing is further complicated by difficulties with communication, changing goals of care, and a high prevalence of multi-morbidity. Dementia patients may receive suboptimal care for diseases, as well as could be exposed to potentially inappropriate medications (PIMs) (3). Potentially inappropriate prescribing (PIP) has been associated with an increased risk of adverse drug events, hospitalization, mortality, and lower quality of life in older people with and without dementia (4,5).

Polypharmacy defined as the concurrent use of multiple (i.e., five or more) medications by a patient and it is common in dementia patients (6,7). Polypharmacy is not always means inappropriate but adds possible adverse side effects and lead potential drug interactions (8). Polypharmacy and PIMs could cause serious medical problems, increased hospitalizations, costs, falls and

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deaths (9-11). Herewith, several tools have been developed to identify PIMs and PPOs in older people for use in research and in clinical settings. Beers criteria and STOPP/START criteria are the most commonly used tools (12,13). Prescribing habits and locally available drugs may vary between countries. Recently, The Turkish Inappropriate Medication Use in the Elderly (TIME) criteria were created by national experts for screening PIPs in older adults (14). TIME criteria composed of 112 TIME to STOP and 41 TIME to START criteria (14). The TIME criteria have been developed primarily for use in Turkey and the Eastern European region. However, the validation study suggests that the TIME criteria set could be used in both central and Eastern European countries (15).

The higher number of co-morbidities and excess medications give tendency to PIMs use and adverse drug reactions in dementia patients. So, that could lead to increased risk of hospital admission, higher health care costs and mortality. However, few studies have focused on the appropriateness of prescribing, particularly in the presence of chronic conditions in dementia patients. The aims of the study were describing the prevalence of PIMs and PPOs, report the medications identified as inappropriate, and compared polypharmacy, PIMs, and PPOs rates between the patients with and without dementia.

Materials and Methods

Study population and Data collection

This was a single-center, retrospective, observational study at a tertiary hospital outpatient clinic. We included ≥65 years' old patients according to their first admission records, who were admitted at 2016-2020. The study included patients with and without dementia as control cases. Dementia patients were identified as individuals registered with dementia diagnosis on ICD-9 codes. Also, these patients' diagnosis was confirmed with medical history and/or imagining results. Severity of the dementia was determined according to clinical dementia rating (CDR) scale scores (16). We excluded the patients whom dementia diagnosis was suspicious. Also, individuals were excluded if they had missing medical history, laboratory results, drug name and doses or any data. Among the 24.512 patients admitted to the outpatient clinic between 2016-2020, 265 patient files were selected for statistical analysis as described above protocol (Figure 1). Demographic variables such as age, gender, marital status, body mass index, living condition were recorded. Chronic diseases, current diagnoses, medications were noted, and Charlson comorbidity index score was calculated for each person. Also, we recorded comprehensive geriatric assessment results and geriatric syndromes. Functional capacity was assessed by Katz basic activities of daily living (Katz ADL) and Lawton-Brody instrumental activities of daily living scales (17,18). Cognitive status was assessed by the Mini-Mental State

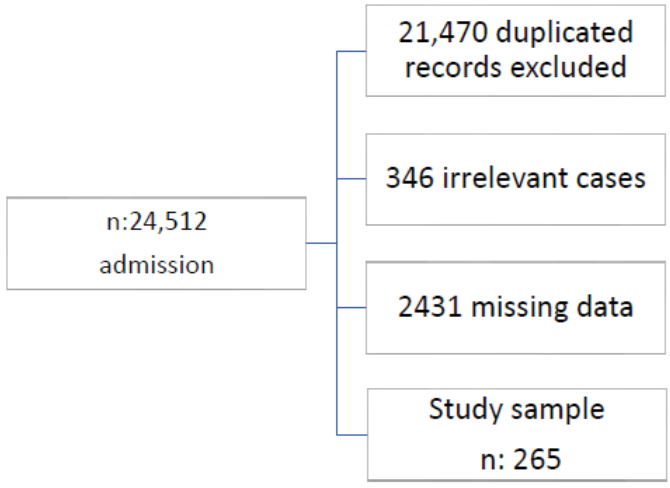

Figure 1. Study flowchart

Examination (MMSE) (19). Mood was evaluated by Yesavage Geriatric depression scale short-form (20). Nutritional status was evaluated by mini nutritional assessment short form which was validated in Turkish culture (21). The study protocol was approved by Local Ethics Committee.

