EJGG
European Journal of Geriatrics and Gerontology

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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
Clinical Geropsychology
Cognitive Disorders
Demography of Older Populations
Dental and Oral Health
Delirium
Diabetes Mellitus
Dizziness
Disability
Drugs & Aging
Experimental Gerontology
Economics of ageing
Falls
Frailty
Geriatrics
Geriatric Bioscience
Geriatric Care Management
Geriatric Depression
Geriatric Emergency Medicine
Geriatric Gynecology
Geriatric Occupational Therapy
Geriatric Ophthalmology
Geriatric Otolaryngology

Geriatric Pain Management
Geriatric Palliative Care
Geriatric Pharmacotherapy
Geriatric Physical Therapy
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Geriatric Psychology
Geriatric Rheumatology
Geriatric Trauma
Geriatric Urology
Geriatric Nursing
Geriatric Syndromes
Gerontechnology
Hypertension
Healthy Aging
Home and Community-Based Services
Incontinence
Long-Term Care
Orthogeriatrics
Polypharmacy
Parkinsons Disease
Parkinsonian syndromes
Pressure Sores
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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Submission is considered on the conditions that papers are previously unpublished and are not offered simultaneously elsewhere; that authors have read and approved the content, and all authors have also declared all competing interests; and that the work complies with the Ethical Approval and has been conducted under internationally accepted ethical standards. If ethical misconduct is suspected, the Editorial Board will act in accordance with the relevant international rules of publication ethics (i.e., COPE guidelines).

Editorial policies of the journal are conducted as stated in the rules recommended by the Council of Science Editors and reflected in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/). Accordingly, authors, reviewers, and editors are expected to adhere to the best practice guidelines on ethical behavior contained in this statement.

Submitted manuscripts are subjected to double-blinded peer-review. The scientific board guiding the selection of the papers to be published in the journal consists of elected specialists of the journal and, if necessary, selected from national and international experts in the relevant field of research. All manuscripts are reviewed by the editor, section associate editors and at least three internal and external expert reviewers. All research articles are interpreted by a statistical editor as well.

Human and Animal Rights

For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 201, www.wma.net) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals, www.nap.edu.catalog/5140. html), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the European Journal of Geriatrics and Gerontology together with the manuscript.

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Data Manipulation/Falsification: Manipulating or deliberately distorting research data to give a false impression.

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The authors who want to submit their study to the journal must ensure that their study is entirely original. The words and sentences getting from the literature should be appropriately cited.

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If one of the editors is an author in any manuscript, the editor is excluded from the manuscript evaluation process. In order to prevent any conflict of interest, the article evaluation process is carried out as double-blinded. Because of the double-blinded evaluation process, except for the Editor-in-Chief, none of the editorial board members, international advisory board members, or reviewers is informed about the authors of the manuscript or institutions of the authors.

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INSTRUCTIONS FOR AUTHORS

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;

Special features include rapid communication of important timely issues,

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Geriatric Urology
Geriatric Nursing
Geriatric Syndromes
Gerontechnology
Hypertension
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Incontinence
Long-Term Care
Orthogeriatrics
Polypharmacy
Parkinsons Disease
Parkinsonian syndromes
Pressure Sores
Psychological Gerontology
Sarcopenia
Sleep Disorders
Syncope
Social Gerontology
Stroke Medicine

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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.

As a peer-reviewed journal that is independent, impartial and in compliance with the principles of double-blinded peer review, after checking the compliance of the submitted manuscript with the writing rules and plagiarism control, all articles are reviewed by the editor-in-chief, section editor, at least two reviewers, and statistic editor. All evaluation process except Editor-in-Chief is done double-blinded. After all these processes are completed, the Editor-in-Chief decides whether to publish or reject the article. In the final stage, the plagiarism review is repeated once more

Following receiving each manuscript, a checklist is completed by the Editorial Assistant. The Editorial Assistant checks that each manuscript contains all required components and adheres to the author guidelines, after which time it will be forwarded to the Editor in Chief. Following the Editor in Chief's evaluation, each manuscript is forwarded to the Associate Editor, who assigns reviewers. Generally, all manuscripts will be reviewed by at least two reviewers selected by the Associate Editor, based on their relevant expertise. An associate editor could be assigned as a reviewer along with the reviewers. After the reviewing process, all manuscripts are evaluated in the Editorial Board Meeting.

European Journal of Geriatrics and Gerontology's editor and Editorial Board members are active researchers. It is possible that they would desire to submit their manuscript to European Journal of Geriatrics and Gerontology. This may be creating a conflict of interest. These manuscripts will not be evaluated by the submitting editor(s). The review process will be managed and decisions made by the editor-in-chief, who will act independently. In some situations, this process will be overseen by an outside independent expert in reviewing submissions from editors.

Preparation of Manuscript

Manuscripts should be prepared according to ICMJE guidelines (http://www.icmje.org).

Original manuscripts require a structured abstract. Label each section of the structured abstract with the appropriate subheading (Objective, Materials and Methods, Results, and Conclusion). Case reports require short unstructured abstracts. Letters to the editor do not require an abstract. Research or project support should be acknowledged as a footnote on the title page.

Technical and other assistance should be provided on the title page.

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Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

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).

Title Page

Title: The title should provide important information regarding the manuscript's content.

The title page should include the authors' names, degrees, institutional/professional affiliations, a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to their institution, listed separately. Please provide contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

Running Head: The running head should not be more than 40 characters, including spaces, and should be located at the bottom of the title page.

Word Count: A word count for the manuscript, excluding abstract, acknowledgements, figure and table legends, and references, should be provided, not exceeding 3000 words. The word count for an abstract should not exceed 250 words.

Conflict of Interest Statement: This statement must be included in each manuscript to prevent potential conflicts of interest from being overlooked. In case of conflicts of interest, every author should complete the ICMJE general declaration form, which can be obtained at: http://www.icmje.org/coi_disclosure.pdf.

Abstract and Keywords: The second page should include an abstract that does not exceed 250 words. Moreover, as various electronic databases integrate only abstracts into their index, significant findings should be presented in the abstract.

Abstract

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.

Conclusion: The study's new and important findings should be highlighted and interpreted.

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).

Original Articles

Original articles should have the following sections;

Introduction: The introduction should include an overview of the relevant literature presented in summary form (one page), and whatever remains engaging, unique, problematic, relevant, or unknown about the topic must be specified. The introduction should conclude with the rationale for the study, its design, and its objective(s).

Materials and Methods: Clearly describe the selection of observational or experimental participants, such as patients, laboratory animals, and controls, including inclusion and exclusion criteria and a description of the source population. Identify the methods and procedures in sufficient detail to allow other researchers to reproduce your results. Provide references to established methods (including statistical methods), provide references to brief modified methods, and provide the rationale for using them and an evaluation of their limitations. Identify all drugs and chemicals used, including generic names, doses, and routes of administration. The section should include only available information when the plan or protocol for the study was devised on STROBE (http://www.strobe-statement.org).

Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Statistically essential data should be given in the text, tables and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

Results: Present your results in logical sequence in the text, tables, and figures. Do not present all the data provided in the tables and/or figures in the text; emphasize and/or summarize only essential findings, results, and observations in the text. Clinical studies provide the number of samples, cases, and controls included in the study. Discrepancies between the planned number and obtained number of participants should be explained. Comparisons and statistically significant values (i.e. p-value and confidence interval) should be provided.

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Academic Geriatrics Society

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Discussion: This section should include a discussion of the data. New and noteworthy findings/results and the conclusions they lead to should be emphasized. Link the conclusions with the study's goals, but avoid unqualified statements and conclusions not completely supported by the data. Do not repeat the findings/results in detail; important findings/results should be compared with those of similar studies in the literature, along with a summarization. In other words, similarities or differences in the obtained findings/results with those previously reported should be discussed.

Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

References

Cite references in the text, tables, and figures with numbers in parentheses. Number references consecutively according to the order they first appear in the text. Journal titles should be abbreviated according to the style used in Index Medicus (consult List of Journals Indexed in Index Medicus). Include among the references any paper accepted but not yet published, designating the journal and followed by, in press. Authors are solely responsible for the accuracy of all references.

Examples of References:

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.

Case Reports

Case reports should be structured as follows:

Abstract: An unstructured abstract that summarizes the case.

Introduction: A brief introduction (recommended length: 1-2 paragraphs).

Case Presentation: This section describes the case in detail, including the initial diagnosis and outcome.

Discussion: This section should include a brief review of the relevant literature and how the presented case furthers our understanding of the disease process.

Review Articles

Review articles should not include more than 100 references. Reviews should include a conclusion in which a new hypothesis or study about the subject may be posited. Do not publish methods for literature search or level of evidence. Authors who will prepare review articles should already have published research articles on the relevant subject. There should be a maximum of two authors for review articles.

Images in Geriatrics and Gerontology

Authors can submit for consideration an illustration and photos that are interesting, instructive, and visually attractive, along with a few lines of explanatory text and references. Images in Geriatrics and Gerontology can include no more than 500 words of text, 5 references, and 3 figures or tables. No abstract, discussion or conclusion is required, but please include a brief title.

Letters to the Editor

Letters can include no more than 500 words of text, 5-10 references, and 1 figure or table. No abstract is required, but please include a brief title.

Invited Review Article: Invited review articles are comprehensive analyses of specific topics in medicine, written upon invitation due to extensive experience and publications of authors on their view subjects. All invited review articles will also undergo peer review before acceptance.

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Academic Geriatrics Society

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Instructions for Authors

Tables, Graphics, Figures, and Images

Tables: Supply each table on a separate file. Number tables according to the order in which they appear in the text, and supply a brief caption for each. Give each column a short or abbreviated heading. Write explanatory statistical measures of variation, such as standard deviation or standard error of the mean. Be sure that each table is cited in the text.

Figures: Figures should be professionally drawn and/or photographed. Authors should identify number figures according to the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend that does not exceed 50 words. Use abbreviations only if they have been introduced in the text. Authors are also required to provide the level of magnification for histological slides. Explain the internal scale and identify the staining method used. Figures should be submitted as separate files, not in the text file. High-resolution image files are not preferred for initial submission as the file sizes may be too large. The total file size of the PDF for peer review should not exceed 5 MB.

Article Type	Abstract (words)	Document (words)		
(excluding references)	References	Total	Tables and Figures	
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Review Articles	300	3500	75	5
Invited Review Article	300	3500	75	5
Case Reports	100	1000	15	2
Images	None	500	10	2
Letters to the Editor	None	600	10	1
Editorial Comment	None	1500	20	2

Authorship

Each author should have participated sufficiently in work to assume public responsibility for the content. Any portion of a manuscript that is critical to its main conclusions must be the responsibility of at least 1 author.

Contributor's Statement

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Acknowledgments

Acknowledge support received from individuals, organizations, grants, corporations, and other sources. For work involving a biomedical product or potential product partially or wholly supported by corporate funding, a note stating, "This study was financially supported (in part) with funds provided by (company name) to (authors' initials)" must be included. Grant support, if received, needs to be stated, and the specific granting institutions' names and grant numbers provided when applicable.

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CONTENTS

ORIGINAL RESEARCH

Association of Primary Sarcopenia with Serum MMP2, TIMP2 Levels, and MMP2/TIMP2 Ratio

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Abstract

Objective: Our aim is to evaluate the association of serum matrix metalloproteinase (MMP2), tissue inhibitor of metalloproteinase (TIMP2) levels, MMP2/TIMP2 ratio, SARC-F with primary sarcopenia, and to investigate the coexistence of primary sarcopenia and osteoporosis in geriatric population.

Materials and Methods: A total of 80 geriatric patients (41 sarcopenic patients) were included in the study. Patients with secondary sarcopenia were excluded. By SARC-F questionnaire, patients who were at risk for sarcopenia were found as mentioned by EWGSOP2. Serum MMP2 and TIMP2 levels were analyzed by ELISA method. Dual energy X-ray absorptiometry (DEXA) was used for the diagnosis of osteoporosis.

Results: The SARC-F score of the sarcopenia group was statistically significantly higher and the incidence of osteoporosis was higher in this group than the group without sarcopenia (p<0.001, p=0.006, respectively). There was no significant difference between the sarcopenic and non-sarcopenic groups in terms of gender, age, serum MMP2, TIMP2 and MMP2/TIMP2 ratio (p=0.959, p=0.182, p=0.366, p=0.225, p=0.641 respectively). In the multivariate regression analysis it was determined that SARC-F and osteoporosis had a significant effect on sarcopenia [p<0.001, odds ratio (OR) (95%) confidence interval (CI) 1.735 (1.292–2.330); p=0.006, OR (95%) CI 4.976 (1.590-15.572) respectively]. The area under ROC curve (AUC) of SARC-F and MMP2/TIMP2 ratio was 0.771 and 0.530 (p<0.001, 95% CI 0.665-0.877; p=0.641, %95 CI 0.403-0.658, respectively). Sensitivity and specificity for SARC-F score ≥4 were 58.5% and 87.2%, respectively.

Conclusion: Our study supports the usage of SARC-F in finding of primary sarcopenia cases. We have revealed that serum MMP2, TIMP2 level and MMP2/TIMP2 ratio are not suitable markers for diagnosing sarcopenia. Since the coexistence of osteoporosis and sarcopenia is common in the elderly, they should be considered together.

Keywords: Sarcopenia, MMP2, TIMP2, SARC-F, osteoporosis

Introduction

Sarcopenia is a complex and multifactorial disease characterized with a decrease in muscle mass and muscle strength, that causes decreased mobility, increased risk of falling, decreased quality of life and ultimately increased mortality (1,2). Sarcopenia is defined as a decrease in skeletal muscle mass as well as decreased muscle strength or poor muscle performance. While age-related sarcopenia without a specific cause is called primary sarcopenia, sarcopenia that develops in the presence of a significant factor other than aging or in addition to aging is called secondary sarcopenia (3). In line with the recommendations of EWGSOP2, the SARC-F questionnaire is applied to individuals at risk for sarcopenia, and those with high (≥4) scores are considered to be at risk for sarcopenia (4). Osteoporosis is a common disease that causes an increased risk of fracture as a result of decreased bone mass and deterioration in microarchitecture. Both sarcopenia and osteoporosis are associated with morbidity, and there are studies suggesting a relationship between these two diseases. There are studies reporting that osteoporosis and sarcopenia

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come from common genetics (5). According to the mechanostat hypothesis expressing that muscle and bone affect each other, muscle contraction is thought to stimulate bone osteogenesis with a mechanical effect (6).

Matrix metalloproteinases (MMPs) are proteases that are responsible for the degradation of extracellular matrix proteins and play a role in many biological and physiological processes such as organogenesis, growth and tissue regeneration. Although the release and activation of MMPs from healthy adult tissue is limited, their levels increase in pathologies that cause tissue destruction (7). The activity of MMPs is regulated in tissue by ''Tissue inhibitors of metalloproteinases (TIMPs)''. TIMPs maintain homeostasis and tissue integrity by controlling MMP enzyme activity and MMP/TIMP balance. The shift of this balance in the direction of MMP activity causes the destruction of the matrix and the occurrence of pathophysiological events. TIMPs show specificity according to MMP species, and MMP-2 is inhibited by TIMP-2 (8).

As for the effects of MMPs on muscle tissue, MMPs break down the extracellular matrix in skeletal muscle, regulate migration, differentiation and regeneration of muscle cells and thus play an important role in the homeostasis of myofibers (9). Studies have clearly demonstrated the importance of MMP2 in myoblast migration and fusion (10,11). With the discovery of this, the role of MMP2, its inhibitor TIMP2 and the balance between them in muscle diseases began to be investigated.

Although many methods are used for the diagnosis of sarcopenia, a practical method has not been found yet. In this study, our aim is to investigate the usability of serum MMP2, TIMP2 level and MMP2/TIMP2 ratio as a markers for diagnosis in addition to the diagnostic methods we use for sarcopenia and to evaluate the relationship between sarcopenia and osteoporosis.

Materials and Methods

Population and setting

Forty-one sarcopenic patients followed up our geriatric outpatient clinic (female 25/male 16) and thirty nine control patients (female 24/male 15) were recruited for this study. In addition, chronic diseases and geriatric syndromes of individuals with sarcopenia were documented and matched with control group patients. Patients with probable secondary sarcopenia (being bed bound, advanced organ failure, malignancy, protein-energy malnutrition, HIV infection, chronic inflammatory disease, rheumatoid arthritis, malabsorption, steroid use) and active infection were excluded from the study.

Sarcopenia and osteporosis diagnosis

EWGSOP2 criteria were considered for the diagnosis of sarcopenia and cut-off values (4). A hand dynamometer was used for muscle

strength measurement. The measurement was made while the patients in sitting position, the elbow flexed to 90 degrees, and the wrist in neutral position. Muscle strength was measured for three times for both hands and one minute rest period was left between measurements. The highest measurement was recorded as the handgrip strength. For a positive handgrip strength test, cut-off value was accepted as 27 kg for men and under 16 kg for women. Bioelectrical impedance analyzer (BIA) device was used to measure skeletal muscle mass index (SMMI) in kg/m^2 after 12 hours of fasting and its cut-off value was <7.0 kg/m^2 in males and <5.5 kg/m^2 in females. A 6 meters long area was determined in the corridor to evaluate physical activity performance. The first 1 meter was determined as acceleration zone, the next 4 meters as timing area and the last one meter as the deceleration zone. The walking speed of each patient was recorded. Gait speed cut-off value was accepted as ≤0.8 m/s. Dual energy X-ray absorptiometry (DEXA) was used for the diagnosis of osteoporosis. Femur and vertebral measurements were taken into account in the diagnosis of osteoporosis. T-score below -2.5 standard deviation (SD) in these measurements was accepted as osteoporosis. While the femoral neck and total score were taken into account when interpreting the femur measurements, total (Lumbar 1-Lumbar 4) or at least two vertebral scores were used in the evaluation of vertebra measurements (12,13).

Biochemical analysis

For MMP2 and TIMP2 levels, blood was drawn from the antecubital vein between 08:00 and 9:00 a.m. after fasting for at least 8 hours from all participants. The blood was first transferred into an 8 mL tube without any additives or gel and centrifuged for 15 minutes. The kit inserts were followed for the analytes planned to be examined in our study. The preanalytical process was carried out by geriatric and biochemistry physicians.

Statistics

Chi-square or Fisher's Exact tests were applied for categorical variables. Student's t-test or Mann-Whitney U test was used for continuous variables. The relationship between sarcopenia and age, gender, MMP2, TIMP2, MMP2/TIMP2 ratio, SARC-F score, and osteoporosis were analyzed by univariate logistic regression (LR) method. Stepwise multivariate LR method was applied to the significant values after univariate LR analysis. ROC analysis was performed to determine the importance of MMP2/TIMP2 ratio and the SARC-F in the diagnosis of sarcopenia. P<0.05 was considered significant. Statistical Package for the Social Sciences- 21.0 was used for the analysis of this clinical data.

Results

In the study, 41 sarcopenic and 39 non-sarcopenic geriatric patients were included. Women constituted 61% of both patient groups. In terms of age (mean ± standard deviation),

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no statistically significant difference was found between the group with sarcopenia (77.65±5.96) and the group without (75.76±6.96) (p=0.182). While there were 23 (56%) individuals with osteoporosis in the sarcopenic group, there were 10 (25%) individuals in the non-sarcopenic group, and this difference was statistically significant (p<0.001). Total lumbar, total femur, femur neck T-score and bone mineral density (BMD) values were significantly lower in the sarcopenic group compared to the non-sarcopenic group (p=0.002, p=0.006, p=0.043 and p=0.008, p=0.008, p=0.028; respectively). Considering the SARC-F score (mean ± standard deviation), the score of the group with sarcopenia (4.04±2.35) was statistically significantly higher than the group without sarcopenia (1.87±1.83) (p<0.001). The sarcopenic group had statistically significant lower grip strength, muscle mass, and gait speed (p<0.001, p<0.001, p=0.006, respectively). There was no significant difference between the two groups in terms of serum MMP2 and TIMP2 (p=0.366, p=0.225, respectively). Considering MMP2/TIMP2 ratio, the median of the group with sarcopenia was 10.34, while it was 10.07 in the group without sarcopenia, and this difference was not statistically significant (p=0.641). These comparisons are given in Table 1.

In univariate logistic regression, no statistical correlation was found between sarcopenia and gender, age, serum MMP2, TIMP2 and MMP2/TIMP2 ratio (respectively p=0.959, p=0.194, p=0.720, p=0.570, p=0.441). On the other hand, a significant correlation was found between sarcopenia, and SARC-F (p<0.001) and osteoporosis (p=0.007). Multivariate logistic regression analysis was performed to these parameters and the results showed that SARC-F and osteoporosis had a significant effect on sarcopenia [p<0.001, OR (95%) CI 1.735 (1.292-2.330); p=0.006, OR (95%) CI 4.976 (1.590-15.572) respectively] (Table 2).

Area under ROC curve (AUC) of SARC-F and MMP2/TIMP2 ratio was 0.771 and 0.530 (Figure 1). Sensitivity and specificity for SARC-F score ≥4 were 58.5% and 87.2%, respectively.

Discussion

Sarcopenia in the elderly, generally accepted as an inevitable part of aging, is attracting more and more attention due to its great impact on morbidity, mortality and health costs. According to EWGSOP2, sarcopenia represents a loss of muscle mass and quality with a decrease in muscle strength. Usage of the rapid screening test, SARC-F, which is a self-administered questionnaire was recommended by EWGSOP2 to identify individuals at risk for sarcopenia (4). It is a simple, inexpensive and non-invasive method. After the recommendation about usage of SARC-F by EWGSOP2, many translation and validation studies have been done. Polish and Spanish version of SARC-F was studied and recommended for assessing sarcopenia in everyday practice (14,15). In a study conducted with Danish population, SARC-F

Table 1. Demographic characteristics, grip strength, muscle mass, walking speed and laboratory findings of sarcopenia and no sarcopenia groups

	Sarcopenia	No sarcopenia	p
Number of patients	41	39	
Gender (female/male)	25/16	24/15	0.959
Age	77.65±5.96	75.76±6.96	0.182
SARC-F	4.04±2.35	1.87±1.83	**<0.001**
Grip strength	16.09±5.63	21.76±6.12	**<0.001**
Muscle mass (SMMI)	5.73±0.78	6.44±0.67	**<0.001**
Gait speed	0.68±0.33	0.83±0.27	**0.006**
MMP2 (ng/mL)	227.7 (196.3-503.4)	260.5 (213.1-726.3)	0.366
TIMP2 (ng/mL)	25.0 (20.5-47.6)	30.1 (22.3-61.4)	0.225
MMP2/TIMP2	10.34 (8.10-12.65)	10.07 (7.07-12.48)	0.641
Osteoporosis (yes/no)	23/18	10/29	**0.006**
Femur total, T-score	-1.6±0.9	-0.9±0.8	**0.006**
Femur total, BMD (gr/cm²)	0.681±0.158	0.779±0.136	**0.008**
Femur neck, T-score	-1.8±0.7	-1.4±0.7	**0.043**
Femur neck, BMD (gr/cm²)	0.643±0.095	0.705±0.115	**0.028**
Lomber total, T-score	-1.9±1.0	-1.2±0.9	**0.002**
Lomber total, BMD (gr/cm²)	0.817±0.108	0.880±0.093	**0.008**

MMP: Matrix metalloproteinase, TIMP: Tissue inhibitor of metalloproteinase, SMMI: Skeletal muscle mass index, BMD: Bone mineral density, data are shown as mean ± standard deviation or median (interquartile intervals), statistically significant p-values are indicated as bold

Table 2. Univariate and stepwise multivariate LR analysis of prediction of sarcopenia

	Univariate LR		Stepwise multivariate LR	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Female Male	1 1.024 (0.416-2.519)	0.959		
Age	1.047 (0.977-1.122)	0.194		
SARC-F	1.635 (1.264-2.115)	<0.001	1.735 (1.292-2.330)	<0.001
No osteoporosis osteoporosis	1 3.706 (1.437-9.554)	0.007	4.976 (1.590-15.572)	0.006
MMP2 (ng/mL)	1.000 (0.999-1.000)	0.720		
TIMP2 (ng/mL)	0.998 (0.991-1.005)	0.570		
MMP2/TIMP2 ratio	1.051 (0.926-1.193)	0.441		

MMP: Matrix metalloproteinase, TIMP: Tissue inhibitor of metalloproteinase, LR: Logistic regression, CI: Confidence interval, Statistically significant p-values are indicated as bold

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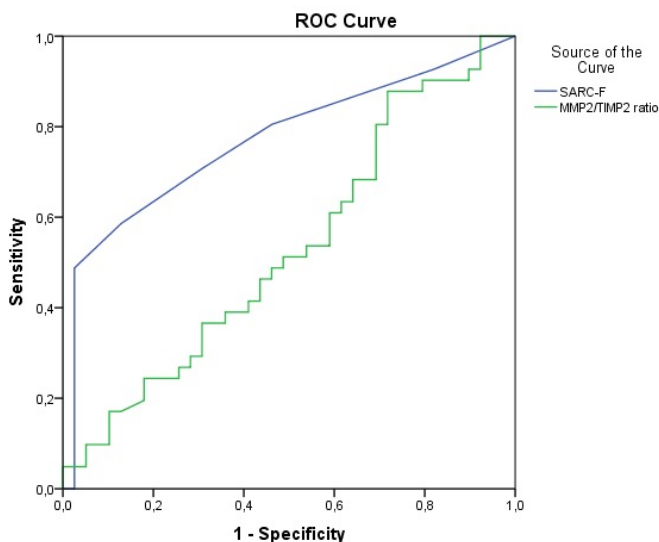
Figure 1. Receiver operating characteristic (ROC) curve analysis for MMP2/TIMP2 ratio and SARC-F for accuracy of sarcopenia. Area under the ROC curve (AUC) SARC-F 0.771 (p<0.001, 95% CI 0.665-0.877), MMP2/TIMP2 ratio 0.530 (p=0.641, 95% confidence interval (CI) 0.403-0.658). Sensitivity and specificity for SARC-F score ≥4 were 58.5% and 87.2%, respectively

was not found to be significant in sarcopenia screening (16). In a study of 1222 elderly Korean individuals, SARC-F was shown to have a high specificity and high negative predictive value (17). In Ida et al's. (18) meta-analysis about SARC-F's accuracy in screening sarcopenia among older adults, screening specifity performance of SARC-F was found to be high, although its sensitivity was poor. Similarly in our study, sensitivity and specifity of SARC-F in screening for sarcopenia were 58.5% and 87.2%, respectively. Thus we can support the usage of SARC-F questionnaire for screening sarcopenia in elderly, as suggested by EWGSOP2.

Detection of more individuals at risk for sarcopenia led to the need for more practical diagnostic tools. In this study, we investigated the usability of MMP2, TIMP2 levels and MMP2/TIMP2 ratio as a marker for the diagnosis of sarcopenia in addition to the current diagnostic methods. MMP2, TIMP2 and MMP2/TIMP2 ratio have been studied in many diseases. Both mRNA transcripts and protein expression of MMP2 are reported to be elevated in class-IV lupus nephritis (19). Also in another study MMP2 was found to have a significant role in glioma pathogenesis and could be used as a potential molecular marker for tumor progression (20). Based on the thesis that balance of the MMP/TIMP ratio is important in maintaining the dynamic balance of tissues, its role in lung damage and repair was investigated in the rat study of Chen et al. (21), and it was concluded that lipopolysaccharide-induced acute lung injury may be related to upregulation of MMP2/TIMP2 ratios. Although there are few studies in the literature evaluating the effect of MMP2 and TIMP2 on muscle cells, in a mice study it has been shown that the absence of MMP2 and MT1-MMP causes

a significant retardation in myoblast fusion and is incompatible with life due to immature muscle fibers and various organ failures (22). In another study investigating the role of TIMP2 on muscle development and function, it was revealed that TIMP2 was expressed in the neuromuscular junction, regulating neuromuscular junction development and its expression was higher in fast-twitch muscles, thus it has been mentioned that this result can open new horizons in the treatment of conditions such as age-related sarcopenia, in which fast-twitch muscle fibers were lost (23). The number of biomarker studies about sarcopenia is increasing day by day. In Bano et al.'s (24) meta-analysis, evaluating the relationship between sarcopenia and inflammation while patients with sarcopenia had a statistically significantly higher C-reactive protein than control groups, no significant difference was found in terms of tumor necrosis factor-alpha and interleukin-6. In a study comparing sarcopenic and non-sarcopenic control groups, MMP9/TIMP1 ratio was found to be increased in sarcopenic patients, while in another study, sarcopenia was found to be associated with increased FGF-21 and low FGF-19 levels (25,26). In our study, there was no statistically significant difference between sarcopenic and non-sarcopenic groups in terms of serum MMP2, TIMP2 levels and MMP2/TIMP2 ratio. The insignificance of these biochemical markers with sarcopenia may be due to the small sample size, or it may be due to the non-dominance of the inflammatory system in sarcopenia.

There are similarities and interrelationships between sarcopenia and osteoporosis. Many mechanisms have been investigated to explain this relationship. Mechanostat hypothesis, which refers to the muscle contraction action that provides a direct mechanical stimulus to the bone that promotes osteogenesis, the effects of hormones and nutritional state that provide both muscle and bone development, physical activity level, common genetic and developmental components are some of them (5,6,27-29). In a study of two hundred thirty-four women whole-body and femoral neck bone mineral density values were found to be significantly lower in sarcopenia group than non-sarcopenia group (30). In another study, Reiss et al. (31) drew attention to the frequent coexistence of these two conditions in the elderly and associated this with poor function and malnutrition in advanced age. Similarly, the coexistence of osteoporosis and sarcopenia was found to be significant in our study. Because of the relationship between sarcopenia and osteoporosis, our study suggests that these two conditions should be evaluated together.

Study Limitations

The main limitation of this study is the small sample size and another limitation is that our study was designed as a case-control study.

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Conclusion

Our study supports widespread use of SARC-F questionnaire to screen for risk of sarcopenia. In addition, since the incidence of osteoporosis is significantly higher in sarcopenia, our study supports the evaluation of sarcopenia and bone mineral density together. Another point to be emphasized about the results of our study is that there is a need for other studies investigating the use of serum MMP2, TIMP2 levels and MMP2/TIMP2 ratio for the diagnosis of sarcopenia.

Ethics

Ethics Committee Approval: This study was approved by the Ethical Review Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine. Ethical Review Committee decision date and number: 2019-22507.

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.S., H.Y., İ.M.B., D.S.E., Concept: V.S., H.Y., A.D., D.S.E., Design: V.S., B.B.K., A.D., İ.M.B., D.S.E., Data Collection or Processing: V.S., B.B.K, İ.M.B., D.S.E., Analysis or Interpretation: V.S., İ.M.B., A.D., D.S.E., Literature Search: B.B.K., H.Y., A.D., D.S.E., Writing: V.S., B.B.K., A.D., H.Y., D.S.E.

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

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ORIGINAL RESEARCH

The Effect of the Fracture Types on the Activity Daily Living and Mortality in Geriatric Patients

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Abstract

Objective: Knowledge of the frequency of geriatric fracture types and independency life rates will provide insights on its prevention in the community. Our study aimed to determine the effect of fracture types on the loss of activity daily living and mortality with a one-year follow-up.

Materials and Methods: This study included a total of 522 patients (>65 years of age) with extremity and axial skeletal fractures. Fractures were classified according to location into 17 types. The incidence of the fracture types, hospitalization and operation rates in geriatric fractures were defined. Barthel and Katz indexes were evaluated for Basic activity daily living scale (BADLs) at the final control. The relationship between fracture types and mortality and decrease of BADLs was determined.

Results: The mean age of the patients was 76.24±7.6 (range: 65-96) and the female-to-male ratio was 7/3. Four fracture types which constitute 60% of the fractures were noted: Hip fracture (29.5%), vertebra fracture (7%), distal radius fracture (16%), and proximal humerus (8%). The mortality was noted in 21% of the patients. Mortality ratio and BADLs were statistically different according to the fracture types. The hip, vertebra, and femur fractures had lower Barthel index compared to other fractures.

Conclusion: High functional dependency and mortality were found in the patients with geriatric fracture, especially in the hip, femur and vertebra fractures. The patients have upper extremity fractures can reach the highest value of BADLs at one-year follow-up.

Keywords: Geriatric fractures, activity daily living, Katz index, Barthel index, mortality

Introduction

In the elderly population, an increase in bone porosity and a decrease in bone tissue proportion are expected (1). In addition, falling is a health problem with a multifactorial etiology, especially over the age of 65 (2). Fractures are more common in older ages, because of lower bone quality and higher frequency of falls. Over the age of 65, the incidence of fractures is four times higher (3). With a worldwide aging population, the importance of the prevention and management of osteoporotic fragility fractures has been emphasized over time.

Hip fractures, distal radius fractures, proximal humerus fractures, and vertebral fractures are the most common four types of geriatric fractures (4-6). While most of the fractures are seen commonly in males, the incidence of fractures in older ages is two times higher in females than in males (7). Another prominent feature in elderly fractures is that while the upper extremity fractures are often treated conservatively, the lower extremity fractures, especially the hip fractures, require hospitalization and surgical intervention (8).

Geriatric fractures are commonly evaluated with health-related quality of life (Qol) instruments, such as short form 36 of the medical outcomes study (SF-36), short-form 12 of the medical outcomes study (SF-12), and EuroQol (EQ-5D) SF-12 (9,10). An important deficiency in the literature regarding geriatric fractures is the fact that the relationship between fracture type and activity daily living (ADL) and mortality in geriatric patients

Cite this article as: Yaradılmış YU, Kılıç A, Evren AT, Kuru T, Özdemir M, Altay M. The Effect of the Fracture Types on the Activity Daily Living and Mortality in Geriatric Patients. Eur J Geriatr Gerontol 2022;4(2):52-57

is yet not to be investigated. Another point is the inadequacy of literature regarding the epidemiological study of fractures. Geriatric fractures have been examined with its subtypes and hip fractures subtypes was shown to emphasize their high mortality and morbidity (7). Alarkawi et al. (11) made attention to the adequate research on fractures besides hip and vertebra fractures. This elderly group experience many comorbidities and major problems, such as osteoporosis and sarcopenia, which are difficult to change (12,13). Perhaps it is important that they can continue their independent life and these patients should be evaluated with ADL.

Knowledge of the frequency of geriatric fracture types and independency life rates will provide insights on its prevention in the community as well as aid the determination of effective treatment strategies.

Our study determined the epidemiological characteristics of geriatric fractures and the effect of fracture types on loss of daily life activities and mortality with one-year follow-up.

Materials and Methods

Patients

In this study, a total of 535 patients (over 65 years of age) who were diagnosed with fractures in orthopedics and traumatology clinic between January and December 2019 were retrospectively analyzed. Multiple fractures (n=8) and periprosthetic fractures (n=5) were excluded. A total of 522 patients with extremity and axial skeletal fractures were included in this study (Figure 1). Fractures were classified into 17 types as to their locations (Table 1). The incidence of the fracture types among geriatric patients was defined. Epidemiological data of these patients, including age, gender, and comorbidities.
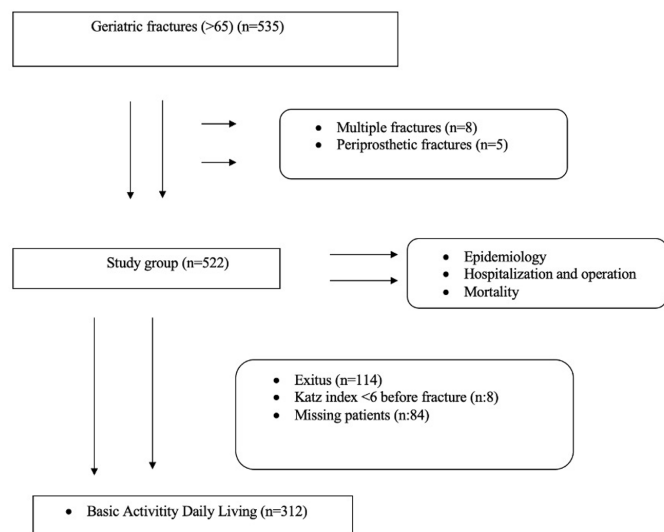
Figure 1. Flow chart of patients enrolled in the study

Hospitalization and operation

General and extremity examinations were performed in the emergency department. Hospitalization was applied to patients who had surgical indications according to the fracture site and who were vitally unstable or expected to have instabile fracture. Patients who did not require surgical intervention and were vitally stable were discharged with their specific recommendations. Surgical treatment was done after hospitalization in line with the anesthesia risk ratio and patient approvals. Mechanical and medical deep venous thrombosis prophylaxis was administered immediately after hospitalization. Hospitalization and operation ratio of the fractures were determined.

Mortality

Mortality was evaluated in 522 included patients. The exitus patients' data were collected from the death reporting system record. Besides fracture types, other variables relationship between mortality was determined.

ADL

A basic ADL scale (BADLs) was applied to the patients at the final control (12-24 months). Barthel and Katz indexes were evaluated for basic ADLs (14,15). The Katz index measures six

Table 1. Classification of fracture types according to the fractures locations	
Fracture types	Subtypes for some fracture
Hip fractures	Intertrochanteric, femoral neck, subtrochanteric fractures
Vertebra fractures	Lombar, thoracal and cervical fractures
Humerus proximal fractures	
Distal radius fractures	
Ankle fractures	All malleol fractures
Foot fractures	Metatars, phalanx and tarsal fractures
Hand fractures	Metakarp, phalanx and carpal fractures
Pelvis and acetabular fractures	
Tibial plateau fractures	
Patella fractures	
Tibial fractures	Tibial saft and distal tibia fractures
Femoral fractures	Femoral saft and distal femur fractures
Humerus fractures	Humeral saft and distal humerus fractures
Radius fractures	Radius saft and proximal radius fractures
Ulna fractures	Ulnar saft and proximal ulna fractures
Clavicula fractures	
Scapula fractures	

items: Bathing, dressing, toileting, transferring (bed to chair and back), maintaining continence and feeding. Each of items was evaluated with one point, with a maximum of 6 points being obtainable. Functional independent patient is indicated by a Katz index of 6, while a functional dependent patient is indicated by a Katz index <6. validity and reliability of the Turkish version of Katz index evaluated in healthy volunteers after 65 years of age Arik et al. (16). The Barthel index comprises 10 items (feeding, bathing, groomimg, dressing, bowel control, bladder control, toilet use, transfers, mobility on level surcafes and stairs) with a maximum of 100 points being obtainable. Validity and reliability of the Turkish version of Barthel index was assessed by Küçükdeveci et al. (17). A total of 114 exitus patients, patients with Katz index <6 before fracture (n=8), and missing patients (n=84) were excluded for BADLs evaluation. BADLs was performed for 312 patients (Figure 1). The relationship between fracture types and decrease of BADLs was determined.

Statistics

Data obtained in the study were analyzed statistically using SPSS v.22 software, and at a confidence interval of 95%. Qualitative data were stated as frequency distribution and quantitative data were stated as mean, minimum and maximum values. The χ^2 test was applied to categorical data and the Student's t-test to quantitative data. Normality of data distribution was tested with the Shapiro-Wilk test. Demografic values were evaluated with the Mann-Whitney U test. Mortality, Barthel and Katz

index of the fractures were evaluated with the Kruskal-Wallis. The relationship between fractures types and mortality, and Katz index evaluated with the Mann-Whitney U test and chi-square test. A value of p<0.05 was accepted as statistically significant.

Results

Mean age of the patients was 76.24±7.6 (range: 65-96) and female-to-male ratio was 7/3. There were 53% lower extremity fractures, 35% upper extremity fractures, 7% vertebra fractures and 5% pelvis-acetabular fractures. The demographic data of the patients are presented in Table 2. While 37.5% of the patients were hospitalized, 32.5% of the patients were operated. The mortality ratio was 21%.

Four fracture types, which constitute 60% of the fractures were noted: Hip fractures (29.5%), vertebra fractures (7%), distal radius fractures (16%) and proximal humerus fractures (8%). Frequency of the geriatric fractures are presented in Figure 2.

The hospitalized patients with hip fractures were 72.5% and other fracture types hospitalized are given in Figure 3. Only 6% of the patients with upper extremity fractures underwent surgery. The mean follow-up period of the patients was 16 (range: 12-24) months and the mortality ratio was 21%. The mortality ratios in the fracture types respectively; hip 46% (n=72), pelvis-acetabular 34% (n=9), vertebra 20% (n=8), tibia plateau 34% (n=4), ankle 14% (n=6), proximal humerus 25% (n=9) and distal radius fractures 6% (n=4). There was a statistical difference between mortality and fracture types (p<0.05). Mortality was affected by variables such as age, comorbidity, and operation (Table 3).

Table 2. Demographic data of the patients		
	n=522	**Frequency**
Age	76.24±7.6 (65-96)	
65-75	247	45.5%
75-85	196	36%
>85	100	18.5%
Gender		
Female/male	384/159	
Follow-up	16±1 (12-24)	
Side		
Right/left	266/237	
Vertebra	36	
Subtype		
Upper extremity	190	35%
Lower extremity	290	53%
Vertebra	37	7%
Pelvis-acetabulum	25	5%
Season		
Summer	147	29%
Spring	157	27%
Winter	123	23%
Autumn	116	21%
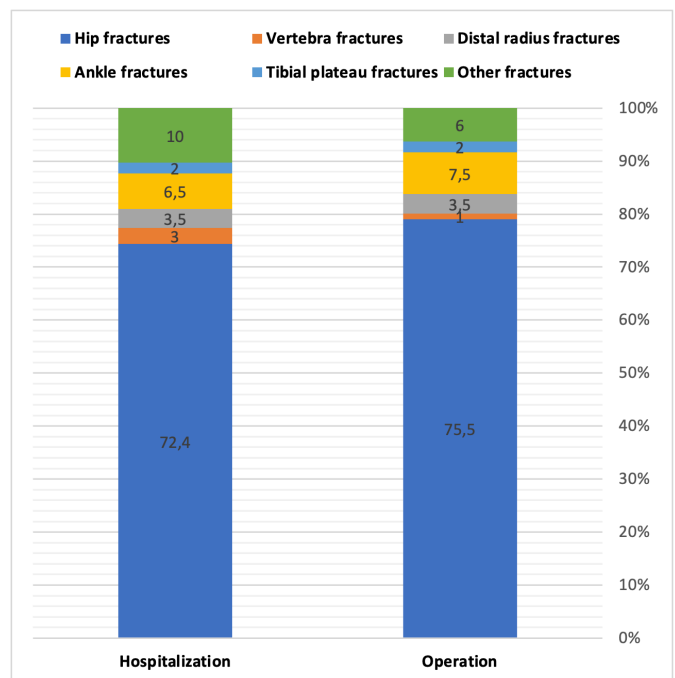
Figure 3. Hospitalization and operation of the fracture types
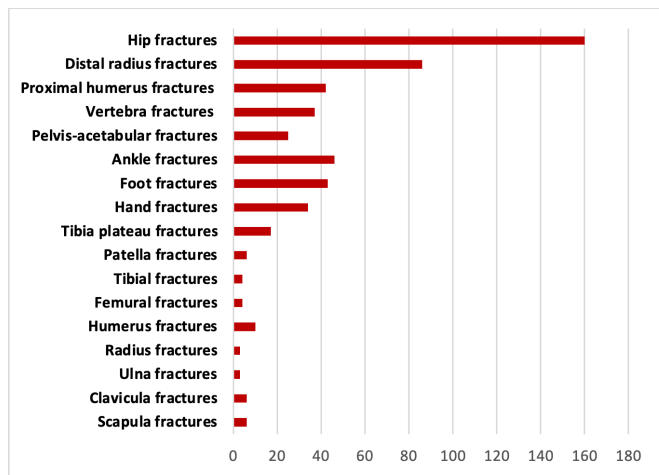
Figure 2. Frequency of fractures types

Table 3. Relationship between demografic values and mortality

	Exitus	Live	p
	114	408	
Age	80.7±7.6	74.7±6.9	≤0.001*
Sex (F/M)	41/16	112/50	0.820
Comorbidity number	2.03±1	1.64±1.1	0.002*
*: p<0.05 and there is a significant statistical difference			

While 75% of the patients had a Katz index of 6 point, 25% of the patients were not completely functionally independent. Regarding the Barthel index values, 70% of the patients had 100 points. There was a statistical difference between BADLs and fracture types (Table 4). Barthel index was lower in the patients with hip, vertebra, and femoral fractures than other fractures. Katz index was affected by variables such as age, comorbidity, and operation (Table 5).

Discussion

Aging is associated with a higher fracture risk and diminished capacity of bone to heal. Bone fractures are common in the elderly, with residual lifetime fracture risk in a person aged 60 years reported to be 29% in males and 56% in females (18). Regeneration of bone defects often presents significant challenges, particularly in these patients with decreased tissue regeneration capacity (19). Many cases of delayed union and non-union are idiopathic in nature, several reports have suggested that these complications are more common in the elderly (20). Geriatric fractures can lead to work absence, decreased productivity, disability, impaired Qol, health loss, and high health-care costs and are a major burden to individuals, families, societies, and health-care systems (21). Our study aimed to determine the frequency of geriatric fracture types and effect of fracture types on loss of ADL and mortality with one-year follow-up.

Table 4. Basic activity of daily life of fracture types

	Frequency (n=512)	Barthel (n=312)	Katz (n=312)
Total		95±11.4	5.5±1
P-value		0.005*	0.004*
Hip fractures	29.5%	90.7±14.1	5±1.3
Vertebra fractures	7%	88.7±19.5	5.1±1.4
Distal radius fractures	16%	98±1.3	5.9±0.3
Proximal humerus fractures	8%	93±11.7	5.3±1
Pelvis-acetabular fractures	5%	98±4.4	5.8±0.4
Tibial plateau fractures	3%	94±8.9	5.4±0.9
Patella fractures	1%	100	6
Ankle fractures	8.5%	100	6
Hand fractures	6.3%	98.5	5.8
Foot fractures	7.9%	100	6
Tibial fractures	1%	90	5
Femoral fractures	1%	90	5
Humerus fractures	2%	100	6
Radius fractures	1%	100	6
Ulna fractures	1%	100	6
Clavicula fractures	1%	100	6
Scapula fractures	1%	100	6
*: p<0.05 and there is a significant statistical difference			

Table 5. Relationship between demografic values and basic activity of daily life

	Katz index<6	Katz index=6	p
	74	238	
Age	78.5±7	73.5±6.5	≤0.001*
Sex (F/M)	25/12	82/37	0.878
Comorbidity number	1.48±1	2.2±1.2	≤0.001*
*: p<0.05 and there is a significant statistical difference			

In studies regarding aged-related fractures, hip fractures, vertebral fractures, and distal radius fractures are common fractures. The incidence of fractures is affected by geographic, ethnic, and socio-economic factors (22). While hip fractures are 11 times more incident in European countries, vertebral fractures were 3 times more incident in Scandinavian countries (23). Geriatric cases were most commonly located at the femur (43.4%), followed by radius (11.8%), humerus (10.6%), and lumbar vertebra (3%). Fractures in geriatric cases are most commonly seen in women (61%), among those treated surgically (67%), and during winter (32.9%). In incident studies, diagnostic determination of vertebral fractures is difficult, since they are ignored over time and since no further examinations are performed (8). In our study, the four most common fractures were respectively: Hip fractures (29.5%), distal radius fractures (16%), proksimal humerus fractures (8%) and vertebra fractures

(7%). In addition, it was seen 2 times more frequently in women. Geritric fractures are more common in summer and spring, but less common in winter and autumn in our study.

Aged-related fractures have never been evaluated with BADL. Katz and Barthel indexes are often used for BADL. Barthel index is one of the most widely-used tools for assessment of functional independence (14). Küçükdeveci et al. (17) in patients with stroke and spinal cord injury. Katz index is a shorter assessment and may be easier for patients (15). Arik et al. (16) determined after 65 years of age the Katz index as 4.7±1.6 and the Barthel index as 86±25. In our study were found Katz index as 5.5±1 and Barthel index as 95±11.4 for geriatric fractures. In line with these values, it is important to note that the rate of complete independence was low in the patients >75 years old. In our study, mild dependence (range: 62-90) was observed in vertebral, hip, and femur fractures according to the Barthel index, while complete independence (range: 91-99) was observed in other fractures. In a prospective evaluation of hip fractures, low ADL values was observed and the mortality rate of these patients was determined (24). In another study, ADL and Charlson comorbidity scores were used during follow-up to determine re-hospitalization after hip surgery (25).

Fractures are more mortal among the elderly than in normal population (11). Hip and vertebral fractures cause more morbidity and mortality than other fractures (26,27). There is limited information about the effect of several fractures on mortality, except for vertebra and hip fractures. Alarkawi et al. (11), in their study, mentioned the significant effect of proximal, non-hip, non-vertebra fractures, and subsequent fractures on mortality, excluding hip fractures. Although mortality is most common in lower extremity fractures; resulted in mortality in 46% of patients with hip fractures and 34% of patients with pelvis fractures in our study. On the other hand, 20% mortality was observed in vertebral fractures and it was not higher than expected. Apart from the type of fracture, variables such as advanced age and comorbidity, also increase mortality. Hip fractures have been frequently investigated in the literature because they are both common and mortal in the elderly. Mortality has been found in many studies to correlate with age and comorbid conditions such as chronic liver, kidney, or cardiovascular diseases and pneumonia and dementia in hip fractures (28,29). The other factors associated with mortality were cognitive impairment, delirium, living with caregiver, smoking and poor function before fracture (29,30). When evaluating mortality for elderly patients, it is necessary to consider a lot of risk factors.

Study Limitations

This study has several limitations, which include collection of data from a single center and its retrospective design. This study is innovative due to its inclusion of all fracture types and the questioning ADLs; however, the addition of multi-center studies with more patients in the future will increase the reliability and generalizability of the data. Another limitation of this study is the lack of data on status of patients in terms of osteoporosis.

Conclusion

Hip fractures in the geriatric forties constitute a major burden in Turkish population. High functional dependency and mortality are expected due to patients with geriatric fractures, especially the hip, femur, and vertebra fractures. The patients have upper extremity fractures can reach a high rate of full BADLs at one year follow up.

Ethics

Ethics Committee Approval: The study was approved by the Review Board and Commission of Keçiören Health Practice and Research Hospital in Turkey (approval date: 04.03.2021 number: 73-929).

Informed Consent: Written informed consent was obtained from participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.U.Y., A.K., M.A., Concept: Y.U.Y., A.K., A.T.E., T.K., M.Ö., M.A., Design: Y.U.Y., A.K., M.A., Data Collection or Processing: Y.U.Y., A.K., M.A., Analysis or Interpretation: Y.U.Y., A.K., A.T.E., T.K., M.Ö., M.A., Literature Search: Y.U.Y., A.T.E., T.K., M.Ö., M.A., Writing: Y.U.Y., A.T.E., T.K., M.Ö., M.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL RESEARCH

A Comprehensive Evaluation of the Relationship Between Fall Risk and Other Geriatric Syndromes

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Abstract

Objective: Falls are important geriatric syndromes that can result in morbidity and mortality in elderly individuals. Many factors increase the risk of falls. To effectively control falls it is important to reveal its relationship with other geriatric syndromes.

Materials and Methods: This cross-sectional study was conducted for a period of 4 months from September 2019 to January 2020. Fall risk assessment was done with the Tinetti test and the timed up and go (TUG) test. All patients underwent comprehensive geriatric assessment tests.

Results: The study population was composed of 93 women and 57 men, and the mean age was 73 ± 9.2 years. It was observed that the scores obtained from the Katz and Lawton-Brody scales were lower in patients with a high risk of falls. Handgrip strength, skeletal muscle mass index, mini-nutritional assessment score, and mini-mental status assessment score were lower in these patients. Geriatric depression scale score, fried and SOF frailty index scores, and the number of drugs used were higher in them. Frailty, handgrip strength, gait speed, and depression were independently associated with Tinetti-measured fall risk in linear regression analysis ($R^2=0.414$; $p<0.001$, $p=0.004$, $p=0.002$, $p=0.027$). IADL and gait speed were found to be independently associated with fall risk according to TUG ($R^2=0.550$; $p=0.012$, $p<0.001$).

Conclusion: In our study, we concluded that there is a close relationship between the risk of falls and other geriatric syndromes. Effective management of geriatric syndromes will help reduce the risk of falls.

Keywords: Fall, geriatric syndromes, timed up and go, Tinetti

Introduction

Falls are important problems that limit independent mobility in older adults and are considered as one of the important geriatric syndromes (1). It is known that falls cause an increase in hospital stays and health expenditures due to complications such as injuries and fractures (2). About 30% of adults aged 65 and over have been experiencing falls each year (3). The causes of falls can be examined under two main headings as intrinsic and extrinsic causes. We can consider intrinsic factors in the two groups as age-related physiological and pathological changes. The decrease in visual sensitivity, age-related hearing loss, decrease in tactile sense and vibration sense, and balance disorders can be considered as examples of age-related physiological changes. An increase in fat mass and decrease in muscle mass with age can also be listed among them. Stroke, dementia, parkinsonism,

epilepsy, and carotid sinus hypersensitivity syndrome are among the pathological causes of falls (4).

Conditions that are more common in old age and known to reduce life expectancy, such as dementia, depression, delirium, incontinence, falls, frailty, sarcopenia, and malnutrition, are called geriatric syndromes (5). Geriatric syndromes are usually seen together, not as isolated clinical conditions. Co-occurrence of geriatric syndromes can be explained by the fact that they have a common pathogenesis. They can be prevented and treated with similar approaches.

It is important to reveal the relationship between falls and other geriatric syndromes to determine preventive and therapeutic approaches. Although studies are describing these relationships separately, there is no study evaluating the relationship between fall risk and all geriatric syndromes together. We aimed to

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examine the relationship between fall risk and other geriatric syndromes in this study.