Polypharmacy was defined as ≥5 drug usage (6). Total number of used drugs excluding topical agents was counted per patient. We used TIME to STOP and TIME to START criteria to define PIMs and PPOs (14). TIME criteria composed of 112 TIME to STOP and 41 TIME to START criteria. Due to the study protocol, we examined all patients' medications and doses according to TIME criteria. Person-based dichotomous variables were constructed indicating whether PIMs and PPOs, by matching the names and formulations of all medications taken by the subject with medications listed in the TIME criteria. Also, we recorded the drug formulations of PIMs and PPOs for the analysis.

Statistics

All statistical analyses were conducted using IBM SPSS 22. Descriptive statistics were shown as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for skew distributed variables, and percentages in case of categorical variables. Patients were divided and compared into two groups as dementia patients and no-dementia patients. Chi-square test was used to determine differences between categorical variables. The comparison of quantitative data was done by independent samples t-test for normal distributed variables and categorical data were compared by chi-square test. For non-normally distributed variables, Mann-Whitney U test were conducted for two groups and Kruskal-Wallis test were conducted to compare parameters for more than 2 groups. Also, Mann-Whitney U test was performed to test the significance of pair wise differences using Bonferroni correction to adjust for multiple comparisons. For the multivariate analysis, the possible factors identified with univariate analyses were further entered

into logistic regression analysis to determine independent correlates for dementia. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type-1 error level was used to infer statistical significance.

Results

Totally 265 patients were recruited for statistical analysis in this study. Mean age was 75.7±6.7 years and 64.5% were female. In the whole group 105 patients (39.3%) had dementia diagnosis; 18.5% had mild dementia, 14% had moderate dementia, and 6.8% had severe dementia according to CDR scores. Dementia patients were more likely to be older and to have lower ADL and IADL scores. Comorbidity rates were similar except depression and urinary incontinence between dementia patients and no-dementia patients. Polypharmacy was seen in 50.2%. According to TIME criteria, there were 57 (21.5%) patients had at least one PIM and 53 (20%) patients had at least one PPO in whole group. Demographic variables, comprehensive geriatric assessment results in the study population are summarized in Table 1.

Table 1. Characteristics of the study population

Properties		Total (n=265)	Normal cognitive functions (n=160)	Dementia (n=105)	p
Age, mean ± SD		75.7±6.7	73.8±6.2	78.7±6.3	<0.001
Gender, female n (%)		14 (53.8%)	109 (68.1%)	62 (59%)	0.13
Education, n (%)	Illiterate	75 (28.3%)	32 (30.8%)	43 (43.5%)	0.46
	<8 years	91 (34.4%)	51 (49%)	40 (40.8%)	
	8-11 years	14 (5.3%)	8 (7.7%)	6 (6.1%)	
	>11 years	22 (8.3%)	13 (12.5%)	9 (9.2%)	
Living status, n (%)	Alone	24 (9%)	18 (11.6%)	6 (5.8%)	0.13
	Non-alone	233 (87.9%)	136 (87.7%)	97 (93.3%)	
	Nursing home	8 (3.1%)	1 (0.6%)	1 (1%)	
Polypharmacy, n (%)		133 (50.2%)	64 (48.1%)	69 (51.9%)	<0.001
N of drug, median (IQR)		5 (4)	4 (4)	6 (3)	<0.001
Charlson comorbidity index score, median (IQR)		4 (2)	4(2)	5 (2)	<0.001
Co-morbidities, n (%)					
- Diabetes mellitus		96 (36.2%)	63 (39.4%)	33 (31.4%)	0.18
- Hypertension		196 (74%)	120 (75%)	76 (72.4%)	0.63
- Coronary artery disease		64 (24.1%)	39 (24.4%)	25 (23.8%)	0.91
- Congestive heart failure		18 (6.8%)	9 (5.6%)	9 (8.7%)	0.34
- Atrial fibrillation		28 (10.6%)	14 (8.8%)	14 (13.3%)	0.23
- COPD/Asthma		30 (11.3%)	20 (7.5%)	10 (3.8%)	0.55
- Chronic renal failure		11 (4.2%)	4 (2.5%)	7 (6.8%)	0.9
- Parkinsonism		9 (3.4%)	5 (3.1%)	4 (3.8%)	0.76
- Cerebrovascular accident		15 (5.8%)	7 (4.4%)	8 (7.6%)	0.26
- Depression		66 (25%)	25 (15.6%)	41 (39%)	<0.001
- Osteoporosis		76 (28.6%)	44 (28.2%)	32 (32.3%)	0.48
- Urinary incontinence		76 (28.6%)	25 (15.6%)	51 (48.6%)	<0.001
- Benign prostate hyperplasia		11 (4.2%)	4 (2.5%)	7 (15.8%)	0.22
Comprehensive geriatric assessment, median (IQR)					
- Katz ADL		6 (1)	6 (0)	5 (4)	<0.001
- Lawton-Brody IADL		7 (4)	8 (1)	3 (6)	<0.001
- MMSE		26 (10)	29 (3)	18 (10)	<0.001
- MNA-SF		13 (3)	14 (2)	12 (3)	<0.001
- Yesavage GDS-SF		2 (4)	1 (3)	2 (5)	0.11