Materials and Methods

Participants

This cross-sectional study was carried out for a period of 4 months from September 2019 to January 2020. Patients who applied to the geriatrics outpatient clinic were included in the study. The Local Research Ethics Committee approved the study (number: 2019/269, date: 03.07.2019). All participants gave informed consent.

Exclusion criteria

Patients, who were below 65 years of age, and had already been diagnosed with any of the geriatric syndromes such as sarcopenia, frailty, malnutrition, polypharmacy, fall, urinary and fecal incontinence were not included in the study. Those with cancer and severe inflammatory disease were also excluded from the study.

Assessment of fall risk

Tinetti balance-gait evaluation scale and timed up and go test (TUG) were used for evaluation of the fall risk. Tinetti assessment tool scores gait and balance according to the ability to perform certain tasks. In the Tinetti balance-gait evaluation scale, a score of >24 means low risk of fall, 19-23 moderate risk of fall, and <19 high risks of fall (6). TUG is a test that evaluates both static and dynamic balance. It uses the time it takes for the person to get up from the chair, walk three meters, turn 180 degrees, walk back to the chair, and sit. Patients who took 14 seconds, or longer from the TUG test, were classified as high-risk for fall too (7).

Comprehensive geriatric assessment

A cognitive evaluation was done by the standardized form of mini-mental state examination (MMSE), assessment of abilities of daily living (ADL) by Katz index, and instrumental activities of daily living (IADL) by the Lawton Brody index. The evaluation of psychological status was done by the short form of the Yesavage geriatric depression scale.

In MMSE, patients were evaluated for six different areas; orientation, attention, registration, language, calculation, and recall (8). Patients whose scores ≤24 were evaluated as dementia (9). Patients were evaluated for personal hygiene, continence, toileting, dressing, feeding, and ambulating by Katz index of ADL. High scores were considered high self-sufficiency (10). Lawton Brody index was used for evaluating IADL like house cleaning, doing the laundry, shopping, managing medications, cooking, communicating with others, using transportation, and doing financial management; higher scores meant higher

independence (11). Patients with GDS scores of 5 and higher were accepted as positive for depression (12).

Malnutrition was assessed by a mini nutritional assessment, short-formed (MNA-SF), long-form (MNA-LF), and the Global Leadership Initiative on malnutrition criteria (GLIM) (13-15). MNA-SF is the first part of the MNA test and takes only a few minutes to complete. The maximum score for MNA-SF is 14; a score of 12 points or greater indicates that the patient has an acceptable nutritional status and the full MNA is not needed to be done. However, a score of 11 points or below is an indication to proceed with the MNA-LF. Completing the MNA-LF takes 10 to 15 minutes. The maximum score for the second part is 16 and the maximum score for MNA-LF is 30. Scores <17 are accepted as malnutrition, 17-23.5 is accepted as the risk for malnutrition, and 24-30 is accepted as normal. GLIM criteria are new criteria for diagnosing malnutrition. These criteria are based on the verification of phenotypic criteria, such as low body mass index, non-volitional loss of weight, or reduced muscle mass, associated with etiological variables, such as reduced food intake, the presence of inflammation, or disease burden. Also, the stage of malnutrition can be determined as moderate and severe according to body mass index, loss of weight, and muscle mass.

Assessment for sarcopenia

For defining sarcopenia, muscle strength, muscle mass, and physical performance were assessed. SARC-F (strength, assistance need for walking, rising from a chair, climbing stairs, and falls) test was used to select cases to be evaluated for muscle strength (16). The handgrip test was performed if the patient had a score ≥4 from SARC-F to diagnose probable sarcopenia. The handgrip test was performed by using a hand dynamometer with the dominant hand. For females <16 kg (kilograms), for males <27 kg were accepted as probable sarcopenic (17). A bioimpedance test was carried out on probable sarcopenic patients to assess skeletal muscle mass. Sarcopenia was diagnosed by skeletal muscle mass index. In this study, we used skeletal muscle mass index (SMMI) adjusted to height. SMMI was calculated by dividing skeletal muscle mass by the square of height (18). We evaluated gait speed with a four-meter gait speed test to diagnose severe sarcopenia (19).

Assessment for frailty syndrome

Frailty was assessed by using the fried frailty index (FFI) and study of osteoporotic fractures (SOF) index. FFI is constituted from five criteria: Unintentional weight loss, self-reported poor energy, weakness (reduced grip strength), slow gait speed, and low physical activity. People who were positive for three and more FFI criteria were defined as frail. Those who were positive for one or two criteria were described as pre-frail (20). The SOF index evaluates frailty syndrome by using three components

(weight loss, inability to rise from a chair five times without using the arms, and reduced energy). The presence of frailty syndrome was determined by the presence of two or more of the three criteria in the SOF index. Patients that were positive for 1 criterion were described as pre-frail (21). People not meeting any criteria were defined as robust in both assessment tools.

Statistics

The variables were analyzed for the normality of their distribution using the Kolmogorov-Smirnov test. All data were normally distributed. Numerical variables were denoted as mean ± standard deviation. Categorical variables were represented as frequencies. Comparison groups were done by independent sample t-test and ANOVA. A univariate linear regression model was used to study the linear relationship between the risk of falls and other geriatric syndromes. The significance check in the linear regression analysis was based on an F-test and the significance of single independent variables was assessed by a t-test. The IBM SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

One hundred and fifty subjects were included in this study evaluating the relationship between fall risk and geriatric syndromes. Fifty-six were women and 94 were men. The mean age was 73±9.2. ADL and IADL seemed to be impaired more in patients with a high risk of fall than in patients with low risk when evaluated with the Tinetti test (p<0.001, p=0.044). Nutritional status evaluated by MNA, MNA-SF, and GLIM criteria were found to be better in patients with a low risk of fall than in patients with moderate and high risk (p<0.001). Handgrip strength was preserved better in those with a low risk than in those with a high risk (p=0.003). Gait speed was also higher in those who were at low risk of fall when compared to the patients who had moderate and high risk (p<0.001). It was observed that low-risk patients met the criteria of fried and SOF frailty indexes less than others (p<0.001). The geriatric depression score was also lower in those with a low risk of fall compared to those with a moderate and high risk of fall (p=0.008, p<0.001). The number of drugs used was higher in high-risk patients than in low-risk patients (p=0.003). The relationship between fall risk and other geriatric syndromes according to the Tinetti test is summarized in Table 1.

When we evaluated the fall risk with TUG, we found that ADL and IADL were better in those with a low risk of fall (p<0.001). The MMSE score was lower in those with a high risk of falls (p=0.003). Fried and SOF frailty index scores were higher in those with a high risk of fall (p=0.003, p=0.001). Handgrip strength, SMMI, and gait speed were decreased in the high-risk group (p=0.023, p<0.001, p<0.001). The number of drugs used was higher in the high-risk group (p=0.032). The relationship

between fall risk and other geriatric syndromes according to the TUG test is summarized in Table 2.

We found that the FFI score, handgrip strength, gait speed, and GDS were independently related to fall risk measured with Tinetti in linear regression analysis (R²=0.414; p<0.001, p=0.004, p=0.002, p=0.027). IADL and gait speed were independently related to fall risk according to the TUG in linear regression analysis (R²=0.550; p=0.012, p<0.001). In the linear regression analysis performed with the risk of falling according to the Tinetti test, the R2 value was 40% in the analysis and 50% in the analysis performed with the TUG. Considering this, we can say that the model fit is moderate. Results of linear regression analysis were summarized in Tables 3 and 4.

Discussion

In our study, we observed that the risk of falls was associated with ADL and IADL. Sekaran et al. (22) had evaluated the association between falls and ADL in a 10-year prospective cohort study in adults aged 65-69 years. The researchers concluded that there is a significant association between increased risk of falls and ADL difficulties (22). Brown et al. (23) revealed that loss of IADL was strongly associated with the risk of falls. The authors suggested that IADL levels could be a powerful and practical tool for screening patients for fall risk (23). Because the risk of fall makes independent movement more difficult, the risk of fall and disability are closely related.

We found a significant relationship between the risk of falls and malnutrition. Bórikova et al. (24) had shown the association between malnutrition and the risk of fall, in their study. The authors revealed that none of the patients with a history of a single fall were suffered from malnutrition at hospitalization, but malnutrition was frequently seen in those with a history of multiple falls (24). Malnutrition can lead to nutrient deficiencies such as vitamin B12 deficiency, leading to loss of balance and fall. In addition, muscle wasting, which is directly affected by malnutrition, can increase the risk of falls. Frailty was also related to fall risk according to our study results. Cognitive and physical fragility, which are components of frailty, can increase the risk of falls (25). Clegg et al. (26) have previously shown that frailty is associated with an increased risk of falls Additionally, more than half of the frail adults suffered from falls.

In our study, high GDS scores and low MMSE were found to be related to falling risk. Kamińska et al. (27) also revealed that the risk of fall is associated with regression in ADL, depression, and cognitive decline. Unlike our study, cognitive functions were evaluated with abbreviated mental test scores in this study. The relationship between depression, dementia, and the risk of falls can be attributed to many reasons. Both situations are accompanied by distraction, we can specify this as one of the reasons. In both cases, antipsychotics that have a place in the

Table 1. Relationship between fall risk and other geriatric syndromes according to Tinetti test

	Low-risk (n=109) (mean ± SD)	Moderate-risk (n=21) (mean ± SD)	High-risk (n=20) (mean ± SD)	p
ADL	5.4±0.9	5.1±1	4.3±1.7	<0.001*
IADL	5.4±2.9	3.9±2.2	4±2.2	0.044*
MNA	23.3±4	20.3±4.9	19.6±3.8	<0.001*
MNA-SF	11.5±3.5	8.4±2.4	8.4±2.1	<0.001*
GLIM (% of malnourished)	11.9%	42.9%	65%	<0.001*
FFI	2±1.2	3.3±1.3	4.3±0.7	<0.001*
SOF	1.1±0.9	1.9±1	2.3±0.6	<0.001*
Handgrip strength (kg)	30.5±15.5	26.2±11.1	20.2±7.1	0.003*
SMMI (kg/m²)	11±1.6	10.9±1.4	11.1±1.5	0.91
Gait speed (m/s)	0.6±0.1	0.4±0.1	0.4±0.2	<0.001*
GDS	9.3±5.6	13.1±6.9	17.1±6.2	<0.001*
Number of drugs used	6.2±3	7.6±4.3	8.6±3.1	0.003*

ADL: Activities of daily living, IADL: Instrumental activities of daily living, MNA: Mini nutritional assessment, MNA-SF: Mini nutritional assessment-short form, GLIM: Global leadership initiative on malnutrition, FFI: Fried frailty index, SOF: Study of osteoporotic fractures, SMMI: Skeletal muscle mass index, GDS: Geriatric depression scale, kg: Kilograms, kg/m²: Kilogram per square meter, m/s: Meter per second, SD: Standard deviation

Table 2. Relationship between fall risk and other geriatric syndromes according to TUG test

	Low-risk (n=57) (mean ± SD)	High-risk (n=93) (mean ± SD)	p
ADL	5.7±0.5	5±1.3	<0.001*
IADL	6±2.5	4.3±2.8	<0.001*
FFI	2.1±1.5	2.9±1.4	<0.001*
SOF	1.04±0.8	1.6±1	<0.001*
MMSE	24±5.5	20.7±7.4	0.003*
Handgrip strength (kg)	30.7±13.3	25.2±12.9	0.023*
SMMI (kg/m²)	11.6±1	10.6±1.7	<0.001*
Gait speed (m/s)	0.6±0.07	0.4±0.1	<0.001*
Number of drugs used	6.1±3.1	7.3±3.2	0.032*

ADL: Activities of daily living, IADL: Instrumental activities of daily living, FFI: Fried frailty index, SOF: Study of osteoporotic fractures, SMMI: Skeletal muscle mass index, GDS: Geriatric depression scale, kg/m²: Kilogram per square meter, m/s: Meter per second, SD: Standard deviation

treatment may also increase the risk of falls in older individuals. In both cases, deterioration of nutritional status can lead to muscle loss and falls.

We revealed that the risk of fall was found to be associated with the parameters evaluating sarcopenia. Different studies have shown that sarcopenia is one of the parameters that increase the risk of falls in older adults. These studies were reviewed in a meta-analysis by Yeung et al. (28). The positive association between sarcopenia and falls in older adults reinforces the need to take measures to see the impact of sarcopenia prevention on falls.

We also concluded that the increase in the number of drugs used increases the risk of falls. In the study of Dhalwani et al. (29), the

use of ≥4 drugs increased the frequency of falls by 18%, while the use of ≥10 drugs increased the frequency of falls by 50%. The relationship between the increase in the number of drugs used and the increase in the risk of fall may be related to the use of drugs that increase the risk of fall. According to the study of Woolcott et al. (30) antidepressants, neuroleptics, antipsychotics, benzodiazepines, sedative-hypnotics, and antihypertensive drugs were shown as the drugs that increase the risk of falling the most. In addition, it should be taken into account that people with multimorbidity will use drugs more and these people may have co-morbid diseases that may trigger falls.

In their article, van der Velde and Seppala (31) stated that there is a lack of knowledge about the role of drugs as a fall risk factor in caregivers of the elderly. They also stated that the members of the task & finish group of European Geriatric Medicine Association are engaged in activities aimed at raising public awareness and disseminating information to facilitate appropriate (de)prescription in elderly people at risk of fall. It is important to increase such educational activities for healthcare professionals, caregivers, and patients about drugs that increase the risk of falls (31).

Measures that can be taken to prevent falls are not limited to deprescribing risky drugs. Exercises aimed at strengthening muscles and increasing balance are among them too. Correction of visual and hearing disorders, improvement of nutrition, and support of cognitive functions are other measures that can be taken. It is also important to make the environmental conditions safe for the patients at risk of falls (32).

Although there have been studies evaluating the relationship between fall risks and different geriatric syndromes, there is no

Table 3. Results of linear regression analysis

Independent variables	B	St. error	Beta	T	p
ADL	–0.053	0.076	–0.069	–0.696	0.488
IADL	0.021	0.028	0.076	0.752	0.454
Handgrip strength	0.001	0.005	0.018	0.212	0.004*
SMMI	0.111	0.037	0.235	2.961	0.833
Gait speed	–1.348	0.417	–0.272	–3.233	0.002*
FFI	0.245	0.062	0.481	3.967	<0.001*
SOF	0.022	0.091	0.030	0.243	0.808
MNA	–0.005	0.017	–0.030	–0.241	0.771
MNA-SF	0.005	0.020	0.023	0.237	0.813
GLIM	0.007	0.103	0.008	0.069	0.945
GDS	0.02	0.009	0.181	1.239	0.027*

ADL: Activities of daily living, IADL: Instrumental activities of daily living, MNA: Mini nutritional assessment, MNA-SF: Mini nutritional assessment-short form, GLIM: Global leadership initiative on malnutrition, FFI: Fried frailty index, SOF: Study of osteoporotic fractures, SMMI: Skeletal muscle mass index, GDS: Geriatric depression scale

Table 4. Results of linear regression analysis

Independent variables	B	St. error	Beta	T	p
ADL	0.019	0.036	0.042	0.527	0.559
IADL	–0.045	0.018	–0.258	–2.537	0.012*
MMSE	0.001	0.006	0.017	0.187	0.852
FFI	0.011	0.033	0.033	0.334	0.739
SOF	–0.038	0.049	–0.076	–0.786	0.434
Handgrip strength	–0.003	0.003	–0.083	–1.172	0.244
Gait speed	–2.327	0.214	–0.709	–10.859	<0.001*
Number of drugs used	0.000	0.010	0.001	0.014	0.989

ADL: Activities of daily living, IADL: Instrumental activities of daily living, MMSE: Mini-mental state examination, FFI: Fried frailty index, SOF: Study of osteoporotic fractures

study evaluating the effect of many geriatric syndromes on fall risk at the same time. This is a strong side of our work.

Study Limitations

The most important limitation of our study is that multiple analyzes were performed with data from a relatively small sample. In a prospective study with a larger sample, the relationship between geriatric syndromes and falls, fall-related morbidity, and mortality can be revealed. Another limitation of the study is that the assessment of depression made by the geriatric depression scale was not confirmed by the clinical assessment made by a psychiatrist. The relationship between depression and fall can be better demonstrated with a prospective study in which both detailed psychiatric evaluation and response to depression treatment and drug side effects are evaluated.

Conclusion

In our study, it was concluded that disability, malnutrition, frailty, sarcopenia, depression, and polypharmacy were more common in patients with a high risk of falls. In addition, deterioration in cognitive functions was also higher.

Falls are important geriatric syndromes that can result in morbidity and mortality in the elderly. Predicting situations that increase the risk of falling is important for effective planning of the measures to be taken. Revealing the relationship with geriatric syndromes leads us to the conclusion that effective management of geriatric syndromes can reduce the risk of falls. It would be useful to carry out studies evaluating the measures and effectiveness that can be taken in this regard.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Research Ethics Committee (number: 2019/269, date: 03.07.2019).

Informed Consent: All participants gave informed consent.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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ORIGINAL RESEARCH

Comprehensive Geriatric Assessment in a Mexican Long-term Care Facility During a COVID-19 Outbreak

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Abstract

Objective: The Coronavirus disease-2019 (COVID-19) pandemic has greatly affected long-term care facilities worldwide. In Mexico, there are no studies that assess the impact between COVID-19 and the comprehensive geriatric assessment (CGA). This article aims to investigate the effect on the geriatric assessment before and after COVID-19 infection had in residents of a long-term care facility, as well as the factors that influenced the virus transmission and its associated mortality.

Materials and Methods: This is a prospective observational study that included 90 older adults during an outbreak of COVID-19 in a long-term care facility in Monterrey, Nuevo León, Mexico. Participants' geriatric assessments were designed using their history records, comorbidities and Barthel index, Folstein's mini-mental state examination, geriatric depression scale, mini nutritional assessment, and polypharmacy.

Results: When comparing the CGA before and after the COVID-19, Barthel index median was 90 vs 57.7 (p=0.001), the mini-mental state examination median was 23 vs 19 (p=0.001), the geriatric depression scale median was 4 vs 5 (p=0.007), the weight mean was 59.63 vs 56.95 (p=0.001), the body mass index mean was 23.9 vs 23.19 (p=0.009), and the mini nutritional assessment median was 23 vs 21.5 (p=0.001). Mortality in positive residents of COVID-19 was significantly higher in those with a polypharmacy >8 and mini-mental state examination <10 points.

Conclusion: This study highlights the vulnerability of older adults to COVID-19 infection associated with high mortality and their global deterioration in the post-infection stage. Likewise, mortality in our population was higher in those with polypharmacy and cognitive impairment. These results guide us to create preventive measures that improve the quality and survival of geriatric COVID-19 patients.

Keywords: COVID-19, comprehensive geriatric assessment, older adults, long-term care facilities

Introduction

Coronavirus disease-2019 (COVID-19) has had a devastating impact in Mexico, ranking among the top five countries most affected by the virus with 10.4% in an observed case-fatality ratio (vs 2.8% in the United States) and 65.56 deaths per 100,000 people (vs 64.74 per 100,000 in the United States) (1). By August 2021, Mexican government statistics have reported 1,637,836 excess deaths, from which it is estimated that 360,034 were caused by COVID-19; this represents an increase of 44.2% in the excess mortality (2). Of these deaths, 910,464 were found within the population over 65 years of age, resulting in an excess mortality of 41.2%. These data are similar to the ones reported in the State of Nuevo León (42.4%) and, unfortunately, a significant percentage of these deaths do not have a confirmatory test for a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (2).

In March 2020, the first COVID-19 case was confirmed in Monterrey, Mexico. By August 12, 2021, the State of Nuevo Leon statistics reported 138,406 accumulated cases and 11.780

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deaths due to COVID-19 (3). Of these, 138 infections in older adults occurred in multiple long-term care facilities (LTCF's) in Monterrey; nonetheless, data have not been updated in months. A potential reason is that most of these institutions are private and are afraid that the government regulatory bodies will close down the facilities (3).

Evidence has shown an exponential mortality increase in patients over 50 years; therefore, there has been an emphasis on protecting LCTF's residents since early in the pandemic (4). However, research on LTCF's is limited (5). In the United States, by May 21, 2021, over 35,000 deaths have been reported in LTCF's, representing 42% of total deaths due to COVID-19; LTCF's with more than 50 residents are the most affected (6). A study published in September 2020 reported that the mortality in 12 member countries of the organization for economic co-operation and development was 47.3% in LTCF's and 44.7% in older adults living in the community (7). In addition to the greater risk in the elderly population, it is extremely important to consider the frailty syndrome in this population, since mortality reaches up to 33.7% in frail adults infected by COVID-19 (8).

Literature on COVID-19 infections at LCTF's and their post-infection impact on the elderly measured by the comprehensive geriatric assessment (CGA) in Mexico is scarce. Therefore, this study aims to i) Describe the COVID-19 outbreak in a LTCF in Monterrey, ii) Recognize factors that could have influenced the transmission of the SARS-CoV-2 and the mortality caused by COVID-19, and iii) Measure geriatric assessments after residents re-entry to the LTCF.

Materials and Methods

An observational, prospective study was carried out in a LCTF in Monterrey, Mexico. The CGA was evaluated in two stages: 1) In May 2020, representing the period patients received a confirmatory COVID-19 active infection, and 2) After their readmission to the LTCF in July 2020. The SARS-CoV-2 infection was confirmed through a reverse transcription-polymerase chain reaction test. Nuevo Leon's Health Ministry collected and processed COVID-19 tests.

Residents' socio-demographic characteristics and medical history were collected from patients' health records. Participants' functional status was evaluated using the Barthel index (BI) to measure their performance on activities of daily life (ADLs) (9), cognitive status was evaluated with Folstein's mini-mental state examination (MMSE) (10), and emotional status was measured according to the geriatric depression scale (GDS) (11). Additionally, we evaluated the participants' nutritional status using the mini nutritional assessment (MNA), including their measurements to calculate their body mass index (BMI) (12). Polypharmacy was also evaluated and defined as patients receiving a prescription of 8 or more drugs (13).

Statistics

Statistical analysis was done by IBM SPSS v22 software. Continuous variables are presented as the median and interquartile range or mean $\pm$ standard deviation. Categorical variables are described as frequencies with their respective percentages (%). The distribution of numeric variables was measured with the Kolmogorov-Smirnov test. Differences between groups were evaluated using the Mann-Whitney U test for numeric variables without a normal distribution, while the student t-test for independent groups was used for numeric variables with a normal distribution. The Wilcoxon test and the paired t-test were used for numeric variables with a non-normal and normal distribution, respectively, to evaluate the differences before the outbreak and after the patients' readmission. Differences in proportions were evaluated with the chi-square test. A binary logistic regression was performed adjusting for age and sex and including all the variables with a p-value <0.1 in the bivariate analysis. Statistical significance was defined as a p-value <0.05.

Results

Ninety patients were examined prior to the COVID-19 outbreak. The mean age was 84.71±7.47, and the range was 67-101 years. Sixty-one (67.8%) were females and twenty-nine (32.2%) males. The median outcome of the BI evaluation was 80 (38.75-95), and 17 (18.9%) patients were classified as totally dependent. The cognitive evaluation resulted in a median MMSE of 21 (13-26); 29 (65.4%) patients had a degree of cognitive impairment. The median GDS score was 4 (2-6); 21 (23.3%) were classified as having depression. Finally, patients' nutritional status had a mean weight of 57.66±14.46 kg, with a mean BMI of 23.7±4.6 and a median MNA of 23 (19.25-25). 33 (36.7%) were underweight, 19 (21.1%) were overweight or obese, 39 (43.3%) were at risk of malnutrition, and 11 (12.2%) were malnourished.

The median of prescribed drugs was 6 (4-9) and 30 (33.3%) residents reported having polypharmacy. The most frequently prescribed drug groups were antidepressants in 52 (57.8%), acetylsalicylic acid in 35 (38.9%), and lipid-lowering drugs in 33 (36.7%) (Table 1). Regarding chronic degenerative diseases, 52 (57.8%) were hypertensive, 24 (27.7%) were diabetic, and 25 (27.8%) had hypercholesterolemia. Since March 2020, 49 (54.4%) residents have taken vitamin C 1.000 mg and zinc 50 mg daily.

On May 2, 2020, 5 people (two staff and three residents) reported fever. The following day, six additional residents reported fever, and health authorities were notified. On May 4, 10 residents had a positive test for COVID-19, and in the next 24 hours, over 50 COVID-19 tests from people within the LTCF were positive. Consequently, all residents were transferred to different healthcare facilities. On May 9, 2020, the staff positive

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Table 1. Baseline characteristics of residents before the outbreak

Socio-demographic features	N (%)
Age, mean ± SD, years	84.71±7.47
Sex, female	61 (67.8)
BI, median (IQR)	80 (38.75-95)
BI >90	36 (40)
BI 61-90	21 (23.3)
BI 21-60	16 (17.8)
BI <21	17 (18.9)
MMSE, median (IQR)	21 (13-26)
MMSE >24	31 (34.4)
MMSE 17-24	29 (32.2)
MMSE 10-16	15 (16.7)
MMSE <10	15 (16.7)
GDS, median (IQR)	4 (2-6)
GDS >5	21 (23.3)
MNA, median (IQR)	23 (19.25-25)
MNA 24-30	36 (40)
MNA 17-23.5	39 (43.3)
MNA <17	11 (12.2)
Weight, mean ± SD, kg	57.66±14.46
BMI, mean ± SD, kg/m²	23.7±4.6
BMI <18.5	9 (10)
BMI >24.9	33 (36.7)
Arterial hypertension	52 (57.8)
Type 2 diabetes mellitus	24 (27.7)
Hypercholesterolemia	25 (27.8)
Medications, median (IQR)	6 (4-9)
Polypharmacy	30 (33.3)
Antidepressants	52 (57.8)
Acetylsalicylic acid	35 (38.9)
Lipid-lowering agents	33 (36.7)
PPI	31 (34.4)
ACE inhibitors	26 (28.9)
Benzodiazepines	25 (27.8)
ARBs	23 (25.6)
Antipsychotics	22 (24.4)
Analgesics	20 (22.2)
Oral antidiabetics	16 (17.8)
Anti-dementia	15 (16.7)
Diuretics	12 (13.3)
Insulin	10 (11.1)
Antiprostatic hypertrophy agents	10 (11.1)
Beta-blockers	7 (7.8)
Oral contraceptives	3 (3.3)

SD: Standard deviation, BI: Barthel index, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, MNA: Mini nutritional assessment, BMI: Body mass index, PPI: Proton-pump inhibitors, ACE: Angiotensin-converting enzyme, ARBs: Angiotensin II receptor blockers

for COVID-19 was isolated in a shelter, and the 90 residents were taken to different medical units, separating the positive cases from the negatives. As for the residents with a positive test for COVID-19, 41 (62.1%) were transferred to private centers, 22 (33.3%) to public centers, and 3 (4.5%) to their homes.