Continuous variables with normal distribution were presented as mean (SD), and non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were given as numbers and percentages. ADL: Activities of daily living, COPD: Chronic obstructive pulmonary disease, GDS-SF: Geriatric depression scale-short form, IADL: Instrumental activities of daily living, MMSE: Mini mental state examination, MNA-SF: Mini nutritional assessment-short form

According to TIME to STOP criteria, there were 57 (21.5%) patients with at least one PIM. Moreover, according to TIME to START criteria, there were 53 (20%) patients with at least one PPO in whole group. The more common PIMs were proton pump inhibitors (PPI) in non-ulcer patients, non-steroidal anti-inflammatory drugs (NSAIDs) in hypertension or long-term osteoarthritis management, acetylsalicylic acid with no history of vascular disease or primary protection and prolonged usage of atypical antipsychotics. The more common affected systems from PIMs were gastrointestinal system (36%), central nervous systems (21%) and cardiovascular system (19%). The more common PPOs were oral nutritional supports (ONS) for malnutrition risked patients, vitamin D and calcium supplement in osteoporosis or osteomalacia, fiber and vitamin supplementation in necessary situations. Prevalence of frequently used PIMs and PPOs summarized in Table 2.

Comparing people with and with-out dementia, polypharmacy was more frequent in people with dementia (mild: 67.3%, moderate: 62.2%, severe: 72.2%) versus no-dementia (39.8%) (p<0.001). Moreover, number of used drugs was higher in dementia patients. Post-hoc analysis showed that the difference in number of used drugs was between CDR 0 vs 1-2-3 group (CDR 0 vs 1group, p=0.004; CDR 0 vs 2 group, p=0.006; CDR 0 vs 3 group, p=0.001). Figure 1 shows the number of drug usage stratified by dementia status according to CDR score. When we compare people with and without dementia, PIMs rates were similar in people with dementia and no-dementia (p=0.52). However, PPOs was more frequent in people with dementia versus no-dementia (p<0.001). Figure 2 shows number of used drugs stratified for dementia status. Figure 3 and Table 3 shows polypharmacy, PIMs and PPOs stratified by dementia status according to CDR score.

Moreover, a binary logistic regression analysis was performed to detect the possible parameters that affect dementia. Polypharmacy, TIME to STOP and TIME to START rates were put into the equation for logistic regression analysis. Logistic regression analysis demonstrated that polypharmacy was associated with greater odds of dementia status [relative ratio (RR): 3.32 95% confidence interval (CI): 1.88-5.87, p<0.001]. Also, logistic regression analysis demonstrated that TIME to STOP and TIME to START rates were associated with dementia status (TIME to stop RR: 0.48, 95% CI: 0.24-0.97, p=0.04, TIME to START RR: 3.79, 95% CI: 1.95-7.32, p<0.001).

Discussion

To our knowledge, this is the first study to examine polypharmacy, PIMs, and PPOs among dementia and no- dementia patients with TIME criteria. Both were widespread in the older population, but significantly more in people with dementia where almost half of them were exposed to polypharmacy and quarter to