Out of the 90 residents (R), 66 (73.3%) had a positive test for COVID-19 (R+) and 24 (26.6%) a negative one (R-). When comparing both groups, the R+ group had a lower mean age, fewer women, and a lower vitamin C and zinc intake; however, none of these differences resulted in a statistically significant p-value (Table 2). Further, we found a BI median of 90 (50-100) in the R+ group and of 45 (16.25-92.5) in the R- group, suggesting that a greater independence in the ADLs, greater the risk for contagion (p=0.003). Similarly, when evaluating the cognitive status, we observed a median MMSE in the R+ group of 23 (15.75-27) and of 15 (1-23.75) in the R- group, suggesting that a higher cognitive performance, the greater the risk of infection (p<0.001). The nutritional assessment resulted in a median of MNA in the R+ group of 23.5 (21-25.5) and 18.5 (16.62-24) in the R- group, suggesting that a higher MNA result, greater is the risk of infection (p=0.006). The BMI was higher in the R+ group (23.9±3.81 vs 23.19±6.28); however, statistical significance was not reached (p=0.524). Nonetheless, a higher proportion of low-weight residents was found in the R- group (p=0.010). The GDS score and weight were higher in the R+; however, no statistically significant difference was observed. In addition, the proportions of residents with polypharmacy, hypertension, diabetes, and hypercholesterolemia were higher in the R+ group without reaching a statistically significant difference (Table 2).

Of the 90 residents, 26 (28.9%) died, 20 before returning to the LTCF, and six within the five months after returning. Out of the residents who died, the majority were women (57.7% vs 42.3%; p=0.192) and were R+ (80.8% vs 19.2%; p=0.309). Participants were most frequently admitted to a public medical centre (57.1% vs 42.9%), with patients treated in a private medical facility reporting fewer deaths (p=0.008).

From June 15, 2020, residents started to return to the LTCF. By October 1, 2020, there were 59 residents due to the relatives' decision of 5 (7.8%) not to return. Out of the 59 residents, 17 (28.8%) were R- and 42 (71.2%) R+; 41 (69.5%) women and 18 (30.5%) male. When evaluating participants with the CGA, we compared the results between the R+ survivors and those who died, 20% had an MMSE <10 (p=0.048), 60% had polypharmacy (p=0.030), and the rest of the variables were not statistically significant (Table 3). In addition, the CGA was compared with the assessment prior to the outbreak, finding that after readmission to the LTCF, there was a greater functional dependence in the ADLs (p<0.001), lower cognitive performance (p<0.001), a higher score on the GDS (p=0.007), a lower nutritional status (p<0.001) and a lower BMI (p=0.009) in the residents (Table 4).

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Table 2. Comparison of residents with a positive (R+) and negative (R-) test for SARS-CoV-2

	R+ (n=66)	R- (n=24)	p-value
Age	84.14±7.64	86.29±6.9	0.228
Sex, female	42 (63.6%)	19 (79.2%)	0.163
Vitamin C + zinc	35 (53%)	14 (58.3%)	0.655
BI	90 (50-100)	45 (16.25-92.5)	0.003*
BI >90	30 (45.5%)	6 (25%)	0.079
BI <21	7 (10.6%)	10 (41.7%)	<0.001*
MMSE	23 (15.75-27)	15 (1-23.75)	<0.001*
MMSE <10	7 (7.6%)	10 (41.7%)	0.101
GDS	4 (2-6)	4 (2-5)	0.694
GDS >5	18 (27.2%)	3 (12.5%)	0.142
Weight	58.86±10.62	54.55±21.44	0.217
BMI	23.9±3.81	23.19±6.28	0.524
BMI <22	19 (28.7%)	14 (58.3%)	0.010*
MNA	23.5 (21-25.5)	18.5 (16.62-24)	0.006*
MNA <17	5 (7.57%)	6 (25%)	0.025*
Number of prescribed drugs	7 (4-9)	4 (2.25-8.5)	0.113
Polypharmacy	24 (36.4%)	6 (25%)	0.312
Hypertension	40 (60.6%)	12 (50%)	0.368
Type 2 diabetes mellitus	21 (31.8%)	3 (12.5%)	0.067
Hypercholesterolemia	28 (42.4%)	9 (37.5%)	0.675

BI: Barthel index, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, MNA: Mini nutritional assessment, BMI: Body mass index, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, *a p-value <0.05 is statistically significant

Table 3. Comparison between the residents with a positive COVID-19 who survived (R+ survivors) and died (R+ deceased)

	R+ survivors (n=48)	R+ deceased (n=15)	p-value
Age	83.79±7.82	85.2±7.02	0.536
Sex, women	31 (64.6%)	8 (53.3%)	0.434
Vitamin C + zinc	27 (56.3%)	5 (33.3%)	0.121
BI	90 (61.25-100)	80 (40-95)	0.148
BI >90	23 (47.9%)	6 (40%)	0.591
BI <21	4 (8.3%)	3 (20%)	0.209
MMSE	23 (18-27)	21 (11-25)	0.228
MMSE <10	2 (4.2%)	3 (20%)	0.048*
GDS	4 (2-5.5)	5 (2-9)	0.446
GDS >5	11 (24.4%)	6 (46.2%)	0.129
Weight	59.93±10.53	56.02±10.57	0.230
BMI	23.55±5.27	23.41±3.29	0.925
BMI <22	14 (31.1%)	4 (28.6%)	0.857
MNA	24 (21-25.5)	23 (20-24.25)	0.260
MNA <17	4 (8.9%)	1 (7.1%)	0.838
Number of prescribed drugs	7 (4-8.75)	9 (4-10)	0.150
Polypharmacy	14 (29.2%)	9 (60%)	0.030*
Hypertension	30 (62.5%)	9 (60%)	0.862
Type 2 diabetes mellitus	14 (29.2%)	6 (40%)	0.431
Hypercholesterolemia	20 (41.7%)	8 (53.3%)	0.427

COVID-19: Coronavirus disease-2019, BI: Barthel index, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, MNA: Mini nutritional assessment, BMI: Body mass index, *a p-value <0.05 is statistically significant

Lastly, the binary logistic regression did not show a statistically significant value between the included variables and the risk for infection. However, having an MMSE <10 and reporting polypharmacy increased the risk of mortality in the R+ group by 11 and 4 times more, respectively (Table 5).

Discussion

To the authors' knowledge, this is the first study in Mexico that evaluates the impact of COVID-19 on LTCFs using the CGA and compares the physical, psycho-affective, mental, and nutritional status before and after a COVID-19 outbreak. The LTCF evaluation has been characterized by providing daily rehabilitation services to the patients from their admission to the unit, fostering the preservation and improvement of the physical, cognitive, and emotional health according to the individual resident's needs.

Among the residents of the LTCF, 66 of them were diagnosed with COVID-19, and 15 died, resulting in an attack rate of 73.3% and a fatality rate of 22.7%. Similar results were observed compared to studies in different European countries, where attack rates in nursing homes long stay due to COVID-19 outbreaks oscillated in 60% and the fatality rates have been between 15 and 34%

Table 4. Comparison of residents' performance prior to the outbreak and after their readmission to the LTCF

	Prior the outbreak	After readmission	p-value
BI	90 (45-100)	57.5 (10-95)	<0.001*
MMSE	23 (13-27)	19 (11-26)	<0.001*
GDS	4 (2-5)	5 (3-7)	0.007*
Weight	59.63±15.41	56.95±14.93	<0.001*
BMI	23.9±4.85	23.19±4.83	0,009*
MNA	23 (19.75-25.5)	21.5 (18.75-23.12)	<0.001*
Number of prescribed drugs	6 (4-9)	6.5 (4-8.25)	0.246

BI: Barthel index, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, MNA: Mini nutritional assessment, BMI: Body mass index, *a p-value <0.05 is statistically significant, LTCF: Long-term care facilities

(14,15). This demonstrates the increase in mortality that has been described with increasing age (16).

A significantly higher incidence of COVID-19 cases was detected in older adults with low physical dependence in the ADLs, with a median BI of 90 (50-100) in residents with COVID-19. This could

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Table 5. Regression analysis of factors that increased the risk of transmission and mortality due to COVID-19

	OR	95% CI	p-value
Variables related to an increased risk of COVID-19 infection			
BI <21	0.466	0.081-2.675	0.392
MMSE	1.051	0.971-1.137	0.217
BMI <22	0.621	0.157-2.466	0.499
MNA	1.026	0.816-1.292	0.824
Type 2 diabetes mellitus	2.142	0.489-9.386	0.312
Variables related to an increased risk of COVID-19 mortality			
MMSE <10	11.111	1.369-90.909	0.024*
Polypharmacy	4.651	1.218-17.765	0.025*

COVID-19: Coronavirus disease-2019, BI: Barthel index, MMSE: Mini-mental state examination, MNA: Mini nutritional assessment, BMI: Body mass index, CI: Confidence interval, OR: Odds ratio, *a p-value <0.05 is statistically significant

be related to the route of transmission of the virus: Mainly from person to person (staff-residents), and the increased social contact in adults with greater functionality. Compared to Spanish LTCF's, where residents with moderate to total dependence were more vulnerable to the risk of transmission of SARS-CoV-2, associated with closer physical contact between workers and residents, facilitating transmission (17). Likewise, significant results were found when evaluating the functionality in ADLs before and after the COVID-19 outbreak at the facility, finding a considerable 32.5 decrease in the BI median. This decrease might be the consequence of the length of stay, functional depression, and the need for restrictive mobility in most of them, thus increasing dependency (18).

A significant cognitive decline (4-point median MMSE score decrease) was found in COVID-19 positive older adults after readmission to the LTCF. It is important to emphasize that progress to a moderate cognitive impairment was observed in the vast majority of the residents. Moreover, higher mortality was found in residents with a positive test for COVID-19 and an MMSE <10 points. Post-acute manifestations have been described as associated with cognitive impairment with or without fluctuations, including memory problems manifesting as difficulty in concentration, memory, receptive language, and/or executive function (19). Furthermore, long-term cognitive impairment is well recognized after a critical illness occurring up to 20-40% of patients discharged from intensive care (20).

Regarding the affective mood behaviour, we found a significant change in the GDS-15 scale items of the residents evaluated after returning to the institution, resulting in an overall median increase of 4 to 5 points, considering that most of the residents before the pandemic did not report symptoms of depression. Our results coincide with studies where depression, measured with the same instrument, was exacerbated by up to 86.6% two weeks after being discharged from the hospital in patients aged 65 or older who survived COVID-19 (21). Demonstrating that

social disconnection and isolation are risk factors for presenting a depressive mood in older adults (22).

Concerning nutritional status of the residents, a significantly higher proportion of underweight and malnutrition was observed in the non-infected residents. This aligns with the explanation that the highly dependent population in the ADLs with a higher risk of sarcopenia has less mobilization and less social contact with other residents and staff; thus, reducing the risk of infection. Similarly, a significant change was observed in the decrease in residents' weight, BMI, and MNA after the COVID-19 outbreak. For these reasons, it is vital to identify and prevent a nutritional decline in hospitalizations and improve clinical outcomes in patients at nutritional risk. It has been found that the MNA-SF (short-form) scale predicted in a good way the worst clinical results after COVID-19 infection (23). On the other hand, when using the MNA scale in full version in patients with COVID-19, found a positive correlation between poor nutritional status and a prolonged stay in the intensive care unit (24).

It was observed that polypharmacy was significantly associated with higher mortality in residents who tested positive for COVID-19. Sixty percent of the residents who died had polypharmacy, and the regression analysis resulted in four times the risk of dying in this sub-group compared to the rest of the residents with COVID-19. Polypharmacy has unpredictable consequences as cohort studies reported that up to 50% of American older adults use at least five drugs, of which 1 in 2 have been found to have significant interactions with drugs tested for COVID-19, such as hydroxychloroquine (25). In the REACT-SCOT study, an evident association was found between the severity of COVID-19 and polypharmacy, mainly in using more than four drugs of different classes. In addition, it was found that the severity of the infection is strongly associated with antipsychotics, proton pump inhibitors, opioids, and gabapentinoids, since an increase in activity associated with pneumonia has been found by different routes, mainly anticholinergic and by mechanisms that increase the severity such as sedation, respiratory depression, and dyskinesia (26).

Among the chronic-degenerative diseases, we found a statistical trend between the presentation of COVID-19 and type 2 diabetes mellitus (27). This could be explained by the alterations in the expression of the surface receptors of the converting enzyme angiotensin 2, which has a binding region with a high affinity for the S protein of the SARS-CoV-2 virus (28). In addition, there is a dysregulation of the immune system due to the increase in interleukin-6 and the weakening of anti-inflammatory signals producing more significant damage to the affected organs (29). On the other hand, a meta-analysis found that hypertension and diabetes are highly associated with an increase in severity and mortality from COVID-19 of 2.3 and 2.5 times, respectively (30).

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Study Limitations

Our study had limitations worth mentioning: we do not know the evolution that the patients had during their infection and what could have influenced their outcome (e.g., clinical evolution, possible complications, laboratory findings, received treatment, and whether or not they received any rehabilitation). It is important to emphasize that a significantly lower mortality rate was found in private medical centers than public ones, which would be associated with better availability of human, pharmacological, and medical devices resources. Lastly, the results should be interpreted with caution due to the size of the study group.

Conclusion

The COVID-19 pandemic, as observed in other countries and Mexico, not being the exception, confirms the vulnerability in the functional, cognitive, emotional, and nutritional aspects of the elderly. An essential factor to consider is that most of the residents evaluated in this study who were positive cases were patients with a better global status in all indicators considered in the study, which would be associated with a greater risk of infection. In our population, we found higher mortality in residents with polypharmacy and with an MMSE <10 points. In addition, a significant change was found in functional dependence in the ADLs, cognitive impairment, emotional mood changes and nutritional status after the COVID-19 outbreak in the LTCF. Currently and with the growing information that we have about COVID-19, changes are needed in the CGA to provide measures that promote preventive, diagnostic, and therapeutic options to preserve and improve the quality of life and even decrease mortality in the elderly associated with COVID-19 infection.

Ethics

Ethics Committee Approval: The Ethics Committee of Asilo Luis Elizondo through its members of the Council formed by Fomento Moral y Educativo A.C. authorized the preparation of this manuscript entitled: Comprehensive Geriatric Assessment in a Mexican Long-Term Care Facility during a COVID-19 Outbreak.

Informed Consent: All the relatives and residents of the Asilo Luis Elizondo upon admission sign an informed consent on the use of their personal and clinical data to carry out clinical research work.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G., Concept: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G., Design: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G., Data Collection or Processing: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G., Analysis or Interpretation: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G., Literature Search: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G., Writing: F.C.F., J.D.D.G.R., L.E.F.G., J.V.G.

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

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL RESEARCH

Short-term and Long-term Outcome Predictions of Older Adults Based on Geriatric Scores: A Prospective Study

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Abstract

Objective: With the increasing proportion of older patients (≥80 years) requiring medical care, it becomes highly essential to determine their health outcomes, which will further aid in providing personalized medical care. However, there are limited studies suggesting the use of geriatric scores, namely, frailty score, comorbidity-polypharmacy score (CPS), and Katz index for outcome prediction in the Indian population. Thus, the objective of the current study was to assess the reliability of each of the aforementioned three parameters in predicting the health outcomes (survival) of older patients.

Materials and Methods: The study population consisted of 300 patients, aged 80 years and above, admitted to the intensive care unit (n=150) and wards (n=150) during the study period of 18 months. We recorded patient demographics and sequential organ failure assessment scores at 24 hours of hospitalization, categorized patients based on clinical frailty scale (CFS), activities of daily life index and CPS at admission and examined their survival at 30 and 180 days.

Results: The prevalence of the older population among the overall patient population in the hospital was estimated to be 8.85%. Through our analyses, we found that both 30-day and 180-day survival rates were decreased with lower Katz scores ≤4 and higher CFS >3 and CPS >7 scores, suggesting the use of the three scores as independent predictors of short-term and long-term outcomes in the older population.

Conclusion: We suggest the potential use of the geriatric scores (CFS, CPS, and Katz index) for outcome prediction in the Indian population.

Keywords: Activities of daily life, comorbidity-polypharmacy, older patients, frailty, outcome prediction, survival

Introduction

The outcome prediction plays a pivotal role in determining the health conditions of patients, particularly in intensive care medicine wherein increasing attention has been on developing severity models for the outcome prediction (1). In recent years, outcome prediction in the older population (≥80 years) has gained substantial attention because of the increased life expectancy in several countries (1). Thus, predicting the short-term and long-term outcomes in the aforementioned group would help in better prognostication and in providing personalized medical care to this biologically heterogeneous population.

Previous research has demonstrated that associating age with the severity of illness at admission could only partially explain the survival of older patients, suggesting the inefficiency of traditional prognostic scoring systems (2). Furthermore, it has been suggested that, in older patients (≥80 years), the ability to deal with severe stressors such as critical illness correlates with the geriatric syndromes, including frailty (3), cognitive decline, and deteriorating performance on the activity of daily life (ADL) scale along with comorbidity (2). Frailty is a clinical state of older patients characterized by age-associated failures of multiorgan systems, thereby rendering the patients with increased vulnerability for adverse health outcomes (4). Additionally, several studies have suggested the importance

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of frailty score in geriatric medicine as frailty is associated with increased risk of poor outcomes such as falls, depression, disability, and mortality (5). A study by Hao et al. (6) reported the prevalence of frailty among older adults and showed an increase in death and hospital readmission rates of frail patients when compared with those of non-frail patients. Moreover, the care of old frail patients is often complicated by conditions such as comorbidity and polypharmacy; however, the correlation between frailty and comorbidity-polypharmacy remains to be investigated. Multiple chronic health conditions usually develop along with the increasing age, and modern medical management of chronic medical conditions often put the patients at a risk of polypharmacy or multiple medications. Evans et al. (7) introduced the comorbidity-polypharmacy score (CPS), a sum of the number of pre-injury medications and the number of comorbidities, to better quantify the severity of comorbidities and complement existing injury severity scoring tools for precise prediction of clinical outcomes in the older population. Amemiya et al. (8) stated that more than 10% of patients older than 80 years may have extended postoperative disability. Additionally, postoperative performance of patients, assessed by ADL and quality of life, have become essential to accurately predict outcomes of surgical treatment for the older population (8). Frequently, the ADL is determined using the Katz index of independence as it assesses the basic activities of daily living. Necessity of supervision, personal assistance, directive assistance, or total care for any dependent function of the Katz index are used as parameters to examine the functional ability of older people (9).

Thus, the aforementioned factors will help in more accurately predicting the functional recovery of older patients from major illness after hospitalization. However, there is limited evidence suggesting the use of frailty score, CPS, and Katz index of independence in ADL for predicting the short term and long-term outcomes of older population. Therefore, in this study, we aimed to assess the reliability of each of the three factors, namely, frailty score, comorbidity-polypharmacy score, and ADL index in predicting the health outcomes (survival) of older patients. Upon admission of the patient to the hospital, each of the three scores were correlated with survival at 30 and 180 days to establish trends in the short-term and long-term survival of patients, thereby suggesting the potential use of the three scores for outcome prediction in the Indian population.

Materials and Methods

Patients and methods

The study population consisted of 300 patients, aged 80 years and above, admitted to the intensive care unit (ICU) (n=150) and wards (n=150) during the study period of 18 months from November 21, 2019, to May 21, 2021. The study was conducted at the Department of Critical Care Medicine and Clinical Medical Wards, Sir H. N. Reliance Foundation Hospital & Research Centre (RFH), Mumbai, India and approved by the Institutional Ethics Committee of the hospital (IEC number: HNH/IEC/2019/OCS/IMED/11). All patients, aged 80 years and above, admitted for more than 24 hours in ICU and wards were considered for the study. Consistently, patients who were discharged, left against medical advice, or died within 24 hours of hospitalization were excluded from the current study. Additionally, patients or substitute decision makers who refused to provide study-related information were excluded from the study. The sample size was decided based on the study outcomes reported by Siriwardhana et al. (10). The study suggested that the prevalence of frailty is 26% in the age group 80 years and above in low-income and middle-income countries. Therefore, the study population consisted of 300 patients based on the fact that if 26% of the subjects in the population have the factor of interest, the study would require a sample size of 296 for estimating the expected proportion with 5% absolute precision.

This present study is a prospective, observational, analytical study without any control group. No additional intervention such as drugs, diagnostic procedures, or surgery were performed on the patients, except those as per usual hospital treatment protocols and methods. Informed consent was obtained from patients included in this study. Data were collected and analyzed from the electronic medical record of RFH for all adult patients admitted to the ICU and wards, as per the inclusion criteria. The following 19 parameters were recorded after 24 hours of hospitalization: Demographic profile of the patient such as age, sex, and comorbidity; date of ICU/ward admission; reason for ICU/ward admission; habitat before hospital admission; sequential organ failure assessment (SOFA) score at 24 hours; clinical frailty scale [minor (CFS $\leq$3), moderate (CFS 4-6), and severe (CFS 7-9)] at admission (11); ADL index (Katz ADL) [no impairment (Katz index=6), moderate impairment (Katz index $\leq$4), and severe impairment (Katz index $\leq$2)] at admission (9); CPS [minor (CPS $\leq$7), moderate (CPS 8-14), and severe (CPS >15)] at admission (12); intubation and ventilation; non-invasive ventilation; tracheostomy; vasoactive inotropes drugs; renal replacement therapy; length of stay in ICU; length of stay in hospital; withholding/withdrawal of life sustaining care; and survival at 30 and 180 days. We used CFS to describe patients' frailty prior to hospital admission with 9 possible classes varying from very fit prior to the acute illness to terminally ill. Similarly, we used Katz index to assess the patients' ability to perform activities of daily life independently and was stratified into 6 classes ranging from patient independent to very dependent, whereas CPS was used to determine the number of pre-injury medications and comorbidities associated with the patients. Based on CPS, patients were classified into 3 categories, namely,

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mild (CPS 0-7), moderate (8-14), and severe (CPS >15). The scoring of these geriatric tests was performed by physicians.

Statistics

We estimated the mean and standard deviation or median and interquartile range for continuous variables. We estimated the proportions for categorical variables. The mean values were compared using the t-test (for independent groups), and the non-normal data were compared using the Mann-Whitney U test. The proportions across groups were compared using the chi-square test or the Fisher's Exact test for low expected cell counts. We used the logistic regression models for multivariate analysis. The outcome in the variable was survival (short term: 30 days or long term: 180 days). The primary explanatory variable was score category (Katz index, frailty score, and CPS). The additional variables in the models were: Type of patient (ward or ICU), age, and gender. We built separate models for each score and p-values of <0.05 were considered statistically significant. Data were analyzed using the stata version 15.1 software (©StataCorp, College Station, Texas, USA).

Results

1. Patient characteristics of older patients (≥80 years) in a tertiary care hospital

In total, 300 patients were included in this study, which consisted of 150 patients each admitted to the ward and ICU. The prevalence of older population (≥80 years) among the overall patient population in the hospital was found to be 8.85% [95% confidence interval (CI): 8.27% to 9.46%]. Of the overall patient population, we found that the distribution of older male and female population (≥80 years) was 9.00% (95% CI: 8.21% to 9.85%) and 8.69% (95% CI: 7.87% to 9.57%). In our study group, the number of males admitted to the hospital were higher than that of females (58.7% vs 41.3% in ward and 52.0% vs 48.0% in ICU) (Table 1). Moreover, the average age (± standard deviation) of patients admitted to the ward and ICU was estimated to be 83.7±3.4 years and 84.9±4.3 years, respectively. Majority of the patients admitted to the hospital ward did not receive both invasive (intubation and tracheostomy) and non-invasive ventilation, vasoactive medication, and renal replacement therapy. Median length of stay in the ICU was 4.5 days. Furthermore, no considerable differences in the median SOFA scores between patients admitted to the ward and ICU were found. We also determined the reasons for hospital admission of patients and found that the most common cause of admission among ward patients was cardiovascular diseases (25.3%), whereas that among ICU patients was neurological diseases (2.3%) (p<0.001). Most of the information regarding ICU patients was collected from family and physicians, whereas almost all of the information regarding ward patients were collected from patients, family, and doctors. Survival records

for all patients were obtained through telephonic conversations and family physicians.

2. Association of CFS, CPS, and ADL index with survival at 30 days

Geriatric scores, namely, CFS, CPS, and Katz ADL index were estimated for all the patients included in our study group, and these scores were correlated with survival at both 30 and 180 days. The 30-day survival among ICU patients was estimated to be 83%, whereas 98% patients admitted to the ward survived after 30 days of admission (Figure 1). The number of impaired patients with a high degree of comorbidity was higher in the ICU than in the ward. Overall, 60.67% patients admitted to the ICU were impaired (Katz index ≤4) and 4% patients had a high degree of comorbidity (CPS >15), whereas 48.67% patients admitted to the ward were impaired (Katz index ≤4) and only 1.33% patients had a high degree of comorbidity (CPS >15), as expected. Interestingly, the number of frail patients to the ICU (12%) were lower than those admitted to the ward (20%) (Figure 2). Among ward patients, the 30-day survival of patients with moderate impairment was estimated to be 98%, whereas that of patients with severe impairment was estimated to be 82% (p<0.001). Similarly, significant differences between the 30-day survival of patients with CPS >7 (97%) and CPS >15 (50%) (p<0.001) were observed. However, no statistically significant differences were observed between the short-term survival of non-frail and frail patients in both the ward [99% (CFS ≤3), 93% (CFS 4-6), and 100% (CFS 7-9), p=0.10] and ICU patients [83% (CFS ≤3), 78% (CFS 4-6) p=0.56] (Table 2). On further analysis, we found that lower Katz scores (Katz index ≤4) and higher frailty (CFS >3) and comorbidity–polypharmacy scores (CPS >7) suggested decreased 30-day survival of older patients admitted to both the ICU and the ward (Table 3).