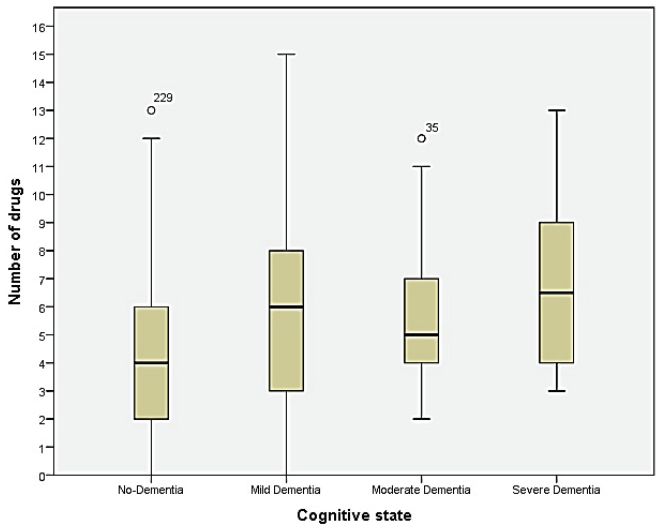

Figure 2. Number of used drugs stratified for dementia status

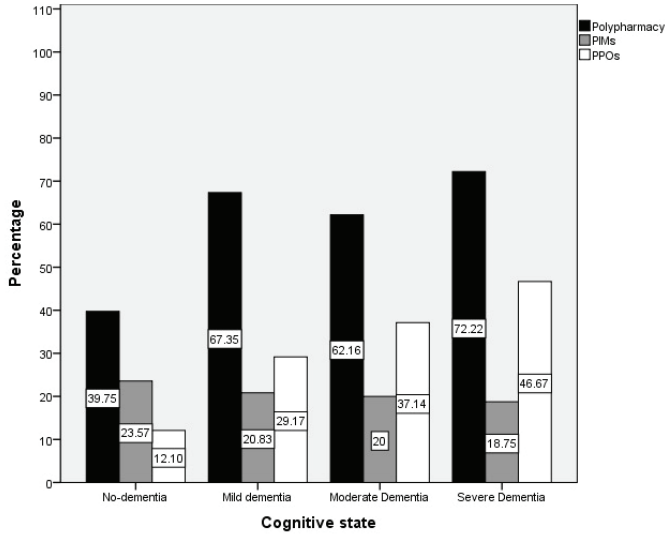

Figure 3. Polypharmacy, PIMs, and PPOs rates according to TIME criteria

PIM: Potentially inappropriate medication, PPOs: Potential prescription omissions

PIM as defined by the TIME criteria. Interestingly, although polypharmacy rate was higher, the frequency of PPOs was also higher in dementia patients. Additionally, PPOs were more widespread in severe stage people with dementia.

Polypharmacy is a common problem in the geriatric population, lead to increase the risk of drug-drug interaction, adverse drug events, and could cause serious medical problems such as hospitalization, increase risk of falls and death. In our study, polypharmacy was more frequent among dementia patients than no-dementia (51.9% versus 48.1%). Other studies using the same definition of polypharmacy have found a comparable, albeit slightly higher, prevalence of 63-69% in Turkish population (22,23). However, these studies were focused on

community dwelling older people or hospitalized patients. A study from Turkey, Bahat et al. (24) reported that polypharmacy rate was 52.5% in a geriatric outpatient clinic. Our results were consistent with similar settings. This study showed that polypharmacy rate was 51.9% in dementia patients. There is a limited information in the literature about polypharmacy rate in Turkish dementia patients. In a recent study from Turkey reported that polypharmacy rate was >65% in Alzheimer dementia patients (25). Other studies from different countries reported that polypharmacy prevalence was 33.5-52.0% in community-dwelling people with dementia (26-28). Our results were similar with the literature.

Gender, education status, chronic diseases frequencies were similar between dementia and no-dementia patients, except depression and urinary incontinence. Charlson comorbidity index score was higher in dementia patients, but that 1-point score difference is due to the dementia disease itself. This study showed that median number of the used drug was higher in dementia patients. We could consider this result as the necessity of the treatment for depression and dementia. Although, the number of the used drug is high in dementia patients, similarity of PIMs ratio, supports our opinion.

Nowadays, adverse drug reactions in older persons and PIMs represent a serious and escalating problem in public health. The explicit and updated screening tools are needed, within this background several criteria have been developed to estimate the appropriateness of some drug. The classification system for medications and their use might differs by countries. Consequently, TIME criteria had been developed for all types of clinical settings in Turkey and validated for European countries (14,15). The PIM prevalence was detected as 21.5% in the whole group and there was no statistically significant difference between no-dementia and dementia patients (23.6% vs 20% respectively) in the present study. Recent trials in Turkey showed significantly high documented PIMs prevalence as 33.3-41.2% detected by START/STOPP and Beer's criteria in older patients (23,24). The prevalence of PIMs among individuals with cognitive impairment or dementia ranged from 10.2-56.4% (28). The PIMs rates that we reported in dementia patients are in the range of other studies in the literature. However, general study population PIMs rates was different from the literature. These results might be related with the study population, screening tool difference or due to the medical trainee. A group of patients admitted after consultation, as well as patients who were followed up in another clinic. This group of patients' medications may have been adjusted before admission to geriatric outpatient clinic. Moreover, the presented study was conducted in a university hospital where provides geriatric education. Due to the trainings