3. Association of CFS, CPS, and ADL index with survival at 180 days

Similarly, 180-day survival of patients admitted to the ward and the ICU was determined, and we found that 89% patients survived after 180 days of ward admission, whereas 75% patients admitted to the ICU survived (Figure 1). Among ward patients, significant differences between the long-term survival of patients with moderate (82%) and severe impairment (45%) in comparison to no impairment (100%) were observed (p<0.001) (Figure 2). Similarly, significant differences were observed between the 180-day survival of frail [54% (CFS 4-6) and 50% (CFS 7-9)] and non-frail patients (98%) (p<0.001) and those between CPS ≤7 (98%) and CPS >7 [79% (CPS 8-14) and 50% (CPS >15)] (p<0.001) admitted to the ward (Table 2). Thus, patients with lower Katz scores (Katz index ≤4) and higher frailty (CFS 3) and comorbidity–polypharmacy scores (CPS >7) were less likely to survive. We found significant differences in 180-day survival between the patients with Katz scores of 6

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Table 1. Patient characteristics

Variables	Ward	ICU	p
	n (%)		
	150 (100)	150 (100)	
Demographics			
Age			
Mean (SD)	83.7 (3.4)	84.9 (4.3)	0.005
Gender n (%)			
Female	62 (41.3)	72 (48.0)	0.296
Male	88 (58.7)	78 (52.0)	
Reasons for admission			
Acute gastrointestinal diseases	11 (7.3)	15 (10.0)	
Acute kidney injury	1 (0.7)	4 (2.7)	
Cardiovascular diseases	38 (25.3)	20 (13.3)	
Chronic liver disease	2 (1.3)	1 (0.7)	
Chronic kidney diseases	2 (1.3)	1 (0.7)	
Elective surgery	3 (2.0)	7 (4.7)	
Endocrine disorders	1 (0.7)	1 (0.7)	
Malignancy	5 (3.3)	5 (3.3)	
Haematological diseases	0 (0)	14 (9.3)	<0.001
Neurological disease	25 (16.7)	32 (21.3)	
Respiratory diseases	31 (20.7)	8 (5.3)	
Sepsis	22 (14.7)	24 (16.0)	
Trauma	9 (6.0)	18 (12.0)	
Clinical Features			
SOFA median (IQR)	1 (0, 1)	1 (0, 3)	<0.001
ICU stay median (IQR)	-	4.5 (3, 8)	
Hospital stay median (IQR)	4 (3, 6)	8 (5, 12)	<0.001
Invasive ventilation	0 (0)	34 (23)	<0.001
Non-Invasive ventilation	1 (1)	37 (25)	<0.001
Tracheostomy	0 (0)	5 (3)	0.06
Vasoactive drug support	0 (0)	36 (24)	<0.001
Renal replacement therapy	0 (0)	9 (6)	0.003
Withdrawal of life sustaining care	1 (0.7)	5 (3)	0.21

SOFA: Sequential organ failure assessment, ICU: Intensive care unit, SD: Standard deviation, IQR: Interquartile range

and ≤2 (p=0.004); however, no significant differences in the long-term survival of patients with a CPS of 8-14 and >15 were observed when compared with those of CPS <7. Additionally, we found significant differences in 180-day survival between frail (CFS >3) and non-frail patients (CFS ≤3) (p<0.001). Using each of these geriatric scores individually, we found that male patients were less likely to survive than female patients, and ward patients were more likely to survive than ICU patients, as expected, in both long and short terms (Table 3).

Discussion

According to the population census and United Nations Population Fund estimates there were 104 million older persons (above 60 years of age) in India in 2011 and this number is projected to be 173 million by 2026, thereby leading to an increase in the demands on the health infrastructure (13). Therefore, having efficient prognostic tools are important in making treatment decisions and counselling family members and patients on choices of treatments and outcomes. Thus, we conducted a prospective observational study on 300 patients, which consisted of 150 ICU and ward patients each, to assess the health outcomes of older patients (≥80 years) using CFS, CPS, and Katz ADL index. We found that the prevalence of older patients in tertiary care hospital was 8.85% and no considerable difference between the male and female populations was observed among the study groups. Through our analyses,

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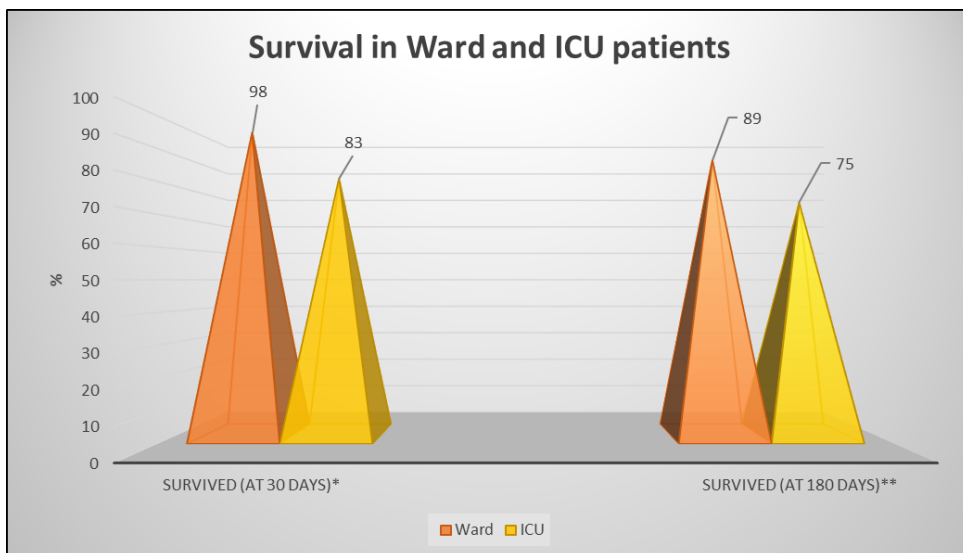
Figure 1. Survival of older ward and intensive care unit (ICU) patients at 30 and 180 days

*p<0.001, **p=0.003
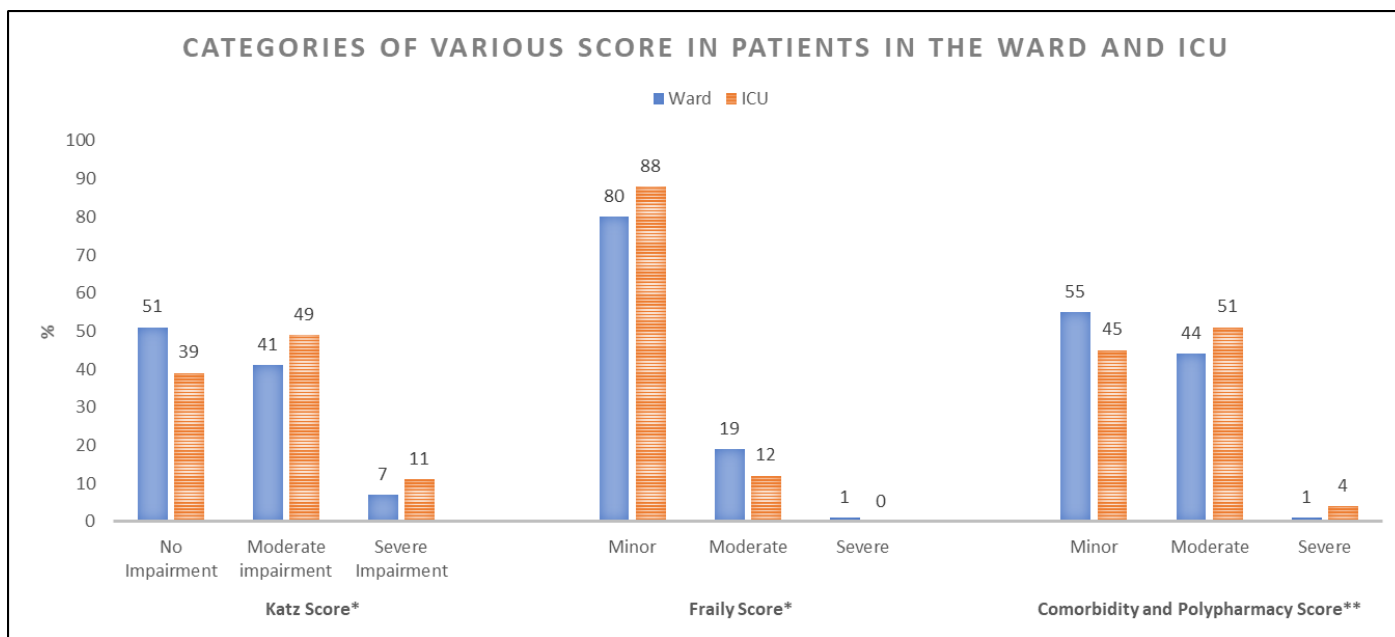
Figure 2. Categorization of older ward and intensive care unit (ICU) patients based on Katz, frailty, and comorbidity-polypharmacy scores

*p<0.09, **p=0.11

we found that both 30-day and 180-day survival rates were decreased with lower Katz scores ≤4 and higher CFS >3 and CPS >7; thus, the three scores can be suggested as independent predictors of short-term and long-term outcomes in the older population.

Frailty is a state of increased vulnerability, characterized by weakness, fatigue, decline in physical activity, and the prevalence of which increases with aging (14). Frailty is an important geriatric syndrome that is dynamic, fluctuates with time, and reflects multisystem dysfunction. In our study, the prevalence of frailty among ward and ICU patients was found

to be 20% and 12%, respectively. As per the findings of Hewitt et al. (15), the prevalence of frailty (CFS 5-8) was 49.4% among patients aged 74 years and above, and frailty was associated with early death. Moreover, it has been reported that frailty is significantly associated with 30-day mortality compared with those that were fit or non-frail (16). As expected, we found that the short-term survival rate was 78% for frail ICU patients, whereas that of non-frail patients was 83%, suggesting the use of CFS in determining health outcomes in the older population. Moreover, as per the study by Shamliyan et al. (17), the correlation of frailty with poor survival was significant in both

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Table 2. Association of Katz score, frailty score, and comorbidity–polypharmacy (CPS) score with short-term and long-term survival of ward and ICU patients

	Short term (30 days)				Long term (180 days)			
	Ward		ICU		Ward		ICU	
	All	Survived	All	Survived	All	Survived	All	Survived
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All	150 (100)	147 (98)	150 (100)	124 (83)	150 (100)	133 (89)	150 (100)	113 (75)
Scores								
Katz score								
No impairment	77 (51)	77 (100)	59 (39)	50 (85)	77 (51)	77 (100)	59 (39)	46 (78)
Moderate impairment	62 (41)	61 (98)	74 (49)	61 (82)	62 (41)	51 (82)	74 (49)	54 (73)
Severe impairment	11 (7)	9 (82)	17 (11)	4 (24)	11 (7)	5 (45)	17 (11)	13 (76)
p		<0.001		0.73		<0.001		0.80
Frailty score								
Minor	120 (80)	119 (99)	132 (88)	110 (83)	120 (80)	117 (98)	132 (88)	101 (77)
Moderate	28 (19)	26 (93)	18 (12)	14 (78)	28 (19)	15 (54)	18 (12)	12 (67)
Severe	2 (1)	2 (100)	0 (0)	0 (0)	2 (1)	1 (50)	0 (0)	0 (0)
p		0.10		0.56		<0.001		0.36
Polypharmacy score								
Minor CPS	82 (55)	82 (100)	67 (45)	55 (82)	82 (55)	80 (98)	67 (45)	49 (73)
Moderate CPS	66 (44)	64 (97)	77 (51)	64 (83)	66 (44)	52 (79)	77 (51)	59 (77)
Severe CPS	2 (1)	1 (50)	6 (4)	5 (83)	2 (1)	1 (50)	6 (4)	5 (83)
p		<0.001		0.99		<0.001		0.80
ICU: Intensive care unit, CPS: Comorbidity-polypharmacy score								

men and women, however, men were at a greater risk of death than women, which was consistent with our findings wherein men were less likely to survive than women at both 30 and 180 days [odds ratio (OR) 0.74 (95% CI 0.33-1.67), p=0.47; OR 0.50 (95% CI 0.26-0.97), p=0.04, respectively].

Furthermore, CPS is used an assessment for outcome prediction based on the patient's comorbidities and pre-injury medications (18,19). Severity of CPS is usually categorized as minor (0-7), moderate (8-14), and severe (>15) (12). In our study, the number of patients with high CPS >7 was higher in ICU patients than in ward patients. Moreover, the survival rates were found to be decreased among patients with high CPS in both ICU and ward patients, thereby suggesting that CPS can be used as a parameter to determine the short-term and long-term outcomes of older hospitalized patients. Moreover, several studies have suggested that high CPS is associated with increased mortality (20) and longer hospital and ICU stay (21) in the older population.

ADL is one of the most important factors used for outcome prediction of frail older patients. Several epidemiological studies have suggested the association of ADL with mortality prediction in older patients. Moreover, Nakazawa et al. (22) reported that patients with low ADL scores had higher mortality rates and another study by Mossakowska et al. (23) reported that a higher ADL score is a good predictor of survival. Similar observations

were made in our study group wherein both short-term and long-term survival rates were lower in moderately and severely impaired ICU and ward patients than in those with minor or no disability; thus, suggesting that low Katz scores could be a predictor of patient outcomes.

Therefore, to the best of our knowledge, this is the first study on determining the health outcomes of older Indian population (≥80 years) using three parameters, namely, CFS, CPS, and Katz index. The current study highlights the prevalence of older patients in a tertiary care hospital, and the potential use of each of the aforementioned factors in determining the short-term and long-term outcomes of older patients in the Indian population. Finally, one of the limitations of the current study is that the study was conducted based on the data collected from a single centre and may not reflect the same from other centres. Further studies are, therefore, needed to be carried out in the Indian population using the data collected from different centres across the nation for better prognosis among older hospitalized patients aged 80 years and above. Additionally, further studies are needed to be performed to understand the relation between SOFA score and mortality for our study population. Thus, our model needs to be further modified by taking into consideration the patients' nutritional status and SOFA score and correlating them with mortality. Moreover, in this study, we analyzed the association of each of these scores

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Table 3. Health outcome prediction models using Katz score, frailty score, and comorbidity–polypharmacy score in older ward and ICU patients

	Model 1 OR (95% CI); p		Model 2 OR (95% CI); p		Model 3 OR (95% CI); p	
	30–day survival	180–day survival	30–day survival	180–day survival	30–day survival	180–day survival
Katz score						
No impairment	Reference	Reference				
Moderate impairment	0.79 (0.32, 1.96); p=0.61	0.41 (0.20, 0.85); p=0.02				
Severe impairment	0.34 (0.10, 1.13); p=0.08	0.23 (0.09, 0.62); p=0.004				
Frailty score						
Minor			Reference	Reference		
Moderate/severe			0.52 (0.18, 1.45); p=0.21	0.17 (0.08, 0.36); p<0.001		
Polypharmacy score						
Minor					Reference	Reference
Moderate					0.86 (0.37, 1.97); p=0.72	0.60 (0.32, 1.13); p=0.12
Severe					0.37 (0.06, 2.23); p=0.28	0.62 (0.11, 3.39); p=0.58
Type of patient						
ICU	Reference	Reference	Reference	Reference	Reference	Reference
Ward	9.48 (2.77, 32.44); p<0.001	2.38 (1.24, 4.57); p=0.009	10.73 (3.10, 37.13); p<0.001	3.55 (1.75, 7.23); p<0.001	9.46 (2.77, 32.36); p<0.001	2.45 (1.28, 4.68); p=0.007
Gender						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	0.76 (0.33, 1.72); p=0.51	0.52 (0.27, 1.00); p=0.05	0.74 (0.33, 1.67); p=0.47	0.50 (0.26, 0.97); p=0.04	0.75 (0.33, 1.70); p=0.49	0.53 (0.28, 0.99); p=0.049

CPS: Comorbidity-polypharmacy score, ICU: Intensive care unit, OR: Odds ratio, CI: Confidence interval

individually; however, further studies need to be carried out to predict health outcomes of older patients based on a model using the interaction of three scores.

Ethics

Ethics Committee Approval: Institutional review board approved the study with the IEC number HNH/IEC/2019/OCS/IMED/11.

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: The authors declare no conflict of interest.

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ORIGINAL RESEARCH

Impact of the COVID-19 Pandemic on Frailty in Older Adults

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Abstract

Objective: This study examines the effects of the Coronavirus disease-2019 (COVID-19) pandemic on frailty in a group of older adults at the end of the first year of the pandemic.

Materials and Methods: The cross-sectional study was conducted at the end of the first year of the pandemic. Our study included 394 older adults who were contacted at primary care health centers. The FRAIL scale, the coronavirus fear scale and the scale of adjustment to measures in respiratory disease outbreaks in the Elderly were used.

Results: The average age of the 394 individuals who participated was 70.38±5.68 years. Overall, 33% of the individuals have been infected with COVID-19. It was found that the prefrail and frail older populations increased by 2.7% and 13.8%, respectively, in the first year of the COVID-19 pandemic. The pandemic was found to have a moderate effect on the frailty scores. The risk of frailty was found to be 2 [odds ratio (OR)=2.04, confidence interval (CI) (95%)=1.28-3.23] times higher in individuals that tested positive for COVID-19. The fear of coronavirus increased the risk of frailty by 1.08 times [OR=1.08, CI (95%)=1.03-1.13]. The risk of frailty was reduced by 1.03 [OR=0.96, CI (95%)=0.94-0.99] times in the older adults who complied with the precautions.

Conclusion: COVID-19 and the fear of COVID-19 it causes increase the risk of frailty among the older adults. Compliance with the recommended measures reduces the risk of frailty.

Keywords: Aged, COVID-19, frail elderly, pandemics

Introduction

Turkey confirmed its first case of Coronavirus disease-2019 (COVID-19) on March 11, 2020. Since then, six million people have tested positive for COVID-19, and 53,000 people have died. COVID-19 is highly heterogeneous, with some patients being asymptomatic to others presenting mild to severe symptoms that can lead to death. Factors including age, sex, and comorbid conditions are key determinants of the disease severity and progression. Older age is a prominent risk factor for severe disease and death from COVID-19 (1). There is overwhelming evidence from around the world suggests that age itself is the most significant risk factor for severe COVID-19 disease (2). Early data from China demonstrated that the case fatality ratio (CFR) of COVID-19 increases with age, from 0.4% or lower in patients aged in their 40s or younger to 1.3%, 3.6%, 8%, and 14.8% in people in their 50s, 60s, 70s, and 80s or older, respectively.

The overall CFR was 2.3% (3). In comparison, the overall CFR was approximately 2.8% worldwide and 2.7% in the United States as of October 19, 2020. The rising number of older adults worldwide, coupled with the unique socio-economic context, ongoing healthcare reform, and the growing development of geriatrics, creates significant challenges in combating the spread of COVID-19 (4). There is a consensus that older adults are one of the most vulnerable groups at risk of COVID-19. Therefore, public authorities have implemented a number of measures to address the needs of older adults and have increased their compliance with these measures. The older adults are expected to isolate if need be and comply with the preventive measures more easily than younger people (5). Frailty is a condition characterized by declining function across several homeostatic systems leading to increased vulnerability to stressors and the risk of adverse health outcomes. Thus, it is very likely that frailty, together with

comorbidities, may have contributed to the high vulnerability to severe clinical manifestations and death from COVID-19 among older people. Although social isolation seems beneficial in preventing the spread of COVID-19 in older adults, it may have adverse psychological and physiological consequences. Frailty is a medical syndrome that increases the dependency on another individual in daily life and/or death risk and is characterized by reduced physical function, resistance, and strength involving several factors and causes. Frailty is regarded as a significant cause of morbidity and mortality in the older adults. Although frailty has several adverse outcomes, it can be prevented and remedied (6). This study aimed to examine the effects of the COVID-19 pandemic on frailty in a group of older adults at the end of the first year of the pandemic.

Materials and Methods

This cross-sectional study was conducted in Adana Province, Turkey, in 2021 in compliance with Helsinki Declaration. Approvals for the study were obtained from the Turkish Ministry of Health and Çukurova University's Ethical Committee (number: 112). The study population consisted of people aged 65 years and older. The minimum number of patients required for a sample with a type 1 error of 0.05, type 2 error of 0.2, and effect size of 0.222 was 345 (7). A total of 394 people were included. Convenience sampling was used as the sampling method. The older adults were contacted through primary care health centers (i.e., family medicine centers, community health centers) of Çukurova University Faculty of Medicine, Public Health Department's Practice and Research Areas in Adana City. Questionnaire forms were filled in during face-to-face interviews. Written informed consent was obtained from each participants. While filling out the questionnaires, infection control measures like physical distancing, mask wearing, and hand hygiene were implemented. The data collection form consisted of four parts and collected information on patients' socio-demographic data, FRAIL scale score, Scale of Adjustment to Measures in Respiratory Disease Outbreaks in the Older adults and fear of coronavirus scale score. The socio-demographic section collected information on age, sex, place of residence, education level, income, occupation, height, weight, comorbidities, smoking status, number of medicines taken daily, and the number of household members.

Fear of COVID-19 scale

This scale consists of a single dimension and comprises seven items. The scale did not contain any reverse items. The total score obtained from all the scale items reflects the level of COVID-19 fear experienced by the individual. The scores can range from seven to 35, with higher scores indicating a higher level of COVID-19 fear (8). The validity and reliability of the scale were assessed by Bakioğlu et al. (9) previously.

Frail scale

The FRAIL scale was used to determine a patient's frailty state. A validity-reliability study of the Turkish FRAIL scale was conducted by Muradi et al. in 2017. This scale has five components: Fatigue, resistance, ambulation, illness, and weight loss. Each component is scored as zero or one, with the total score ranging from zero to five. Scores are evaluated as 0, 1-2, and 3-5 as normal, prefrail, and frail, respectively (10). Frailty was evaluated in two sub-dimensions: The pre-pandemic period and pandemic period (the end of the first year). The individuals were asked to evaluate the sub-dimensions before and at the first year of the pandemic.

Evaluation of the change in frailty

The participants were asked to evaluate the sub-dimensions of the frailty scale once in the pre-pandemic period and during the sixth month after the start of the pandemic and the declaration of curfews (social isolation). The questions were as follows: Fatigue: "Before the start of the pandemic, how much time would you feel tired over a four-week period?" "After the start of the pandemic (now), how much of the time over the past four weeks did you feel tired?" Resistance: "Before the start of the pandemic, by yourself and not using aids, did you have any difficulty walking up ten steps without resting?" "After the start of the pandemic (now), by yourself and not using aids, did you have any difficulty walking up ten steps without resting?" Ambulation: "Before the start of the pandemic, by yourself and not using aids, did you have any difficulty walking several hundreds of meters?" "After the start of the pandemic (now), by yourself and not using aids, do you have any difficulty walking several hundreds of meters?" Illnesses: "Before the start of the pandemic, how many chronic illnesses did you have?" "After the start of the pandemic (now), how many chronic illnesses do you have?" Loss of weight: "Before the start of the pandemic, how much did you weigh with your clothes on but without shoes?" "After the start of the pandemic (now), how much do you weigh with your clothes on but without shoes?" A change of >5% in weight was interpreted as frailty. The total frailty scale score was calculated by summing the scores for each sub-dimension for both the pre-pandemic period and at the sixth month of the pandemic. The difference between the pre-pandemic and post-pandemic scores (post-pandemic scores - pre-pandemic scores) yielded the final score change, with positive scores interpreted as an increase, negative scores as a decrease, and zero as unchanged.

Scale of adjustment to measures in respiratory disease outbreaks in the elderly

We recently developed the scale of adjustment to measures in respiratory disease outbreaks in the elderly. The scale contained 19 questions. An expert's council was utilized for the content

validity of the scale, and only questions with a content validity index score of above 0.60 were included. The actual scale used was a five-point Likert scale consisting of 19 questions, with scores ranging from zero to four. The Kaiser-Meyer-Olkin measure of sampling adequacy coefficient was 0.916, and Bartlett's test of sphericity had a p-value of <0.001 for suitability analyzes concerning the factor analysis for the data set. These data were confirmed as suitable for factor analysis. The Eigenvalues were 1 when obtaining the factors, with those above 1 accepted as factors. To determine the items to be included in the scale, an item analysis was performed, and item-total correlations were done. After these analyzes, the principal component analysis and Varimax rotation technique were used to determine the structure of the scale. In determining the scale items, the item-total correlation coefficients were required to be above 0.30, factor load to be over 0.50 in the factor analysis, and for a single factor to have at least a difference of 0.1 from other factor structures for convergence assumption. Two items that did not meet these assumptions and two items were removed from the scale. The scale explains 62.36% of the total variance. The final version of the scale consisted of 17 questions and three factors. The first factor was "avoiding close physical contact" and consisted of six questions. The second factor was "hand-respiratory hygiene" and consisted of seven questions. The third factor was "self-isolation" and consisted of four questions. A minimum of zero and a maximum of 68 points can be obtained from the scale. An increase in the scores indicates more compliance with the measures. Cronbach's alpha method was used for the reliability analysis. The Cronbach's alpha coefficient for the final version of the scale was 0.915 (11).

Statistics

SPSS version 22 was used for the data analysis. Normal distribution was tested using the Kolmogorov-Smirnov test. A marginal homogeneity test, Wilcoxon test, and binary logistic regression analysis were performed to analyze the data. In the effect size analyses, Cohen's d values of greater than one indicated a very large effect, 0.8 a big effect, 0.2-0.5 a moderate effect, and 0.2 a small effect. p-value <0.05 was considered statistically significant.

Results

The average age of the 394 older adult individuals who participated in our study was 70.38±5.68 years (range: 65-92 years). The socio-demographic characteristics of the study population are presented in Table 1. Of the older adults included in the study, 33% were infected with COVID-19 and 86.8% had inactivated severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccine. Moreover, 75.9% of individuals had a chronic disease, with the most common being hypertension (Table 1).

When the change in frailty among older adults individuals between the pre-pandemic period and at the end of the first year of the pandemic was analyzed, it was found that the number of older adults individuals in the "normal" group decreased by 16.1%. Consequently, this resulted in an increase of 2.7% in the prefrail group and 13.8% in the frail group (p<0.001). The difference between the pre-pandemic and pandemic frailty scores was found to be statistically significant (p<0.001). At the end of the first year of the pandemic, the effect of the pandemic on the frailty scores was found to be moderate, with Cohen's d of 0.403 (Table 2).

The logistic regression model set was found to be significant (Omnibus test p<0.001) for predicting the changes in the frailty group, including the presence of chronic diseases, the presence of COVID-19, the coronavirus fear score of the participants, vaccine status of participants and scale of adjustment to measures in respiratory disease outbreaks in the elderly. The accuracy of the model was found to be 70.6%, with a Nagelkerke R square value of 0.099. It was found that the following variables contributed significantly to the model: Being infected with COVID-19, scale

Table 1. Socio-demographic characteristics and comorbidities of the individuals

Characteristics	n/%
Sex (male/female)	196 (49.7)/198 (50.3)
Age (65-74/75-84/85 and above)	311 (78.9)/72 (18.3)/11 (2.8)
Education (illiterate/primary/ elementary/high school/ university)	83 (21.1)/138 (35.0)/67 (17.0)/59 (15.0)/47 (11.9)
Income (2700 and lower/2701-9300/9301 TL and higher)	142 (36.4)/224 (57.4)/24 (6.2)
Residential (city/town/village)	189 (48.3)/144 (36.8)/58 (14.8)
Chronic diseases (yes/no)	299 (75.9)/95 (24.1)
Hypertension	187 (47.6)
Diabetes mellitus	156 (39.6)
Cardiovascular diseases	101 (25.6)
Chronic obstructive pulmonary disease	67 (17.0)
Rheumatological diseases	25 (6.3)
Malignancy	5 (1.3)
Other	49 (12.4)
Number of daily drug (0/1-3/4-7/8 and above)	96 (24.4)/181 (45.9)/100 (25.4)/17 (4.3)
Smoking (yes/no/quit)	48 (12.2)/278 (70.6)/68 (17.3)
COVID-19 disease (yes/no)	130 (33.0)/264 (67.0)
Clinical severity (mild/moderate/ serious)	17 (13.1)/48 (36.9)/65 (50.0)
COVID-19 vaccination (yes/no)	342 (86.8)/52 (13.2)
Total	394 (100.0)
COVID-19: Coronavirus disease-2019	

of adjustment to measures in respiratory disease outbreaks in the older adults and fear of COVID-19. The risk of frailty was found to be 2.04 times higher in individuals that tested positive for COVID-19. The 0.078 unit increase in the scores of the coronavirus fear scale increased the risk of frailty by 1.081 times. Every 0.031 unit increase in the scale reduced the risk of frailty by 1.031 times (Table 3).

When the scores obtained from the scale of adjustment to measures in respiratory disease outbreaks in the Older adults were compared according to the status of having COVID-19 infection, it was found that there was a statistically significant difference between the total score obtained from the scale and the scores obtained from the hand-respiratory hygiene factor. It was found that the scores obtained from the sum of the scale and the hand-respiratory hygiene sub-factor were statistically lower in people who had COVID-19, that is, their compliance with non-pharmacological measures was less (Table 4).

Discussion

The COVID-19 pandemic moved across the globe at an unprecedented speed and has a number of health and socio-economic effects (1). The older adults are one of the risk groups most affected by the COVID-19 pandemic, with it having many direct and indirect effects on the elderly population. Its direct effects are the negative effects of the disease itself (post-COVID-19 syndrome). To mitigate these effects, patients who recover should be examined for post-COVID-19 manifestations and followed up for a long time (12). There is also a need for studies on indirect effects, which may become a problem in the future. In a study by Heckman et al. (13), it was argued that the measures applied to the elderly during the pandemic period would indirectly increase the strain on hospitals. It can be expected that the number of frail elderly will increase due to both the measures implemented to stop the spread of COVID-19 and the disease itself.

Table 2. Change in frailty before and at the end of the first year of the pandemic

Frailty groups	Before the pandemic n (%)	At 1st year of the pandemic n (%)	Change (%)	p
Normal	191 (49.2)	129 (33.1)	-16.1	
Prefrail	148 (38.1)	159 (40.8)	2.7	<0.001
Frail	49 (12.4)	102 (26.2)	13.8	
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	Cohen's d	p
Frailty score	0.98±1.18	1.50±1.39	0.403	<0.001
SD: Standard deviation				

Table 3. Logistic regression model for predicting the impact of the COVID-19 pandemic on frailty

Variables	B	p	OR	95% confidence interval for odds ratio	
				Lower	Upper
Fear of COVID-19	0.078	0.001	1.081	1.032	1.132
Scale*	-0.031	0.004	0.969	0.949	0.990
COVID-19 vaccine	0.056	0.869	1.058	0.542	2.064
COVID-19 disease	0.713	0.002	2.040	1.286	3.235
Chronic diseases	0.171	0.539	1.186	0.689	2.042
* Scale of adjustment to measures in respiratory disease outbreaks in the elderly, COVID-19: Coronavirus disease-2019, OR: Odds ratio					

Table 4. Comparison of scores from the scale according to COVID-19 disease

Scale score	COVID-19 diagnosis				
	No		Yes		
	$\bar{X} \pm SD$	Median	$\bar{X} \pm SD$	Median	p
Total score	44.49±12.40	45.0	42.58±11.09	43.0	0.047
Factor 1	15.84±5.75	17.0	15.66±4.59	16.0	0.185
Factor 2	21.17±5.34	21.0	19.79±5.58	19.0	0.009
Factor 3	7.47±3.42	7.0	7.01±3.11	7.0	0.114
COVID-19: Coronavirus disease-2019, SD: Standard deviation					

A study by Vetrano et al. (14) argued that social isolation measures taken to reduce viral transmission might have significant adverse effects on the elderly living with multiple morbidities. Social isolation is likely to affect formal and informal care, leading to loneliness, depression, anxiety, accelerated functional and cognitive decline, falls, and fractures (15). A study by Mete et al. (7) found that frailty, falls at home, and cognitive decline increased among elderly individuals during heightened periods of social isolation. It is also possible that the burden of care of these older adults might increase with mild complaints worsening enough to require hospitalization. When hospitalized, these individuals will be more isolated and at higher risk for functional decline, resulting in longer hospital stays and the need for post-discharge home care, rehabilitation, or further hospitalization (15). Increased frailty among the elderly may increase these problems and increase the indirect burden in the post-pandemic period. According to the results of our study that evaluated a group of older adults at the end of the first year of the pandemic, the rate of prefrail and frail elderly increased by 2.7% and 13.8%, respectively. The impact of the pandemic on frailty in this elderly population was found to be moderate. According to a study we conducted in the first six months of the pandemic in the same region, the percentage of pre-frailty and frailty among the elderly increased by 4.4% and 6.6%, respectively, and the impact of the pandemic on frailty was small (7). It is seen that the rate of frail older adults and the magnitude of the effect of the pandemic on frailty have increased in the second six-month period. The increase in the number of older adults with COVID-19 may partly explain this increase in frailty. We found that the risk of frailty increased two-fold in those older adults who had tested positive for COVID-19, while the fear of getting sick increased the risk of frailty by 1.081-fold. In addition, it has been observed that increasing compliance with the measures taken reduces the risk of frailty. In particular, compliance with hand-respiratory hygiene (hand disinfection and wearing a mask) is lower in people who have had the disease. There is evidence that the implementation of universal mask reduces the spread of COVID-19. In a study conducted on healthcare workers in a hospital, after a mandatory mask application, new infections among health workers (HCWs) with direct or indirect patient contact were increasing exponentially, from 0% to 21.3% (a mean increase of 1.16% per day). However, after the universal masking policy was in place, the proportion of symptomatic HCWs with positive test results steadily declined, from 14.7% to 11.5% (a mean decrease of 0.49% per day). Although not a randomized clinical trial, this study provides critically important data to emphasize that masking helps prevent transmission of SARS-CoV-2 (16).

Pre-COVID studies reported a difference between frailty categories in terms of clinical outcomes (17). Acute disease is less tolerated among the more frail older adults. The severity of the disease and the degree of frailty are important for clinical outcomes (18). Frailty is not synonymous with end-of-life. In a non-COVID-19 related study of 15,613 patients aged ≥80 years in intensive care units across Australia, those with a CFS ≥5 had significantly poorer health outcomes than age-matched peers who were less frail. However, the prevalence of in-hospital mortality (17.6% versus 8.2%) and new discharges to residential aged care facilities (4.9% versus 2.8%) suggest the majority of frail patients do survive and return home to the community (19). It was found in a systematic review conducted by Maltase et al. (20) during the COVID-19 period that intensive care hospitalization and mortality were higher among frail older adults compared to healthy older adults. Moreover, in a cohort study by Aw et al. (21) that classified 674 patients in terms of frailty, the risk of mortality was found to be 2.13 times higher in patients with high frailty during an average follow-up period of 34.3 days. The COVID-19 pandemic increases both the frailty and risk of negative outcomes in frail elderly.

Study Limitations and Conclusion

This study has several limitations in that it was conducted in a single region and used non-probability sampling.

In our study, both the fear of getting sick and the disease itself was found to increase the risk of frailty in older adults at the end of the first year of the COVID-19 pandemic. Testing positive for COVID-19 was found to be the factor that increased the risk of frailty the most. It has been found that compliance with the measures implemented to combat the pandemic protected from frailty. We assert that the risk of frailty will be reduced by ensuring that all older adults have at least two doses of a COVID-19 vaccine and comply with the recommended hand-respiratory hygiene measures. Otherwise, indirect effects of the pandemic on older adults, such as social isolation, will create a significant burden in the post-pandemic period.

Ethics

Ethics Committee Approval: This cross-sectional study was conducted in Adana Province, Turkey, in 2021 in compliance with Helsinki Declaration. Approvals for the study were obtained from the Turkish Ministry of Health and Çukurova University's Ethical Committee (number: 112).

Informed Consent: Written informed consent was obtained from each participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.M., Concept: B.M., A.İ., C.K., Design: B.M., F.T., A.İ., C.K., Data Collection or Processing: B.M.,

H.D., A.İ., C.K., Analysis or Interpretation: B.M., H.D., Literature Search: B.M., F.T., Writing: B.M., H.D.

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Examining the Awareness of Turkish Pilgrims on Protection from Respiratory Tract Infections Before the Hajj Visit: A Descriptive Study

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Abstract

Objective: Hajj is an important form of worship to which a high value is attributed by Muslims. The presence of many pilgrims approximately over the age of 60 together significantly increases the risk of developing respiratory tract infections (RTIs) and viruses [Middle East respiratory syndrome, severe acute respiratory syndrome (SARS), SARS-coronavirus-2]. This study aimed to examine the awareness of Turkish pilgrims on the prevention of infections in the airways before the Hajj visit in 2019.

Materials and Methods: A total of 382 Turkish pilgrims traveling to Mecca from Ankara in 2019 constituted the population of the study. The study was conducted in a qualitative and descriptive design. The data were collected through an acquisition information form. The participants were asked to fill out the "Acquisition information form for pilgrim candidates" prepared using a triple scale.

Results: According to the results obtained from the study, 96.9% of the pilgrim candidates stated that they should wash their hands frequently and 88.7% of them stated that they use hand sanitizer when they cannot reach any water source. 91.6% of them indicated that the handkerchiefs they used should be disposable. Over 45% of the pilgrim candidates stated that they do not know how to use air conditioners and that they do not need to know it. The statistical results showed that there was a significant relationship between the age, gender, chronic disease, educational status of the pilgrims, and their awareness levels on protective factors to prevent RTIs.

Conclusion: Pilgrims are likely to encounter many health problems in the Hajj visits. Therefore, healthcare professionals should be able to determine the accurate care that is needed by pilgrims before and after the hajj. It was determined that pilgrims need training in preventing RTIs.

Keywords: Pilgrims, geriatrics, awareness, respiratory tract infections, nursing

Introduction

World Health Organization defines a mass gathering as a planned or unplanned event that attracts a large number of people and threatens to exceed the host community's, city's, or county's health planning and response capability (1). These gatherings may be planned or unplanned and recurring or sporadic. The process of Hajj is one of the largest gatherings in the world and every year 2 million pilgrims from more than 180 countries come to Mecca (2,3).

For Muslims, Hajj is an essential act of worship. According to the 2018 official Turkish Hajj report, the overall number of pilgrims heading to Hajj was 77.000 and 52.7 percent of the pilgrims were over 60 years old (4). The collection of large masses poses health hazards due to infectious and non-communicable diseases, as well as environmental factors (e.g. temperature differential, dehydration, hypothermia). Although the Hajj missions last only one week, pilgrims frequently spend the entire month in Saudi Arabia. As a result, pilgrims may face many important health problems during the Hajj season. The most important of these health problems are heat exhaustion, heatstroke, diarrhoeal, skin infections, blood-borne diseases, cardiovascular diseases, trauma risks, and infectious disease risks (5,6). The presence of many pilgrims over the age of 60 together, especially during

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Eur J Geriatr Gerontol 2022;4(2):85-90

the Hajj, raises the risk of respiratory tract illnesses (RTIs) (7). Furthermore, due to physical exhaustion, sleep issues, and temperature variances encountered during this journey, each pilgrim's risk of contracting a respiratory system infection rises (3,8).

Infections of the respiratory tract are linked to a variety of acute syndromes and infectious disease processes all over the world. Many viruses are related to these infections, and they generally spread between humans through the respiratory system. As the name suggests, most acute upper respiratory tract infections affect areas of the upper respiratory tract, including the "cold", acute sinusitis, acute laryngitis, conjunctivitis, and otitis media. Viruses in lower respiratory tract infections affect deeper structures below the larynx, including the trachea, bronchi, and bronchoalveolar region, and manifest as bronchiolitis, bronchitis, and acute pneumonia (9). Respiratory diseases are significant public health issues (10,11). According to the literature, the prevalence of respiratory tract infections or symptoms in pilgrims returning from the a pilgrimage ranges from 8% to 90% (12-14). According to data reviewed from multiple studies, at least one symptom of respiratory diseases such as cough, expectoration, and dry cough, was reported by pilgrims during the Hajj (15,16). The most common reason for pilgrims to apply to hospitals is respiratory problems. The necessity of RTI prevention strategies has increased as a result of this predicament (17). The causes of symptoms are unknown exactly, but RTI symptoms are caused by a variety of variables that are known by health professionals. Pre-Hajj immunization, masks, disposable handkerchiefs, hand washing, hand hygiene, cough etiquette, social distancing, hand disinfectant, good diet, and proper air conditioning are all recommended by healthcare professionals (18-20). Informing pilgrims via pre-Hajj health workers is one of the methods that are effective in minimizing respiratory infection symptoms, however the literature in Turkey lacks the studies conducted in this field by nurses. This study aims to identify and demonstrate to what extent Turkish pilgrims are knowledgeable about preventing respiratory infections when they are using airways to the Hajj in 2019.

Materials and Methods

Study population

The population of the study consisted of 382 Turkish pilgrims traveling from Ankara to Mecca between April 18, 2019 and May 30, 2019, who were interviewed in collaboration with the Turkey Presidency of Religious Affairs. Pilgrims who were older than 18 years old were voluntarily included and all the participants were informed of the necessary explanations before they were provided with the consent form which was obtained from those who agreed to participate in the study.

Sample collection tools

The participants were requested to complete an "Acquisition information form for pilgrim applicants" which was produced by the researchers using a triple scale in line with the necessary literature (18-20). The questionnaire includes demographic questions with the aim of measuring pilgrims' level of awareness about RTIs before their Hajj visits (e.g. preventive vaccination, using masking, use of disposable handkerchiefs, hand washing, hand hygiene). The data of the study were collected in face-to-face interviews with the pilgrim applicants who visited government facilities for training. The forms of the participants who are illiterate and willing to participate in the study were filled in with the help of the researchers. Filling the form took approximately 5 minutes for each pilgrim.

Research ethics committee permission

Before the study was conducted, the official permission from the Republic of Turkey Presidency of Religious Affairs was provided to conduct the research, and Ethics committee approval was obtained from Ankara Yıldırım Beyazıt University Clinical Research Ethical Board (2019-no: 16).

Statistics

SPSS was used to perform the statistical analysis of the data (IBM SPSS Statistics 24). The findings were interpreted using frequency tables and descriptive statistics. The Pearson's chi-square test and Fisher's Exact test were applied to the data in the analysis of the categorical variables. P<0.05 was considered significant.

Results

Socio-demographic characteristics of the pilgrim candidates and their answers to the questions about protective factors for preventing RTIs

The mean age of the total 382 pilgrim candidates who participated in the questionnaires was 60±8.83. Pilgrim candidates who had only primary school degrees constituted 45.8% (175 people) of the sample. It was also determined that 89.8% (343 people) of pilgrim candidates did not smoke and had at least one chronic disease 55.5% (212 people). Table 1 illustrates the data results of the questionnaire.

What stands out in Table 2 is that most of the pilgrim candidates (96.9%) stated that they should wash their hands frequently and 88.7% of them used hand sanitizer when they could not reach any water source. 91.6% of those who were interviewed indicated that the handkerchiefs they used should be disposable.

According to the findings of the study, 74.9% of the participants stated that they needed influenza vaccination before going Hajj visit. Another outstanding finding of the study revealed the fact that the participants did not know how to use air conditioners

and that they did not need to know how to use them, which constitutes 45% of the sample (Table 2).

The relationship between the demographic characteristics of the pilgrim candidates and the protective factors

The data analysis revealed that there were statistically significant connections between the age, gender, presence of the chronic condition, educational status of the pilgrim candidates, and

Table 1. Socio-demographic characteristics of pilgrim candidates

Socio-demographic characteristics (n=382)	n (%)
Gender	
Male	129 (33.8%)
Female	253 (66.2%)
Age status	
65 years old and under	261 (68.3%)
Over 65 years old	121 (31.7%)
Education status	
Illiterate	23 (6.0%)
Primary school	175 (45.8%)
Intermediate school	58 (15.2%)
High school	90 (23.6%)
Bachelor	35 (9.2%)
Master's/doctorate degree	1 (0.3%)
Smoking status	
Smoking	39 (10.2%)
No smoking	343 (89.2%)
Presence of chronic disease	
No chronic disease	170 (44.5%)
1 chronic disease	168 (44.0%)
2 chronic diseases	29 (7.6%)
3 chronic diseases	12 (3.1%)
4 and above chronic diseases	3 (0.8%)

protective variables to prevent RTIs, according to the answers collected from the 382 Turkish pilgrims (100%) before traveling to Saudi Arabia.

Our results demonstrated that as the age of the pilgrim candidates decreased, both the status of knowing how to use the air conditioner and the awareness to use the hand sanitizer increased ($\chi^2=8.990$; p=0.011, $\chi^2=7.019$; p=0.030).

The other important finding of the study revealed that there was a significant difference between gender and having enough information about protection from RTIs. This fact is explained based on the gender of the pilgrim candidates who knew how to use the air conditioner in Hajj ($\chi^2=13.912$, p=0.001) and who thought that they had enough information about protection from RTI ($\chi^2=9.342$, p=0.009). One hundred-thirty two (52.2%) of the pilgrim candidates who were female stated that they did not know how to use air conditioners or did not need to know while 87 (67.4%) of them who were male stated that they knew how to use air conditioners. In parallel with this result, it was determined that more than half of the female pilgrim candidates (53.0%) thought that they had enough information on protection from RTIs, while male pilgrim candidates (67.4%) had a higher level of knowledge on this subject.

The data analysis also revealed that there were significant connections between the age, gender, chronic disease condition, educational status of the pilgrim candidates, and protective variables to prevent RTIs, according to the answers collected from the 382 Turkish pilgrims (100%) before traveling to Saudi Arabia ($\chi^2=9.613$, p=0.008). One-hundred seventy (80.2%) of the pilgrim candidates who had at least one chronic disease stated that they knew that they should be an influenza vaccine before the Hajj. The other outstanding and meaningful finding of the study was related to the educational status of pilgrim candidates and their responses to preventive measures. It was determined that with the increase in educational status, the knowledge level

Table 2. Pilgrim candidatesW answers to the questions about protective factors for preventing RTIs

Options	Yes		No		I don't know	
Variable (n=382)	n	%	n	%	n	%
Avoiding sick individuals	292	76.5%	20	5.2%	70	18.3%
Frequents of washing of hands	370	96.9%	3	0.8%	8	2.3%
Avoiding crowded areas	286	74.8%	40	10.5%	56	14.7%
Use of hand sanitizer in case of failure to reach a water source	339	88.7%	14	3.7%	29	7.6%
Disposable handkerchiefs use	350	91.6%	5	1.3%	27	7.1%
Being the flu (influenza) vaccine before Hajj	286	74.9%	31	8.1%	65	17.0%
Thinking it is necessary to know how to use the air conditioner	208	54.5%	37	9.7%	137	36.0%
Thinking it is necessary to have enough information about protection from RTIs	221	57.9%	41	10.7%	120	31.4%
Thinking that good and balanced nutrition can prevent RTIs	338	88.5%	5	1.3%	39	10.2%
Thinking it is necessary to wear a mask outside during the Hajj period	199	52.1%	69	18.1%	114	29.8%
RTIs: Respiratory tract infections						

of pilgrim candidates about protective factors had increased. There was a significant relationship between education status and getting the influenza vaccine, and between knowing how to use air conditioners and having enough information about protection from RTIs (p=0.008, p=0.007, p=0.021) (Table 3).

Discussion

RTI is one of the most important health problems that threaten almost all pilgrim candidates during the Hajj. According to many research results, respiratory tract infection symptoms are the leading causes of hospital admission during and after the Hajj (15,21,22). Therefore, pilgrim candidates must have accurate and enough information about protective measures. Considering the answers given by Turkish pilgrim candidates to the form, they are thought to be very careful about personal issues (hand and face hygiene, disposable handkerchiefs use, etc.). These results are compatible with the literature (18,20,23). However, it was thought that they did not have enough information about influenza vaccination, the use of air conditioning, wearing a mask, avoiding sick individuals, and crowded areas. Whereas, the importance and necessity of mask using, and avoiding sick individuals and crowded areas have been shown in a lot of studies (18).

One of the most important issues in protecting RTI is vaccination. Although it is not a requirement, both the CDC and The Ministry of Health of Saudi Arabia strongly recommend that the pilgrims receive a seasonal influenza vaccine before Hajj (24,25). Unfortunately, the rate of thinking about getting the influenza vaccine before Hajj was found to be 74.9% in our study. When the result of this analysis is compared with the other researches, it has been seen that the rate is quite inadequate (23,26). In addition, it was determined that having a chronic disease and having a high educational status had a positive effect on pilgrims' vaccination status. Considering that having a chronic illness and a high educational level increase individual awareness and knowledge, we thought that it is important to inform all pilgrims about the importance of vaccination by healthcare professionals (nurses, doctors) before the Hajj. According to these useful findings, it is thought that gender has no impact on knowledge, awareness, and behavior against protection from RTI.

In our study, it was determined that men have more knowledge and awareness about protection from respiratory infections. Although studies on the subject are limited, in a study evaluating pilgrims' vaccination status, men were reported to have more influenza vaccines than women (27). In a meta-analysis in which the effect of gender on behavior to prevent respiratory diseases is evaluated, it has been reported that women are approximately 50% more likely to apply protective behaviors regarding RTI than men (28). These useful investigations showed that gender does not affect the awareness of respiratory tract infections.

Before long-term visits are planned to any country, it is necessary to obtain information about the factors that may affect our health in the country to be visited. The Hajj is one of

Table 3. Distribution of data on the answers given by pilgrim candidates to questions about protective factors to prevent RTIs

Socio-demographic characteristics	Age	Gender	Smoking status	Presence of chronic disease	Education status
Avoiding sick individuals	x^2=5.057 p=0.080	x^2=1.809 p=0.405	x^2=0.139 p=0.933	x^2=0.788 p=0.674	x^2=1.858 p=0.762
Frequents washing of hands	x^2=1.878 p=0.391	x^2=2.117 p=0.347	x^2=0.351 p=0.839	x^2=0.626 p=0.731	x^2=5.127 p=0.275
Avoiding crowded areas	x^2=2.459 p=0.292	x^2=2.126 p=0.345	x^2=3.817 p=0.148	x^2=4.522 p=0.104	x^2=2.121 p=0.714
Use of hand sanitizer	x^2=7.019 **p=0.030***	x^2=0.749 p=0.688	x^2=3.408 p=0.182	x^2=3.240 p=0.198	x^2=5.005 p=0.287
Disposable handkerchiefs use	x^2=0.637 p=0.727	x^2=0.735 p=0.692	x^2=0.039 p=0.980	x^2=0.646 p=0.724	x^2=1.599 p=0.809
To be the flu (influenza) vaccine before Hajj	x^2=1.450 p=0.484	x^2=0.046 p=0.977	x^2=0.377 p=0.828	x^2=9.613 **p=0.008***	x^2=13.916 **p=0.008***
Thinking it is necessary to know how to use the air conditioner	x^2=8.990 **p=0.011***	x^2=13.912 **p=0.001***	x^2=2.634 p=0.268	x^2=1.501 p=0.472	x^2=14.246 **p=0.007***
Thinking it is necessary to have enough information about protection from RTI	x^2=0.755 p=0.686	x^2=9.342 **p=0.009***	x^2=2.624 p=0.269	x^2=1.290 p=0.525	x^2=11.564 **p=0.021***
Thinking that good and balanced nutrition can be prevented from RTI	x^2=0.637 p=0.727	x^2=0.437 p=0.804	x^2=0.800 p=0.670	x^2=1.263 p=0.532	x^2=5.815 p=0.214
Thinking it is necessary to wear a mask outside during the Hajj period	x^2=0.328 p=0.849	x^2=1.726 p=0.422	x^2=0.065 p=0.968	x^2=0.124 p=0.940	x^2=8.510 p=0.075

*Significance level was set at 0.05, RTI: Respiratory tract infection

the longest international visits in the world. During the Hajj, in the summer months, daytime temperatures can reach 122 °F (50 °C), thus climate conditions are also one of the most important topics about which enough information should be collected before traveling. Particularly, the high air temperature poses serious health threats for pilgrims who come from different countries (24,29). There are substantial differences between Turkey and Saudi Arabia on climate conditions. This situation causes more potential health threats for Turkish pilgrims. In Saudi Arabia, there are many air conditioners around the Kaaba in hotel rooms and tunnels to reduce the negative effects of air temperature (24). Despite the poor knowledge, we can say that pilgrims who are traveling from Turkey have high average age, and the education level is generally low. It is thought that these factors increase the risk of Turkish pilgrims becoming ill in Hajj more. By the Directorate of Religious Affairs of Turkey, it is distributed a handbook to all pilgrims before every Hajj. These handbooks contain information on how air conditioners should be used. Unfortunately, in our study, more than 45% of the pilgrim candidates stated that they did not know how to use the air conditioner and that they did not think it is necessary to know. According to our study results, pilgrim candidates do not have enough awareness of this matter. In the literature, no research has been found to evaluate the knowledge of pilgrims on the use of air conditioning to prevent respiratory infections. It is suggested in this study that demonstrating the simple physical use of air conditioners to the pilgrim candidates can contribute to reducing the risk of illness and increasing awareness with the aim of preventing respiratory infections caused by air conditioning.

Nurses who have an important role in the provision of health services must take responsibility for the protection of pilgrim health (30). The needs of pilgrims should be determined by nurses (such as climate differences, preventive measures for respiratory infections, vaccination, lack of knowledge, individual hygiene, etc.) before the Hajj. Then, the content of the services to be offered should be planned and implemented. It is obvious that the care, education programs, and consultancy services that nurses offer for pilgrim health will contribute positively to the pilgrims' quality of life.

Conclusion

Pilgrims can encounter many health problems in the Hajj. Healthcare professionals should be able to determine the right care needed by pilgrims before and after the Hajj. Our research results showed that high age, low education status, presence of chronic disease affect the pilgrims' awareness and behaviors regarding RTI preventive measures. In the light of the data and results of the study, it can be concluded that vaccination and many non-pharmaceutical interventions were effective in preventing respiratory tract infections, which can be seen during

the Hajj. However, the current protective interventions are mostly inadequate. The health of the pilgrims will be protected through preventive training and follow-ups. Moreover, this study is of great importance for the protection of older adults who are considered as one of the cultural heritages of Turkish society. It is thought that future studies will contribute to the protection of pilgrim health.

Ethics

Ethics Committee Approval: Before the study was conducted, the official permission from the Republic of Turkey Presidency of Religious Affairs was provided to conduct the research, and Ethics committee approval was obtained from Ankara Yıldırım Beyazıt University Clinical Research Ethical Board (2019-no: 16).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ç., B.İ., Concept: B.Ç., Design: B.Ç., B.İ., Data Collection or Processing: B.Ç., B.İ., Analysis or Interpretation: B.Ç., B.İ., Literature Search: B.Ç., Writing: B.Ç.

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

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ORIGINAL RESEARCH

Overview of COVID-19 Vaccine and Investigation of Side Effects in Patients Over 65 Years of Age with Chronic Kidney Disease

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Abstract

Objective: The entire population should be vaccinated to prevent the spread of Coronavirus disease-2019 (COVID-19). In this study, we aimed to evaluate the acceptance of the COVID-19 vaccine and the frequency of side effects in patients over 65 years of age with chronic renal failure.

Materials and Methods: Patients with chronic renal failure over the age of 65 who applied to the nephrology outpatient clinic between 14.03.2021 and 15.04.2021 were included. Demographic characteristics, comorbidities, whether they were vaccinated, and post-vaccination symptoms were recorded.