Table 2. Prevalence of frequently used PIMs and PPOs in the TIME criteria list

		No-dementia (n=160)	Dementia (n=105)
PIMs (TIME to STOP)		(n)	(n)
Proton pump inhibitors		16	6
NSAIDs		8	0
Antipsychotic drugs	Aripiprazole	0	1
	Clonazepam	0	1
	Quetiapine	0	4
Acetylsalicylic acid		5	3
ß blocker		4	0
HMG-CoA inhibitors		2	0
Betahistine		2	3
Piracetam		1	2
Nitrazepam		0	1
Gingko biloba		2	0
Theophylline		0	1
PPOs (TIME to START)			
Oral nutritional support		4	18
Calcium supplement		1	3
Vitamin D		8	8
Vitamin B12		3	1
Depression treatment		3	1
HMG-CoA inhibitors		3	0
Proton pump inhibitors		3	3
Diet fiber		1	2

PIM: Potentially inappropriate medication, PPOs: Potential prescription omissions, NSAID: Non-steroidal anti-inflammatory drugs

Table 3. Cognitive state and polypharmacy, PIMs, and PPOs prevalence according to TIME criteria

	Normal cognitive function (CDR-0)	Dementia CDR-1	Dementia CDR-2	Dementia CDR-3	p
Polypharmacy, n (%)	64 (39.8%)	33 (67.3%)	23 (62.2%)	13 (72.2%)	<0.001
N of drugs, median (IQR)	4 (4)	6 (5)	5 (3)	7 (5)	<0.001
TIME to START, n (%)	19 (12.1%)	14 (29.2%)	13 (37.1%)	7 (46.7%)	<0.001
TIME to STOP, n (%)	37 (23.6%)	10 (20.8%)	7 (20.0%)	3 (18.8%)	0.52

Non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were given as numbers and percentages, PIM: Potentially inappropriate medication, PPOs: Potential prescription omissions

or increased awareness about polypharmacy and PIMs usage could lead to this result. Otherwise, this study showed that most common PIMs were proton pump inhibitors, NSAIDs and acetylsalicylic acid for primary prevention, similar with previous studies (23,24).

Although, several pharmacological therapies are safe in older adults, under-prescription is widespread as ranging from 22-70% (29). However, there is limited evidence of PPOs for dementia patients in the literature, Lombardi et al. (29) showed that dementia is a risk for under prescription. In our study, PPOs was more frequent among dementia patients than no-dementia (34.3% versus 12.1%). Moreover, prevalence of PPOs and lack of oral nutritional supplementation increased with the severity of dementia. This study showed that, oral nutritional supplementation and vitamin D support was the most common PPOs. Studies in the literature have shown that the most common PPOs included calcium-vitamin D supplementation, cardiovascular medications, HMG CoA inhibitors and acetylsalicylic acid (23,29). Our results were similar with the literature. Multi-morbidity, frailty, dementia, living in an institutional setting are related with under treatment. Due to the decreased life expectancy, careful evaluation is important for decision making and treatment goals. However, beneficial effect of preventive treatments should not underestimate in older people. The most important message of this study is that we should suggest oral nutritional supplement and vitamin D for older patients in necessary situations. The diagnosis of dementia should not inhibit us to start preventive or necessary treatments.

Strengths of the current study includes sample size, comparison of dementia and no-dementia patients and using national tools for PIMs and PPOs evaluation. The limitations of this study could be mentioned. The study design was retrospective, and it is not possible to detect causal relationships. Furthermore, a group of patients' medications might be revised in other follow-up clinics before admission to geriatric clinic. This may lead to the fact that we reported different results from the literature. Depression was more common in dementia patients. However, geriatric depression scale scores were lower in dementia patients. This could be due to the communication problems in moderate and severe stages of dementia. Further researches about the effect of polypharmacy and PIM on the general health of older people with and without dementia will guide clinicians in prescription. More details on the causal relationship need to be determined through longitudinal research and interventional research in the future.

Conclusion

Optimal drug treatment for older dementia patients is complex and might lead to inappropriate drug usage or under treatment. Although polypharmacy has been related with concrete adverse outcomes as mortality and morbidity in people with dementia, inappropriate drug usage in older adults could decrease with recently developed national guides and increasing awareness. Despite these encouraging findings, clinicians should remember to provide appropriate and preventive treatments such as nutritional support in necessary situations for older adults.