Results: In our study, 112 patients with chronic renal failure were evaluated. 94% of the patients (105/12) reported a positive opinion about the vaccine. The most common cause of COVID-19 vaccine opposition was related to vaccine side effects (54%). Of the patients included in the study, 89 were vaccinated with CoronaVac. Side effects were seen in 23% of patients after at least one dose of CoronaVac. The most common side effects were uncontrolled blood pressure and pain at the injection site. In patients reporting adverse events after at least one dose of CoronaVac and 1st dose of vaccine; coronary vascular diseases (CVD) was significantly higher (p=0.012, p=0.001), patients receiving hemodialysis treatment had fewer adverse events (p=0.005, p=0.032), and injection site pain was more common in female patients (p=0.023, p=0.023). The most common adverse event after the 2nd dose was uncontrolled blood pressure and was significantly higher in female patients (p=0.023, p=0.001).

Conclusion: Although the rate of vaccination against COVID-19 is high in individuals over 65 years of age with chronic kidney disease, the most common reason for vaccine opposition was vaccine side effects. In addition, although the frequency of side effects was lower in our study population, uncontrolled blood pressure was observed differently and it was observed that the presence of cardiovascular disease increased the frequency of side effects.

Keywords: COVID-19 vaccine, vaccine side effects, chronic kidney disease, geriatrics

Introduction

Coronavirus disease-2019 (COVID-19) can cause a variety of illnesses, from mild respiratory infection to severe pneumonia. The COVID-19 pandemic is a life-threatening global pandemic, especially for patients and the elderly with concomitant diseases such as kidney disease (1). Controlling the COVID-19 pandemic is very important for public health. Because immunization is one of the most successful and cost-effective health interventions to prevent infectious diseases, vaccines against COVID-19 are considered of paramount importance to prevent and control COVID-19 (2). In many countries, COVID-19 vaccine hesitancy

and misinformation about COVID-19 vaccines pose significant barriers to the provision of community immunity with the COVID-19 vaccine. The main reasons for COVID-19 vaccine hesitancy are the side effects that may develop due to vaccines and the lack of belief in the vaccine's protection against infections (3,4).

Uremia caused by chronic renal failure causes inflammation and immune suppression at the molecular level (5). Immunosuppression that occurs in chronic renal failure may change the immune response against viral vaccines (6). COVID-19 vaccines are newly developed vaccines. Although clinical data

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on the side effects of COVID-19 vaccines are available in general population studies, clinical data on the side effects of COVID-19 vaccines in patients with chronic kidney disease are limited (7,8). In our study, we aimed to reveal the acceptance of the COVID-19 vaccine in patients over 65 years of age with chronic renal failure and the side effects that developed in the early period.

Materials and Methods

The vaccination process in our country started on January 13, 2021. At the first stage, only CoronaVac was available in our country. Health workers and individuals over the age of 65 were determined as the groups to be overcome in the 1st stage. Individuals aged 65 and over; 1st group, individuals aged 90 and over, 2nd group individuals aged 85-89, 3rd group individuals aged 80-84, 4th group individuals aged 75-79, 5th group individuals aged 70-74, group 6 was classified to include individuals aged 65-69 years. Vaccination was done according to group order. As of February 12, 2021, the vaccination process started for individuals aged 65-69 years.

Patients with chronic renal failure over the age of 65 who applied to the nephrology outpatient clinic between 14.03.2020 and 15.04.2020 were included in this study. Demographic characteristics of patients (gender, age), chronic diseases [diabetes mellitus (DM), hypertension (HT), asthma, chronic obstructive pulmonary disease, congestive heart failure, coronary artery diseases (myocardial infarction, angina) pectoris, documented coronary heart disease)], vaccine requests/vaccination hesitations, post-vaccination symptoms (arm pain, cough, fever, shortness of breath, diarrhea, vomiting, nausea, abdominal pain, myalgia, conjunctivitis, loss of smell/taste, pruritus), blood pressure uncontrolled, dizziness, allergic reactions) were recorded.

Statistics

Data were analyzed using the SPSS 21.0 statistical program. P-value below 0.05 was accepted as the statistical significance limit. Numerical variables were given as mean + standard deviation for normally distributed variables, and median (minimum-maximum) for skewed continuous variables. Categorical variables are shown as frequencies. Chi-square test was used to evaluate categorical data. Independent sample t-test in the analysis of continuous variables. This study was approved by the local institutional review board and waived the informed consent requirement.

Results

In our study, 112 patients with chronic renal failure were evaluated. Of the patients included in the study, 31 (28%) were hemodialysis patients and 81 (72%) patients were chronic renal failure patients who did not require dialysis treatment. Of all patients, 55 (49%) were female and 57 (51%) were male. The mean age was 72.4±6.6 years. Patients were asked for their opinions on getting the COVID-19 vaccine. While 94% (105/112) of the patients expressed a positive opinion about the vaccine, 6% (7/112) stated that they do not want to be vaccinated against COVID-19. The mean age of 7 patients who did not want to be vaccinated against COVID-19 was 72±7.6 years, and 4 (%57) were female and 3 (%43) were male. From patients who are not vaccinated against COVID-19; 57% (4/7) feared the side effects of the COVID-19 vaccine, and 29% (2/7) reported that they did not have the COVID-19 vaccine because they thought the COVID-19 vaccines were ineffective. Patients who thought they were very well protected against transmission of COVID-19 were 14% (1/7) of patients who were not vaccinated for COVID-19. There was no hemodialysis patient who did not want to have the COVID-19 vaccine. Of 105 patients who gave a positive opinion about getting the COVID-19 vaccine; 15% (16/105) were not yet vaccinated, 85% (89/105) were vaccinated against COVID-19.

Of the total 89 patients who received the COVID-19 vaccine, 27 (30%) were hemodialysis patients and 62 (%70) were chronic renal failure patients who were not on hemodialysis. Forty-six (52%) were male and 43 (48%) were female of the COVID-19 vaccinated patients. The mean age was 72.4±6.8 years. The most common comorbidities were HT (in 83 patients, 93%) and DM (in 49 patients, 54%).

Side effects were identified in 22% of patients (in 20 patients) after at least one of the vaccines. The most common adverse event was uncontrolled blood pressure (in 9 patients, 45%). All patients with uncontrollable blood pressure after the COVID-19 vaccine were previously diagnosed with hypertension. 45% (9 patients) of patients who reported adverse events after at least one of the COVID-19 vaccines, and 16% (11 patients) who did not report any COVID-19 vaccine-related adverse events had cardiovascular disease (p=0.012). Of the patients who reported side effects after at least one of the COVID-19 vaccines, 5% (in 1 patient) were hemodialysis patients, and 38% (in 26 patients) of 69 patients who did not report any side effects were hemodialysis patients (p=0.005). In addition, while there were 5 female patients with arm pain, there were no male patients with arm pain (p=0.023), among the side effects associated with the COVID-19 vaccine. There was no significant relationship between other questioned side effects related to COVID-19 vaccine and gender, age, and comorbidities.

Demographic characteristics of patients with COVID-19 vaccine and the main clinical features of the presence of adverse effects are detailed in Table 1.

After the 1st dose of COVID-19 vaccine, 17% of the patients (in 15 patients) described side effects. The most common side effects were pain at the injection site (in 5 patients, 33%) and uncontrolled HT (in 5 patients, 33%). CVD was present in

Table 1. Characteristics of patients classified according to the presence of adverse events after the COVID–19 vaccines

Parameters	Adverse effect (–) n=69	Adverse effect (+) n=20	Total n=89	p-value
Demographic features, n (%)				
Age, (mean + SD)	72.7±7.0	71.3±5.8	72.4±6.8	0.400
Sex	-	-	-	0.127
Male	30 (43)	13 (65)	46 (52)	-
Female	39 (57)	7 (35)	43 (48)	-
DM	39 (57)	10 (10)	49 (71)	0.620
Hypertension	65 (94)	18 (90)	83 (93)	0.613
CVD	11 (16)	9 (45)	20 (22)	0.012
CHF	8 (12)	4 (25)	12 (13)	0.456
COLD	4 (6)	1 (0.5)	5 (6)	1
Hemodialysis	26 (38)	1 (0.5)	27 (30)	0.005
COVID-19: Coronavirus disease-2019, SD: Standard deviation, DM: Diabetes mellitus, CVD: Coronary vascular diseases, CHF: Congestive heart failure, COLD: Chronic obstructive lung disease				

60% (9/15) of patients who described adverse events after the first dose of the COVID-19 vaccine. CVD was present in 8% of patients who did not describe adverse events associated with the first dose of COVID-19 vaccine (p=0.001). Hemodialysis patients were 7% (1/15) of the patients describing adverse events related to the first dose of the COVID-19 vaccine. Of the patients who did not describe any side effects associated with the first dose of the COVID-19 vaccine, 35% (26/74) were hemodialysis patients (p=0.032). In addition, among the side effects associated with the COVID-19 vaccine, the complaint of arm pain was questioned in 33% (5/15) of the patients, and all of the patients were female. 45% (38/84) of the patients who did not describe arm pain were female (p=0.023). There was no significant relationship between other questioned side effects related to COVID-19 vaccine and gender, age, and comorbidities.

Demographic characteristics of patients who received the first dose of COVID-19 vaccine and the main clinical features of the presence of adverse effects are detailed in Table 2.

After the 2nd dose of COVID-19 vaccine, 15% (in 13 patients) of the patients described side effects. Of the patients who described side effects after the second dose of the COVID-19 vaccine, 92% (12/13) were female and 8% (1/13) were male (p=0.001). The most common side effects were uncontrolled blood pressure (in 5 patients, 38%) and all patients with uncontrolled blood pressure were female. Of the patients who did not describe uncontrolled blood pressure, 45% (38/84) were female (p=0.023). There was no significant relationship between other questioned side effects related to COVID-19 vaccine and gender, age, and comorbidities.

While patients stated that they did not use drugs for side effects, they stated that these complaints of patients whose blood pressure was not under control lasted an average of 2 weeks.

Table 2. Characteristics of patients classified according to the presence of adverse events after the first dose of COVID–19 vaccine

Parameters	n=74	n=15	n=89	p-value
Demographic features, n (%)				
Age, (mean + SD)	72.9±7.0	70.7±5.0	72.4±6.8	0.141
Sex	-	-	-	0.239
Female	34 (46)	9 (60)	43 (48)	-
Male	40 (66)	6 (40)	46 (42)	-
DM	40 (54)	9 (60)	49 (71)	0.826
Hypertension	70 (95)	13 (87)	83 (93)	0.265
CVD	11 (15)	9 (60)	20 (22)	0.001
CHF	8 (11)	4 (27)	12 (13)	0.114
COLD	4 (5)	1 (1)	5 (6)	1
Hemodialysis	26 (35)	1 (1)	27 (30)	0.032
COVID-19: Coronavirus disease-2019, SD: Standard deviation, DM: Diabetes mellitus, CVD: Coronary vascular diseases, CHF: Congestive heart failure, COLD: Chronic obstructive lung disease				

The demographic characteristics of patients who received the second dose of COVID-19 vaccine and the main clinical features of the presence of side effects are detailed in Table 3, and the distribution of side effects after COVID-19 vaccines are detailed in Table 4.

Discussion

Since COVID-19 vaccines are newly introduced vaccines; Data on COVID-19 vaccine acceptance and COVID-19 vaccine-related adverse events are much needed to assist and guide clinicians. In this study, we presented data on COVID-19 vaccine acceptance and post-vaccine side effects in patients over 65 years of age with chronic kidney disease who were vaccinated in the first months of vaccination in our country. To date, several studies on the acceptance of COVID-19 vaccines have been reported in

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Table 3. Characteristics of patients classified by presence of adverse events after the second dose of COVID-19 vaccine

Parameters	Adverse effect (–) n=76	Adverse effect (+) n=13	Total n=89	p-value
Demographic features, n (%)				
Age, (mean + SD)	72.5±6.9	71.7±6.2	72.4 ±6.8	0.609
Sex	-	-	-	0.001
Female	31 (41)	12 (92)	43 (48)	-
Male	45 (59)	1 (8)	46 (42)	-
DM	42 (55)	7 (54)	49 (71)	1
Hypertension	71 (93)	12 (92)	83 (93)	1
CVD	16 (21)	4 (30)	20 (22)	0.325
CHF	10 (13)	2 (15)	12 (13)	0.556
COLD	72 (95)	1 (1)	5 (6)	0.550
Hemodialysis	26 (34)	1 (1)	27 (30)	0.099

COVID-19: Coronavirus disease-2019, SD: Standard deviation, DM: Diabetes mellitus, CVD: Coronary vascular diseases, CHF: Congestive heart failure, COLD: Chronic obstructive lung disease

Table 4. Distribution of adverse effects after COVID-19 vaccines

Parameters	1. Post vaccination n=15	2. Post vaccination n=13	Total n=20
Adverse effects, n (%)			
Fever	2 (13)	0	2 (10)
Myalgia	1 (6)	3 (23)	3 (15)
Dizziness	1 (6)	1 (8)	1 (5)
Ageusia	1 (6)	0	1 (5)
Uncontrolled BP	5 (33)	5 (38)	8 (40)
Arm pain	5 (33)	4 (31)	5 (25)

COVID-19: Coronavirus disease-2019, BP: Blood pressure

the literature. In general population studies, COVID-19 vaccine acceptance rates are seen to be between 46-76% (3,4). Vaccine acceptance rates of patients over 65 years of age vary between 40% and 20% (3,9,10).

In a study conducted in the hemodialysis patient population, the acceptance rate of COVID-19 vaccines was found to be 80%, and it was observed that there was a decrease in COVID-19 vaccine hesitancy with increasing age (11). 6% of our patients hesitated to have the COVID-19 vaccine. The relatively less hesitancy about vaccination in our patients may be due to the high number of deaths due to COVID-19 in our country during the study, the older patient population, and the presence of comorbidities.

Immunization is one of the most successful and cost-effective health interventions to prevent infectious diseases. Side effects of vaccines are among the most important reasons for hesitation against vaccines. In some studies, it has been found that the presence of side effects on COVID-19 vaccine hesitations is associated with COVID-19 vaccine opposition (8,10). In our study, more than half of the patients who did not want to be vaccinated against COVID-19 reported that they were afraid of the side effects of the COVID-19 vaccine in accordance with the literature.

In our study, we analyzed the early side effects of the CoronaVac vaccine and the factors that may be associated with side effects. The side effects associated with CoronaVac was present in 32-62% of individuals in the general population in studies (8,12). In our study, side effects were seen in 22% of patients after at least one dose of CoronaVac vaccine (17% of patients after 1 dose and 15% after 2nd dose). In general population-based studies, it has been shown that the frequency of side effects decreases with increasing age. The lower incidence of side effects in our study may be due to the fact that our study population included patients over the age of 65 (8). In addition, it may cause less reactions to vaccines in immunosuppression due to uremia in patients with chronic kidney disease, especially in the patient group receiving hemodialysis treatment (5,13).

Consistent with the literature, one of the most common side effects after CoronaVac vaccine was pain at the injection site and side effects were more pronounced in females (8,12,14). Unlike other studies on the side effects of COVID-19 vaccines, the frequent uncontrolled blood pressure in our patients may be due to the inadequacy of information about the vaccine and stress disorders caused by the side effects of the vaccine. In many studies in the literature, it is known that psychological and physical stress contribute to both acute and long-term blood pressure variability. *In vitro* studies have shown that acute blood pressure reactivity to emotional stress differs between individuals (15-17). The fact that blood pressure uncontrolled is more common especially in female patients may be associated with factors such as activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system,

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and endothelial dysfunction, which cause an increased incidence of hypertension in postmenopausal women (18).

In addition, the existence of a significant relationship between the presence of cardiovascular disease and the frequency of side effects in our study may be a result of vascular endothelial cell aging and vascular dysfunction, which are involved in the pathogenesis of cardiovascular diseases. Dysregulation of the cell cycle, oxidative stress, altered calcium signaling, hyperuricemia, and vascular inflammation, which contribute to aging, play a role in the development and progression of vascular endothelial cell vascular disease. Vascular endothelial cell aging induces vascular structural and functional changes, increases thrombosis, inflammation and atherosclerosis with deterioration in vascular tone, angiogenesis and vascular integrity (19). Various studies have shown that cardiovascular side effects of COVID-19 vaccines are due to the presence of endothelial dysfunction, especially in the elderly population (20,21). The presence of cardiovascular diseases secondary to endothelial dysfunction, which became evident due to the fact that our study population consisted of elderly patients, may increase the frequency of side effects related to the COVID-19 vaccine by the same mechanisms.

Study Limitations

Our study has some limitations. The small number of patients studied should be noted as a limitation. In addition, the fact that the social characteristics of the study population, such as educational status, were not recorded, should also be noted as a limitation. However, since the number of studies on the side effects of the CoronaVac vaccine in individuals over 65 years of age with chronic kidney disease is low, clinicians interested in managing this patient group should be informed.

Conclusion

The vaccination rate against COVID-19 in individuals with chronic kidney disease over 65 years of age was higher than in general population studies, and the most common reason for COVID-19 vaccine opposition was fear of the side effects of vaccines. In addition, the side effects of those who had CoronaVac were similar to those in the general population, and the frequency of side effects was found to be lower. Unlike other general population studies, it was observed that blood pressure uncontrollability was observed and the presence of cardiovascular disease increased the frequency of side effects.

Ethics

Ethics Committee Approval: This study was approved by the Local Institutional Review Board (Kartal Dr. Lütfi Kırdar City Hospital, no: 2021/514/200/36, date: 28.04.2021).

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Sleep Quality, Depression, Hopelessness, and Quality of Life in Elderly Hemodialysis Patients

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Abstract

Objective: This study aimed to assess and compare the relationships between depression, hopelessness, sleep, and quality of life in two age groups of elderly and young patients with end-stage renal disease undergoing hemodialysis (HD).

Materials and Methods: The study included 130 patients under follow-up for hemodialysis (55 aged <60 years and 75 aged ≥60 years). Depression levels, sleep quality, and quality of life of all participants were evaluated using the Beck depression inventory (BDI), Beck hopelessness scale (BHS), the Pittsburgh sleep quality index, and the short form-36, respectively.

Results: Of the participants, 55% (n=72) were female, and 45% (n=58) were male. The mean age was 59.48±14.57 years. There was no significant difference between the age groups concerning the BHS scores (6.82±4.73 vs. 6.57±4.20) (p=0.756). However, the BDI scores were significantly higher among younger participants (38.67±19.45 vs. 23.45±17.13) (p<0.001). Also, the sleep quality of the elderly group was significantly worse than the younger group (5.16±2.93±6.49±3.01) (p=0.013). Concerning the health-related quality of life, physical performance (45.81±19.33 vs. 39.49±13.07) and mental health (44.63±18.69 vs. 36.80±16.49) subscales were significantly lower in the elderly group (p=0.028 and p=0.013, respectively).

Conclusion: We conclude that age is a significant factor requiring consideration when assessing and managing patients under HD. Although the functional capacity and sleep quality deteriorate with age, younger HD patients are more disadvantaged concerning the possibility of depression. Thus, we suggest age-specific approaches in HD patients with a multidisciplinary team.

Keywords: Sleep, quality of life, depression, hope, elderly, hemodialysis

Introduction

Chronic renal failure is a well-known public health problem, which can result in end-stage renal disease (ESRD) and necessitates renal replacement therapies such as renal transplantation or hemodialysis (HD)/peritoneal dialysis (1). The availability of HD significantly increased in the last decade. However, the prevalence of ESRD also increased and reached 11-13% (2). This rise is related not only to changes in demography and aging but also to the increase in co-morbid diseases such as diabetes and hypertension (3).

Like other chronic diseases, ESRD deteriorates life quality and increases the incidence of psychopathological conditions compared to the normal population (4). The prevalence of

depression is about 2-10% in the general population. However, it may reach 23-29% in people with chronic renal failure (5,6). Despite the escalation of depression in this population, there is no report investigating its relationship to hope and suicidal tendencies in patients on maintenance dialysis.

On the other hand, sleep is a dynamic condition with significant influences on daily functions, including mental and physical health (7). Poor sleep quality may even disturb emotions and thoughts. Patients with poor sleep quality have a poor quality of life with many physical or emotional symptoms, such as concentration difficulties, tiredness, decreased pain tolerance, loss of appetite, depression, and anxiety (8). The survival rates in ESRD patients have increased in relation to renal replacement

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therapies and other therapeutic interventions, which increased the significance of evaluating health-related quality of life (HRQoL) in these patients (9).

Given the extended life expectancy in ESRD patients, the follow-up of quality of life, depression, hopelessness, and sleep becomes more important in elderly patients.

This study aimed to assess and compare the relationships between depression, hopelessness, sleep, and quality of life in two age groups of elderly and young patients with ESRD.

Materials and Methods

Study design

The study was conducted in a cross-sectional design. All participants gave written individual informed consent to participate. The study protocol was approved by the Local Ethics Committee at Malatya Turgut Özal University Medical Faculty and conducted according to the criteria of the Helsinki Declaration. Informed consent was obtained from all the patients included in the study.

Setting

This study was conducted at the department of nephrology at Malatya Training and Research Hospital from July 2018 to January 2019. Established in 1939, the study hospital currently provides secondary-level healthcare services in eastern Turkey with 1.040 inpatient beds, 240 outpatient clinics, 23 surgical intervention rooms, a 90-bed capacity intensive care unit, and a HD unit able to serve 29 simultaneous patients.

Participants

Patients >18 years of age with ESRD, who were receiving HD for at least 3 months were included in the study. The exclusion criteria of the study were patients not able to complete the study questionnaire due to cognitive impairment (n=2), active psychosis (n=1), a history of recent hospitalization (n=2), history of malignancy (n=1). Data could be collected from 130 patients out of the 150 patients under treatment (Figure 1). All patients under follow-up were invited to join the study without sampling.

Variables

Age, gender, marital status, cigarette smoking, dialysis access, dialysis duration, body mass index (BMI), hemoglobin, albumin, C-reactive protein, ferritin, intact parathyroid hormone (iPTH), lipid parameters, and serum 25-hydroxyvitamin D [25(OH) D] were assessed in all patients. Blood samples for laboratory parameters were collected on the day of the survey. Blood samples were taken from the patients just before the dialysis session. Serum 25(OH) D levels were measured by liquid chromatography-tandem mass spectroscopy (Agilent Technologies, Santa Clara, CA, USA), the measurement of iPTH
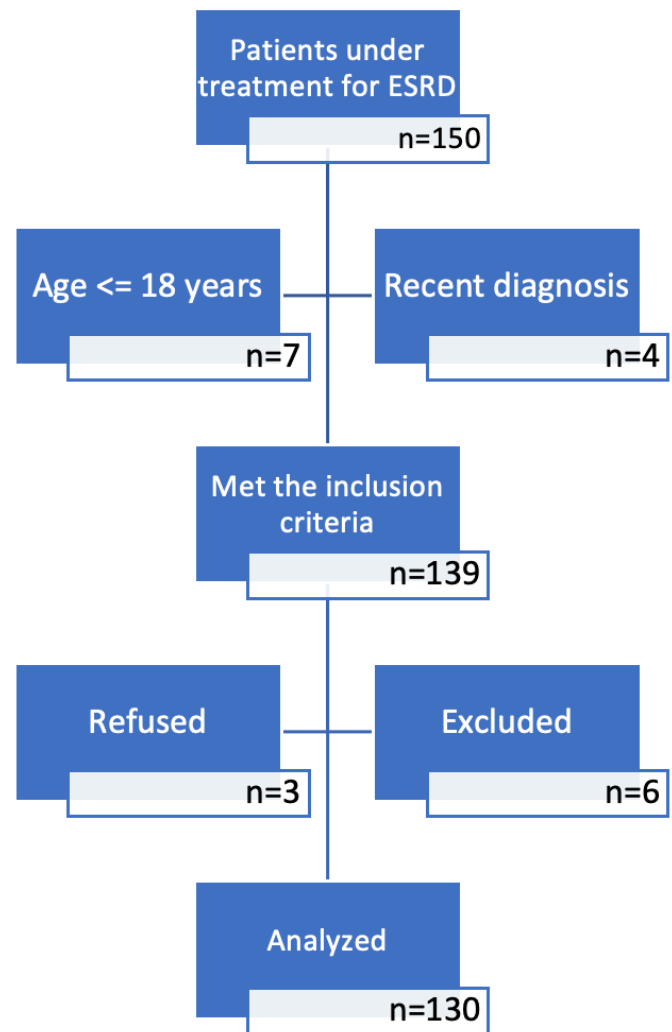
Figure 1. Study flow diagram

levels was made by the chemiluminescence method (ADVIA centaur XPT immunoassay, Siemens, Erlangen, Germany) (10,11). Ferritin levels were measured by ferritin immunoassay (ADVIA Centaur XPT immunoassay, Siemens, Erlangen, Germany), hemoglobin was measured by fluorescence flow cytometry (Sysmex XN 2000, Norderstedt, Germany) (12,13). Albumin and lipid parameters were measured by spectrophotometry (Beckman Coulter AU 2700, Krefeld, Germany) (14). C-reactive protein was measured by the immunonephelometric method (NFL BN-II, Erlangen, Germany) (15).

Short form-36 health survey (SF-36)

The SF-36 consists of eight dimensions, generating a profile of HRQoL (16). These dimensions are: 1) Physical functioning, 2) Role limitations due to physical functioning, 3) Bodily pain, 4) General health perceptions, 5) Vitality, 6) Social functioning, 7) Role limitations due to emotional functioning, and 8) Mental health. Raw scores are transformed into a score between zero and a hundred for each dimension. Higher scores indicate better health.

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Beck's depression inventory (BDI) and the Beck hopelessness scale (BHS)

To facilitate the investigation of despair in various psychopathological situations, Beck has established a tool designed to reflect the negative expectations of the participants (17). The BHS and the BDI were used in this study. The BHS has 20 true/false statements, of which 9 are false, and 11 are correct. Each correct answer is scored as 1, calculating the total "hopelessness score," giving a score range between 0 and 20. The cut-off points are categorized as follows: 0-4: Minimum hopeless, 5-8: Mild hopeless, 9-13: Moderately hopeless, and 14-20: Severe hopeless. Additionally, we defined a score of ≥9 as a suicide predictor in people with serious diseases (4). On the other hand, BDI has questions that describe attitudes and symptoms concerning depression. It comprises 21 groups of statements, and each group investigates a type of depression symptom. The higher the score displayed, the greater is the intensity of symptoms. Cut-off points used for BDI are defined as follows: Minimal depression: 0-11, mild depression: 12-19, light depression: 20-35, and severe depression: 36 and above (18).

Sleep quality

The Pittsburgh sleep quality index (PSQI) was used to assess sleep quality. The standard (past month) version was used at the screening visit, and a modified (past week) version was used at all subsequent administrations. The scores ranged from 0 to 21, with higher values indicating poorer sleep quality (19). A score higher than 5 indicates poor sleep quality.