Ethics

Ethics Committee Approval: The study protocol was approved by Local Ethics Committee (GO 21/755 2021/13-02).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Global Action Plan on the Public Health Response to Dementia 2017-2025 Alzheimer's Disease International. WHO.
2. Andersen F, Viitanen M, Halvorsen DS, Straume B, Engstad TA. Co-morbidity and drug treatment in Alzheimer's disease. A cross sectional study of participants in the dementia study in northern Norway. BMC Geriatr 2011;11:58.
3. Parsons C, Johnston S, Mathie E, Baron N, Machen I, Amador S, Goodman C. Potentially inappropriate prescribing in older people with dementia in care homes: a retrospective analysis. Drugs Aging 2012;29:143-155.
4. Dedhiya SD, Hancock E, Craig BA, Doebbeling CC, Thomas J. Incident use and outcomes associated with potentially inappropriate medication use in older adults. Am J Geriatr Pharmacother 2010;8:562-570.
5. Delgado J, Bowman K, Clare L. Potentially inappropriate prescribing in dementia: a state-of-the-art review since 2007. BMJ Open 2020;10:e029172.
6. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017;17:230.
7. Hukins D, Macleod U, Boland JW. Identifying potentially inappropriate prescribing in older people with dementia: a systematic review. Eur J Clin Pharmacol 2019;75:467-481.
8. Jetha S. Polypharmacy, the Elderly, and Deprescribing. Consult Pharm 2015;30:527-532.
9. Mueller C, Molokhia M, Perera G, Veronese N, Stubbs B, Shetty H, Codling D, Huntley J, Stewart R. Polypharmacy in people with dementia: Associations with adverse health outcomes. Exp Gerontol 2018;106:240-245.
10. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. Br J Clin Pharmacol 2010;69:543-552.
11. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2: Age Ageing 2014;44:213-8.

12. Bahat G, Ilhan B, Erdogan T, et al. Turkish inappropriate medication uses in the elderly (TIME) criteria to improve prescribing in older adults: TIME to STOP/TIME to START. Eur Geriatr Med.2020;113:491-498.
13. Bahat G, Ilhan B, Erdogan T, Halil M, Savas S, Ulger Z, Akyuz F, Bilge AK, Cakir S, Demirkan K, Erelel M, Guler K, Hanagasi H, Izgi B, Kadioglu A, Karan A, Kulaksizoglu IB, Mert A, Ozturk S, Satman I, Sever MS, Tukek T, Uresin Y, Yalcin O, Yesilot N, Oren MM, Karan MA. Turkish inappropriate medication use in the elderly (TIME) criteria to improve prescribing in older adults: TIME-to-STOP/TIME-to-START. Eur Geriatr Med 2020;11:491-498.
14. Bahat G, Ilhan B, Erdogan T, Oren MM, Karan MA, Burkhardt H, Denkinger M, Garfinkel D, Cruz-Jentoft AJ, Morrissey Y, Onder G, Pazan F, Tommelein E, Topinkova E, van der Velde N, Petrovic M. International Validation of the Turkish Inappropriate Medication Use in the Elderly (TIME) Criteria Set: A Delphi Panel Study. Drugs Aging 2021;38:513-521.
15. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-572.
16. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. the index of adl: a standardized measure of biological and psychosocial function. JAMA 1963;185:914-19.
17. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
19. Sheikh JI YJA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. . Aging Ment Health 1986;5:165-173.
20. Sarikaya D, Halil M, Kuyumcu ME, Kilic MK, Yesil Y, Kara O, Ozturk S, Gungor E, Karabulut E, Balam Yavuz B, Cankurtaran M, Ariogul S. Mini nutritional assessment test long and short form are valid screening tools in Turkish older adults. Arch Gerontol Geriatr 2015;61:56-60.
21. Sayın Z, Sancar M, Özen Y, Okuyan B. Polypharmacy, potentially inappropriate prescribing and medication complexity in Turkish older patients in the community pharmacy setting. Acta Clin Belg 2020:1-7.
22. Kara Ö, Arık G, Kızılarslanoglu MC, Kılıc MK, Varan HD, Sümer F, Esme M, Altıner S, Kuyumcu ME, Yesil Y, Yavuz BB, Cankurtaran M, Halil M. Potentially inappropriate prescribing according to the STOPP/START criteria for older adults. Aging Clin Exp Res 2016;28:761-768.
23. Bahat G, Bay I, Tufan A, Tufan F, Kilic C, Karan MA. Prevalence of potentially inappropriate prescribing among older adults: A comparison of the Beers 2012 and Screening Tool of Older Person's Prescriptions criteria version 2. Geriatr Gerontol Int 2017;17:1245-1251.
24. Özsürekci C, Arslan SS, Demir N, Çalışkan H, Şengül Ayçiçek G, Kılınç HE, Yaşaroğlu ÖF, Kızılarslanoğlu C, Tuna Doğrul R, Balcı C, Sümer F, Karaduman A, Yavuz BB, Cankurtaran M, Halil MG. Timing of Dysphagia Screening in Alzheimer's Dementia. JPEN J Parenter Enteral Nutr 2020;44:516-524.
25. Montastruc F, Gardette V, Cantet C, Piau A, Lapeyre-Mestre M, Vellas B, Montastruc JL, Andrieu S; REAL.FR Group. Potentially inappropriate medication use among patients with Alzheimer disease in the REAL. FR cohort: be aware of atropinic and benzodiazepine drugs! Eur J Clin Pharmacol 2018;69:1589-1597.
26. Oesterhus R, Aarsland D, Soennesyn H, Rongve A, Selbaek G, Kjosavik SR. Potentially inappropriate medications and drug-drug interactions in home-dwelling people with mild dementia. Int J Geriatr Psychiatry 2017;32:183-192.
27. Soysal P, Perera G, Isik AT, Onder G, Petrovic M, Cherubini A, Maggi S, Shetty H, Molokhia M, Smith L, Stubbs B, Stewart R, Veronese N, Mueller C. The relationship between polypharmacy and trajectories of cognitive decline in people with dementia: A large representative cohort study. Exp Gerontol 2019;120:62-67.
28. Johnell K. Inappropriate Drug Use in People with Cognitive Impairment and Dementia: A Systematic Review. Curr Clin Pharmacol 2015;10:178-184.
29. Lombardi F, Paoletti L, Carrieri B, Dell'Aquila G, Fedecostante M, Di Muzio M, Corsonello A, Lattanzio F, Cherubini A. Underprescription of medications in older adults: causes, consequences and solutions-a narrative review. Eur Geriatr Med 2021;12:453-462.

CASE REPORT

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A Case of Denosumab-associated Hyperparathyroidism: Differential Diagnosis Challenge

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Abstract

Denosumab is a relatively new medicine that has become the second option in the treatment of bisphosphonate-resistant or intolerant osteoporosis. An 85-year-old female patient was referred to the outpatient clinic of our department with a complaint of waist pain. She stated that her waist pain started 2 weeks before her visit and she had taken the fourth denosumab injection. Her laboratory results revealed normal serum calcium, phosphorus, and vitamin D levels (8.8 mg/dL, 3.1 mg/dL, and 32 ng/L, respectively) before denosumab injection. She had a sensitive point with pain on her lumbar vertebrae. Lower extremity movements were painful and muscle strength was bilaterally reduced. Vital signs and other systemic examinations were normal. Her laboratory tests for serum parathormone (PTH), calcium, phosphorus, and vitamin D levels showed 487 ng/L, 8.6 mg/dL, 0.6 mg/dL, and 30 ng/mL, respectively. She did not have any chronic renal and other bone metabolism diseases, except for osteoporosis. Her X-ray revealed a loss of height in L3 lumbar vertebrae. The spinal magnetic resonance indicated an acute fracture. However, we could not explain hyperparathyroidism in the absence of hypocalcemia and low vitamin D levels. Therefore, we started to investigate primary hyperparathyroidism in the patient. Neck ultrasonography did not show any associated abnormal findings with the parathyroid glands. Parathyroid scintigraphy resulted in normal parathyroid gland activity. During her follow-up, the PTH level decreased with time. Spontaneous regression of PTH led us to suspect an association between denosumab injection and hyperparathyroidism. Mazokopakis (1) reported a similar case in the literature in 2018, reporting a 62-year-old female patient with normal electrolytes and a high PTH level after three months of denosumab injection. The hypocalcemic effect of denosumab combined with inadequate oral calcium and vitamin D intake may have triggered exaggerated PTH secretion.

Keywords: Bone health in older people, clinical geriatrics, denosumab, drugs and aging, geriatrics, osteoporosis

Introduction

Denosumab is a relatively new medicine that has become the second option in the treatment of biphosphonate-resistant or intolerant osteoporosis. Subcutaneous injection with 6-month intervals, approval of its usage in stage 3-4 CKD and not having gastrointestinal side effects are advantages of denosumab. However, it has some disadvantages like requiring monitoring serum levels of calcium and vitamin D before each injection.

Case Report

An 85-year-old female was referred with waist pain to the outpatient clinic of our department. She told that the pain started about 3 weeks ago while she was sitting in the chair. During the last 3 weeks, the pain existed and it was relieved with lying on the bed, aggravated with movement. She needed paracetamol 3 times a day and ibuprofen 2 times a day to alleviate the pain. She said that 2 weeks before the waist pain started, she had had the fourth denosumab injection. When we checked laboratory results history, we found normal serum calcium, phosphorus, and vitamin D levels (8.8 mg/dL, 3.1 mg/dL, 32 ng/L respectively) before denosumab injection. After the injection, she did not apply to the clinic. In her physical examination, she came to the examination room with a wheelchair. She had a sensitive point with pain on her lumbar vertebrae. Lower extremity movements were painful and muscle strength was reduced bilaterally. Vital signs and other systemic examinations were normal. On her laboratory tests serum parathormone (PTH), calcium, phosphorus, vitamin D levels were 487 ng/L, 8.6 mg/dL, 0.6 mg/dL, 30 ng/mL respectively. She did

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not have a chronic renal disease and another bone metabolism disease except for osteoporosis. Her X-ray revealed a height loss in L3 lumbar vertebrae. Spinal magnetic resonance indicated that it was an acute fracture. However, we could not explain hyperparathyroidism in the absence of hypocalcemia and low vitamin D levels. Thus, we started to investigate primary hyperparathyroidism in the patient. Neck ultrasonography did not show any abnormal findings associated with parathyroid glands. Parathyroid scintigraphy resulted with normal activity in parathyroid glands. During her follow-up, the PTH level reduced with time. The challenging point for us was that the patient had normal serum calcium and vitamin D level with normal renal function.

Discussion

In the literature, Mazokopakis (1) first reported a similar case in 2018, a 62-year-old woman with normal electrolytes and high PTH level after 3 months of denosumab injection. In a cohort of 60 patients with metastatic prostate cancer who received at least one dose of denosumab (120 mg), 42 patients (70%) developed hypocalcemia, seven (11.6%) developed high-grade hypocalcemia, and nine (15%) required hospitalization for intravenous calcium supplementation (2). In our case, although the patient's baseline serum calcium, phosphorus and vitamin D levels were normal, the levels were close to the lowest threshold for all markers. Her risk for malnutrition was high and she was not eager to take oral nutritional supplements. Together with inadequate oral calcium and vitamin D intake, hypocalcemic effect of denosumab might have triggered exaggerated PTH secretion. Previous literature suggests that hypocalcemic effects of denosumab starts after the injection, reaches the nadir level on 17th day and resolves spontaneously on the 25th day (3). In this case, her serum calcium and vitamin D levels were normal before denosumab injection. Five weeks after the denosumab injection, on her presentation with osteoporotic vertebral fracture, laboratory tests revealed normal serum calcium and vitamin D levels again. Probably, bone fracture and transient hypocalcemic period which we could not detect during the 5-week period contributed together for hyperparathyroidism.

Conclusion

In conclusion, physicians should take into consideration that high PTH levels might be associated with denosumab therapy if the possibility of primary hyperparathyroidism is eliminated by neck ultrasonography and parathyroid gland scintigraphy. Close following-up the patient and replacing inadequate or near inadequate levels of serum calcium and vitamin D are key factors for preventing denosumab- associated hyperparathyroidism. It should be kept in mind that PTH level may stay at high levels although serum calcium and vitamin D levels return to normal, especially when it exists together with acute bone fracture. Denosumab-associated hyperparathyroidism can spontaneously recover in 2 to 3 months if the patient takes adequate calcium and vitamin D. When clinicians encounter such a clinical course, replacing calcium and vitamin D, close monitoring and eliminating other possible causes of primary or secondary hyperparathyroidism are essential.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.F.S., S.F.A., Concept: S.Ş., Design: Z.F.S., S.F.A., Data Collection or Processing: E.T., Analysis or Interpretation: S.Ş., Z.F.S., S.F.A., Literature Search: E.S.S., S.F.A., Writing: E.T., E.S.S., S.F.A.

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

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References

1. Mazokopakis EE. Denosumab-induced Normocalcemic Hyperparathyroidism in a Woman with Postmenopausal Osteoporosis and Normal Renal Function. Curr Drug Saf 2018;13:214-216.
2. Autio KA, Farooki A, Glezerman IG, Chan A, Schneider CW, Barr HC, Seyboth BM, Kampel LJ, Danila DC, Rathkopf DE, Slovin SF, Scher HI, Morris MJ. Severe Hypocalcemia Associated With Denosumab in Metastatic Castration-Resistant Prostate Cancer: Risk Factors and Precautions for Treating Physicians. Clin Genitourin Cancer 2015;13:e305-e309.
3. Muqeet Adnan M, Bhutta U, Iqbal T, AbdulMujeeb S, Haragsim L, Amer S. Severe Hypocalcemia due to Denosumab in Metastatic Prostate Cancer. Case Rep Nephrol 2014;2014:565393.