Functional capacity

Patients' functional dependency was assessed by the activities of daily living (ADL) and Instrumental Activities of Daily Living (IADL) tests. The Barthel index of ADL was used for evaluating physical disabilities (20). This scale includes dressing, bathing, grooming, using the toilet, eating, transferring, and incontinence. Scores can range from 0 to 100, and higher scores indicate independence. On the other hand, the Lawton index was used to evaluate the disability in IADL. This scale aims to find out subject performance in the following activities: Doing laundry, shopping, taking medicines, housekeeping, food preparation, using the telephone, using transportation, and managing money (21). Higher scores indicate higher independence according to this scale.

Bias

All patients under follow-up were invited to join the study to prevent selection bias. Furthermore, the data collection was done by the same researcher to decrease measurement bias.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., Chicago, IL, USA). Independent samples t-test and chi-square tests were used to compare numerical and categorical variables between the age groups. Besides, the Pearson's correlation test was used to identify if there was any correlation between the changes in outcomes (i.e., if the change scores in depression, sleep, and quality of life outcomes correlated with each other). The threshold for statistical significance was set to p<0.05.

Results

Data of 130 participants were analyzed. While 55% (n=72) of patients were female, 45% (n=58) were male. The mean age was 59.48±14.57 years. Patients were divided to two groups based on age: ≥60 and <60 years. There was no significant difference between the two groups regarding HD duration and BMI. However, when the laboratory results were evaluated, PTH was high in the young age group, while vitamin D levels were found to be significantly low (p=0.006, p=0.047: Respectively) (Table 1). Also, functional capacity assessment, ADL and AIDL were significantly higher in the younger group (Table 2).

The total BHS score ranged from 1 to 19 in the whole group, with a median of 5 points. According to the BHS, 56 (43.1%) patients had minimal, 40 (30.8%) light, 19 (14.6%) moderate, and 15 (11.5%) had severe hopelessness symptoms. When young and old HD patients were compared, there was no significant difference between the scores (Table 2).

BDI scores were significantly higher among the younger participants (Table 2). The BDI score ranged from 4 to 60, with a median score of 29.8. According to the cut-off scores, the proportions of mild, moderate, and severe depression were 18.5% (n=24), 23.8% (n=31), and 35.4% (n=46), respectively. Of the patients, 78 (60.0%) had poor sleep quality. The sleep quality of the elderly group was significantly worse than the younger group (Table 2).

BHS showed a positive correlation with the BDI (r=0.364, p<0.001) and a negative correlation with the Barthel index of ADL (r=-0.173 p=0.049). On the other hand, PSQI positively correlated with age (r=0.282, p=0.001) and BMI (r=0.249, p=0.004).

Concerning the HRQoL, physical performance, and mental health subscales were significantly lower in the elderly group (Table 3).

Discussion

In our study, ESRD HD patients aged 60 years and older had lower functional capacity and depression, similar hopelessness, and poorer sleep quality than similar patients aged less than 60

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Table 1. Comparison of sex, dialysis duration, BMI, and laboratory variables between the age groups

	Young (n=55)	Older (n=75)	p
Sex n (%)			
Women	34 (61.8%)	38 (50.7%)	0.206
Men	21 (32.2%)	37 (49.3%)	
Under dialysis since (months) median (min-max)	48 (2-204)	44 (4-204)	0.786
BMI (kg/m²)	24.82 (17.26-36.0)	24.50 (16.00-42.8)	0.913
Laboratory values			
Urea (mg/dL)	135 (83-216)	130 (67-219)	0.882
Creatinine (mg/dL)	8.25 (2.8-18.25)	7.20 (2.25-13.88)	0.072
Uric acid (mg/dL)	6.4 (4.3-10.9)	6.3 (4.8-8.90)	0.316
Total protein (g/dL)	7 (5.2-8.2)	7. (5.5-8.2)	0.530
Albumin (g/dL)	3.6 (2.0-4.4)	3.6 (2.0-4.4)	0.758
Calcium (mg/dL)	8.8 (7.2-9.9)	8.8 (7.8-11.5)	0.442
Phosphorus (mg/dL)	5 (2.1-9.3)	4.5 (3-9.1)	0.218
Parathormone (PTH) (pg/mL)	447.9 (14.52-1881)	354 (54.95-1228)	0.022*
Vitamin D (ng/mL)	8.47 (3-54.46)	11.71 (3-93.43)	0.049*
C-reactive protein (mg/L)	0.54 (0.003-3.81)	0.79 (0.04-14.67)	0.272
Ferritin (mL/ng)	600.87±425.62	570.12±350.58	0.917
Hemoglobin (g/dL)	11.2 (7.4-14.4)	11.10 (7.20-14.6)	0.567

BMI: Body mass index, *p<0.05 significant

Table 2. Functional capacity, depression, and sleep quality assessment of the groups

Functional assessment	Young (n=55)	Older (n=75)	p
Barthel ADL	100 (15-100)	75 (10-100)	<0.001*
Lawton brody IADL	5 (1-8)	3 (1-8)	<0.001*
BDI	6 (1-18)	5 (1-19)	<0.001*
BHS	36 (8-63)	17 (4-63)	0.915
PSQI	4 (1-14)	5 (1-13)	0.003*

Data are presented as mean ± standard deviation. ADL: Activities of daily living, IADL: Instrumental activities of daily living, BDI: Beck depression inventory, BHS: Beck hopelessness scale, PSQI: Pittsburgh sleep quality index, *p<0.05 significant

Table 3. Health-related quality of life assessment of the age groups

SF-36	Young (n=55)	Older (n=75)	p
PF	45.81±19.33	39.49±13.07	0.028*
SF	44.82±16.98	41.94±15.29	0.313
PR	17.54±22.35	11.17±16.11	0.061
ER	12.021±16.23	12.62±14.14	0.824
MH	44.63±18.69	36.80±16.49	0.013*
V	29.21±18.52	24.54±14.44	0.109
P	37.40±17.35	34.48±14.31	0.295
GH	28.18±16.66	23.66±13.49	0.091

Data are presented as mean ± standard deviation. PF: Physical functioning, SF: Social functioning, PR: Physical role limitations, ER: Emotional role limitations, MH: Mental health, V: Vitality, P: Pain, GH: General health, *p<0.05 significant

years. However, there was no significant difference between the two age groups regarding the quality of life, except for physical functioning and mental health. Also, there was no significant difference in the BHS scores concerning the age groups. Furthermore, both the BHS and PSQI showed some correlations with the other variables.

The prevalence of geriatric depression increases rapidly with the steady aging of the population and the increase in chronic diseases with advancing age (22). Depression has been reported in up to 70% of HD patients (23,24). Tsevi et al. (25) reported that the occurrence of depression was associated with the duration of HD in patients undergoing HD treatment. In another study, it was emphasized that depression was associated with various markers of HD proficiency, such as high blood pressure, serum albumin concentration, and serum creatinine concentration. However, in these studies, patients were not grouped by age (24).

Despite the well-known strong relationship between hopelessness and depression, our study reveals that hopelessness and depression are partly different phenomena. The hopelessness levels in the young and old groups were close to each other, while the depression rate was significantly higher in the young group (26). Similarly, Andrade et al. (4) found a high prevalence of hopelessness, suicidal ideation, and depression symptoms in HD patients. In our study, in the despair assessment according to age, BHS values were very close to each other, but it is surprising that BDI values were higher in younger HD patients. A possible

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explanation for this finding could be that younger people affected by a debilitating chronic disease are more vulnerable because of their impossibility to accomplish plans for their life. Despite the fact that depression is a common disorder in the general elderly population, younger HD patients should be regularly evaluated for depression.

Most HD patients suffer from poor sleep quality. Our study showed that 60% of HD patients had poor sleep quality. Furthermore, there was also a correlation between sleep quality and age as well as BMI. Likewise, other studies have verified a significant relationship between sleep quality and increasing age (27,28).

Increased age-related changes (physical limitations, use of various medications, and lifestyle changes) appear to affect the sleep quality of HD patients. It has been shown in several studies that patients receiving HD treatment have significantly poorer sleep quality compared to the general population (29,30). We found that the majority of patients receiving HD treatment had poor sleep quality. Additionally, we identified an association between poor sleep quality with age and BMI. Hydarinia Naieni et al. (31) reported that sleep quality was significantly associated with age in HD patients, while another study showed that sleep quality had a significant relationship with BMI and diabetes (32). According to our study, quality of life was significantly lower in the elderly group with sleep disorders. Pain, depression, and sleep disorders due to chronic diseases cause a decrease in quality of life. In our study, physical performance and mental health subscale scores of the SF-36 were significantly lower in the elderly group. Similar to our study, Zouari et al. (33) emphasized that being 60 years or older is associated with a poor quality of life.

The aging population and the increase in the number of patients suffering from chronic diseases highlight the imperative links between mental, social and physical health (4,26,29). In addition, thanks to advances in the treatment of chronic kidney disease, many patients can live to old age. In recent years, it has been noticed that many nephrologists actually act as "amateur geriatric specialists", especially by the American and United Kingdom nephrology associations, and steps have been taken to improve kidney education in this area (34). Both specialties are very familiar with the concept of patient-centered care. However, renal services usually focus on holistic symptom control, dietary changes, and the psychological impact of kidney disease, while geriatric comprehensive assessment focuses on functional status, cognitive impairment, and multiple drug use and aims to maintain or improve the quality of life and prevent it future readmissions (35-37). However, there is no specialization in this field in our country. Therefore, the treatment of HD patients should be organized by a multidisciplinary team consisting of nephrologists, geriatricians and psychiatrists.

Study Limitations

Our study should be interpreted in light of some limitations. It is a descriptive study in a local sample with limited generalizability of the findings. Multi-center studies with control groups are needed to verify the results.

Conclusion

We conclude that age is a significant factor requiring consideration when assessing and managing patients under HD. Although the functional capacity and sleep quality deteriorate with age, younger HD patients are more disadvantaged concerning the possibility of depression. Thus, we suggest age-specific approaches in HD patients with a multidisciplinary team.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee at Malatya Turgut Özal University Medical Faculty (IRB number: E-23536505-604.02) and conducted according to the criteria of the Helsinki Declaration.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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Turkish Calf Circumference Cut-offs Derived from Normative Values of Young Reference Population

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Abstract

Objective: Calf circumference (CC) is used as a simple and practical anthropometric measure for evaluating skeletal muscle mass (SMM). CC cut-offs to indicate the presence of low SMM were determined through calculation of CC values that predicted low SMM with receiver operating characteristic analyses. Also, to date CC cut-off points were obtained from older adults. Very recently, the determination of CC cut-off values derived from normative values of young reference population with normal body mass index [using one and two standard deviations (SDs) below the mean] has been suggested as an alternative CC cut-off designation method. Here, we aimed to determine the sex-specific Turkish CC cut-offs by this new CC cut-off designation method.

Materials and Methods: We included healthy young participants aged between 18 and 39, with body mass index between 18.5 kg/m^2-24.9 kg/m^2 who were free from any chronic disease or drug use. CC was measured at the widest circumference of the calf with a non-elastic tape on the non-dominant leg while the subjects were standing and CC cut-off points were calculated as one and two SDs below the mean for moderately low or severely low CC values, respectively in each sex.

Results: There were 164 participants (mean age, 25.7±4.4 years; 50% male, 50% female). Mean CC was 35.5±2.1 cm and 34.2±2.1 cm in males and females, respectively. The rounded cut-off values for moderately and severely low CC were calculated as 33 cm in males and 32 cm in females and 31 cm in males 30 cm in females, respectively.

Conclusion: This study reported CC cut-offs derived from normative values of the Turkish young reference population which can be used as a marker for the muscle mass assessment. The success of these cut-offs in prediction of SMM adequacy should be assessed in further studies.

Keywords: Calf circumference, cut-off, Turkish, normative, young reference, body mass index

Introduction

Sarcopenia is a generalized and progressive skeletal muscle disorder defined as a decline in skeletal muscle mass, strength, and function (1). It is expected that individuals with sarcopenia are increasing worldwide, given the rapid increase in older adults and individuals suffering from chronic conditions that lead to the development of sarcopenia. Sarcopenia is associated with decreased physical capacity, the development of disability, deterioration in respiratory function, reduction of cardiopulmonary performance, decrease in quality of life, decrease in basal and instrumental activities of daily living, frailty, falls and fractures, prolongation in hospitalization

time, and death (2). According to the recommendation of the European Working Group on Sarcopenia in Older People (EWGSOP2), the sarcopenia diagnosis is confirmed by detecting low muscle strength and low muscle quantity or quality (1). A combination of low muscle strength, low muscle mass (LMM)/quality, and low physical performance is considered to be severe sarcopenia.

Muscle mass can be measured with dual-energy X-ray-absorptiometry (DXA), CT, and magnetic resonance imaging. All three of these imaging modalities have served as references for developing skeletal muscle mass (SMM) estimates by use of simpler, less costly means to evaluate SMM, i.e., anthropometry

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and bioelectrical impedance analysis (BIA). An anthropometric approach of interest as a marker of SMM is the calf circumference (CC) measurement. CC has been shown to predict performance and survival in older people (cut-off point <31 cm) (3). In cases where muscle mass measurement is not possible or practical through measuring devices, CC measurement can be a viable option.

CC measurement has been widely used as a muscle marker in geriatric studies and it is the most commonly used tool for muscle mass assessment in clinical practice to have an idea about the presence/absence of LMM and to screen for sarcopenia. The CC is one of the tests recommended as a case finding/screening tool for sarcopenia in the Asian Working Group for Sarcopenia (AWGS) 2019 (4). It has also been suggested as a component of the sarcopenia screening tool proposed by Ishii et al. (5) and for the SARC-CalF score (6). In addition, in EWGSOP2 consensus, CC measure has been considered to be used as a diagnostic proxy for older adults in settings where no other muscle mass diagnostic methods are available.

The calf region is comprised of a skin-fold, subcutaneous fat, and bone in addition to muscle. When a person is obese and has a high-fat mass, subcutaneous fat increases as well (7). The increase in subcutaneous fat amount will naturally translate in increase in CC in obese individuals, independent from an increase in calf muscle mass. The vice-versa is also true when the individuals are underweight. Of note, body mass index (BMI) is the most widely and globally used index to assess obesity/ underweight due to its simplicity and convenience.

EWGSOP2 consensus suggested designation of LMM cut-off values as the sex specific SMM values below two standard deviations of mean values of the normative young reference population (8). On the other hand, while CC has been used as a proxy-marker of muscle mass, until recently CC cut-offs to indicate the presence of low SMM were determined through the calculation of CC values that predicted low SMM with receiver operating characteristic (ROC) analyses, by considering the SMM data derived from use of reference SMM assessment techniques. In addition, CC cut-off points in all these studies were determined from older adults (9-15).

Very recently, in 2021 Gonzalez et al. (15) suggested to derive CC cut-off values from normative values of young reference population for the first time in USA population. Moreover, considering the confounding effect of obesity/underweight in CC values, in this study, the authors suggested that the CC cut-off values should be derived from those that have normal BMI and accordingly, they derived the CC cut-offs from the young reference population that has normal BMI: 18.5-24.9 kg/m² (15).

Populations diverge in terms of lifestyle, environment, ethnicity and genetics, and these factors may have an effect on body composition. Accordingly, cut-off values to predict ideal BMI and obesity differ across different populations (16). Given the differences across the previously published different CC cut-off values derived in different populations (9,11,12) and considering CC as a marker of body muscle composition, this consideration should be valid for CC cut-offs as well. Hence, population-specific CC cut-off values seem to be needed.

In this study, we aimed to determine the Turkish CC cut-off values within the framework of the approach reported by Gonzalez et al. (15), by subtracting one and two SDs from the mean CC value of the young population with a BMI between 18.5-24.9 kg/m².

Materials and Methods

We used the data collected in our previous study at which we reported the cut-off points of LMM and low muscle strength in Turkish population (12). In this study, we identified a reference young, healthy adult reference population which was composed of 301 healthy adults aged between 18 and 39 including 187 male and 114 female individuals. We recruited these participants from the faculty students, patient relatives, and staff working in our university hospital. They were free from any chronic disease or drug use. Data from 164 healthy young adults (18-39 y) with BMI 18.5-24.9 kg/m² was used in this study to represent the reference population from which we calculated CC cut-off values. CC cut-offs were identified as "mean young CC minus one SD" (for moderately low SMM) and "mean young CC minus two SD" (for severely low SMM) as suggested by Gonzalez et al. (15).

Demographic data and clinical data were obtained by face-to-face interviews. Height and weight were measured via a regular stadiometer while participants were in light clothes but without shoes. We assessed the body weight to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was derived by weight (kg)/ height square (m²). CC was measured at the widest circumference of the calf with a non-elastic tape on the non-dominant leg while the subjects were standing. This study was performed according to the guidelines in the Declaration of Helsinki. We received informed consent from all volunteering participants. The study was approved by the Local Ethics Committee (number: 2021/2070).

Statistics

All data entered the database were verified by a second researcher. The variables were investigated to determine if they were normally distributed using the Shapiro-Wilk test. Continuous variables were given as mean ± standard deviation for normally distributed variables. The cut-off thresholds for CC were derived by using the mean and SD values of the young reference study population. The statistical analysis was carried

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out with the statistical package SPSS Version 21.0 for Windows (SPSS Inc, Chicago, Ill, USA).

Results

There were 164 participants (82 male, 82 female). Mean age was 25.7±4.4 years, and mean CC was 35.5±2.1 and 34.2±2.1 cm in males and females, respectively. The summary, including the anthropometric measurements data are given in Table 1. The cut-offs for moderately low CC (mean young CC-one standard deviation) were calculated as 33.4 cm and 32.1 cm in males and females, respectively. The rounded cut-offs for moderately low CC were 33 and 32 in males and females, respectively. The cut-offs for severely low CC (mean young CC-two standard deviation) were calculated as 31.3 cm and 30 cm in males and females, respectively. The rounded cut-offs for severely low CC were 31 and 30 in males and females, respectively.

Table 1. The study parameters across the genders of the healthy young adults' reference population		
Parameters	Males (n=82) Mean ± SD (range)	Females (n=82) Mean ± SD (range)
Age (years)	25.5±4.1	25.8±4.7
Height (cm)	174±6	162±6
Weight (kg)	69.6±6.4	56.6±5.9
BMI (kg/m²)	22.8±1.6	21.5±1.7
Calf circumference (cm)	35.5±2.1	34.2±2.1
SD: Standard deviation, BMI: Body mass index		

Discussion

We have defined the CC cut-off values using one and two SDs below the mean value of a young reference population as 33 cm and 32 cm for moderately low CC and 31 cm and 30 cm for severely low CC in males and females, respectively. In our study, the rounded CC cut-off values for moderately low CC were similar to those reported in the previously published studies which were between 33-34 cm in males (9,12-14) and 32-33 cm for females (9,11-14). Gonzalez et al. (15) determined rounded CC cut-off values for moderately and severely low CC as 34 cm and 32 cm (for males) and 33 cm and 31 cm (for females), respectively. It was also similar to the Turkish CC cut-off value of 33 cm (in both sexes) which was determined by ROC analysis using data of older adult population and reported by our group previously (12). This means that the study applies a reliable methodology for calculating the CC cut-off value and contains reliable data.

In all published studies except and up to the study by Gonzalez et al. (15), CC cut-offs were defined by a statistical method composed of ROC analysis to identify the best CC value detecting LMM measured by DXA or BIA to diagnose sarcopenia (9-14,17,18). However, in consensus reports such as EWGSOP2 and Global Leadership Initiative on Malnutrition and in many others, sex-specific low SMM cut-offs are recommended to be calculated as SMM values one or two SDs below the mean values of the normative young reference population (1,19-23). In line with these recommendations, very recently, Gonzalez et al. (15) used and suggested the use of normative reference data in the identification of low CC. As a modification, the authors suggested to determine the cut-off values from those with BMI 18.5-24.9 kg/m², considering the confounding effect of obesity/underweight in CC values. To ease their clinical use, they determined rounded CC cut-off values for moderately and severely low CC as 34 cm and 32 cm (for males) and 33 cm and 31 cm (for females), respectively. Based on previous studies and the data of their study, the authors stated that a moderately low CC (below the mean- one SD) might be sufficient for the screening of sarcopenia for older adults.

Studies have shown that CC values below 31 cm predicts performance and survival in older people (3). Also, in some consensus reports 31 cm has been recommended as the cut-off for CC until recently (1,24). However, it is a well-known fact that populations differ greatly in terms of genetics, lifestyle, and environment (5,9,14,25). Additionally, it is clear that a diet rich in carbohydrates and fats but poor in protein and limited physical activity affect muscle and fat content in the body. Based on previous studies, it is known that CC values also, differ among the different ethnic and race groups. Therefore, when proposing cut-offs for CC, differences at population-level were recognized, and researchers set population-specific cut-offs for CC. We have seen the accuracy of this situation from the different cut-off values derived in different populations. For example, in a study conducted in Japan, 526 adults aged 40-89 years were included and the optimal CC cut-off values by the ROC analysis were found as 34 cm in men and 33 cm in women for predicting sarcopenia (9). In another study involving 1,458 French women aged 70 and over, the suggested cut-off was 31 cm (10). In AWGS 2019 consensus report, CC cut-offs of <34 cm for men and <33 cm for women are recommended for sarcopenia screening or case-finding. In a study by Akın et al. (26) from Turkey, 879 community-dwelling older adults were recruited. The CC cut-offs were determined by the ROC analyses and they found that the area under curve for CC were significant for males aged ≥75 years (CC cut-off: 34.9 cm) and females aged ≥85 years (CC cut-off: 34.6 cm), concluding that these CC can be used as a marker of LMM especially in the older old Turkish population living in the community (26). In another study from Turkey, Halil et al. (27) conducted a multicenter study in 711 nursing home residents. They reported CC cut-off value by ROC analysis for diagnosing LMM as 35 cm. In this study, the proposed CC cut-off was not specific to age or gender group (27). In another Turkish study reported by our group, the CC

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cut-off was determined as 33 cm by ROC analysis in both sexes (12). Hence all these studies indicate that CC cut-offs differ between the populations and are higher than the standard 31 cm in the Turkish population.

Sarcopenia is a reversible cause of disability, and early intervention may reverse the course of the disease. If sarcopenia is detected at an early stage and necessary interventions such as resistance exercises, optimal nutrition with adequate protein, vitamin D, and energy intake are performed, the physical disability caused by sarcopenia can be prevented. Therefore, early detection with screening and/or assessment tests is essential. Anthropometric measurement is a cheap and easily available method to estimate sarcopenia and if accuracy of CC to identify and assess LMM could be demonstrated, this will aid in earlier identification of LMM/sarcopenia and will have the potential to improve the outcomes related to LMM/sarcopenia. CC was not recommended as an assessment tool for LMM/sarcopenia so far because of the wide variation in CC due to age-related changes in fat deposits and decreased skin elasticity (1,24). While this approach is expected to improve the utility of CC as an estimate of muscle mass and sarcopenia from hypothetical point of view, future studies should be conducted to identify if use of these CC cut-offs are successful as a marker of LMM and risk factor for development of LMM/sarcopenia related adverse events.

Another thing is, a strong correlation was found between CC and appendicular low muscle index (ALMI), in several studies, including the study by Gonzalez et al. (9,15,28,29) but there is no study investigating the relationship between low CC and low appendicular or total SMM with the newly suggested CC cut-off method. Accordingly, studies on these areas are warranted. In addition, future longitudinal studies are needed to explore whether switches in the presence of LMM detected by reference SMM assessment methods can also be identified by this newly proposed CC assessment method.

Study Limitations

Our study has some limitations. The participants were not randomly selected from the Turkish population. Therefore, the sample may not have been representative of the general population. However, Istanbul is a cosmopolitan city where people from various parts of Turkey live. For this reason, we believe that the included healthy young adults may represent the Turkish population. Also, our sample size was moderate. On the other hand, to the best of our knowledge, our study is the second study that determined the cut-offs from normative values of young reference population with normal BMI. Also, it is the first study that determined population specific CC cut-offs with this method in Turkey. In this regard, we expect that our study will fill the gap in this field in our country and will provide data for comparison in studies to be conducted in other populations.

Conclusion

We reported cut-off values for CC with a new approach using one and two SD below the mean of young reference Turkish population that has normal BMI values. These CC cut-offs are intended to be used as a marker of the muscle mass evaluation with a better accuracy. Future validation studies with these cut-offs identified by this new method are needed to explore whether this new cut-off will predict outcomes related to sarcopenia and/or malnutrition (i.e., functional impairments, falls, cardio-metabolic syndrome, and mortality) better than the standard CC cut-off approach.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul University Local Ethics Committee (number: 2021/2070).

Informed Consent: We received informed consent from all volunteering participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL RESEARCH

Are the Psychological Effects of the COVID-19 Pandemic Similar in Old-aged and Young Patients?

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Abstract

Objective: The Coronavirus disease-2019 (COVID-19) pandemic is a life-threatening event with high psychological effects. The old-aged are among the most vulnerable groups to the physical and psychological effects of the pandemic. This study was conducted to determine the psychological effects of the COVID-19 pandemic, such as fear, anxiety, stress, depression, and sleep disturbance, on old-aged patients and evaluate whether these effects are similar to younger patients.

Materials and Methods: A total of 302 outpatients admitted to internal medicine and geriatrics outpatient clinics were included in the study. Participants aged 65 and over were grouped into the ''geriatric group'' and those under 65 years of age in the ''young group''. The COVID-19 Fear Scale was used to assess the COVID-19 fear level of the participants, the Pitsburg Sleep Quality Index (PSQI) was used to assess their sleep, and the Depression Anxiety Stress Scale (DASS-21) was used to assess their mood. Patient groups were compared in terms of all these parameters.

Results: Of the 302 participants, 131 (45.4%) were in the geriatric (mean age 73.07±7.27) and 171 (56.6%) (mean age 42.98±13.83) were in the young group. The mean FVC-19S score (26.12±5.54 in the geriatric group, 15.65±7.51 in the young group) and the mean DASS-21 score (39.43±9.92 in the geriatric group, 25.66±13.89 in the young group) were found to be significantly higher in the geriatric group (respectively p<0.001, p<0.001). Although the mean PSQI score was higher in the geriatric group than in the young group (7.12±4.08 in the geriatric group, 6.78±4.31 in the younger group), the difference did not reach the level of statistical significance (p=0.346).

Conclusion: The rates of fear, anxiety, and depression caused by the COVID-19 pandemic are higher in the old-aged than in the young. More than half of the older adults included in the study have poor sleep quality. Both emotional distress and sleep disorders can predispose to many geriatric syndromes and have the potential to worsen existing problems.

Keywords: Geriatrics, COVID-19 pandemic, fear, depression, anxiety, stress, sleep quality

Introduction

Coronavirus disease-2019 (COVID-19) infection is not only a disease but also a global disaster that affects individuals and societies physically, psychologically, socially, and economically. It was declared a pandemic by the World Health Organization on January 30, 2020 (1). The COVID-19 pandemic poses a significant threat to physical health and deeply shakes the basic sense of trust. Many people have lost their abilities, status, relatives, income, and their daily life routines have changed significantly during the pandemic. Although it is thought that the pandemic causes individuals to experience long-term feelings of fear, anxiety, stress, and sadness, there are limited studies on this subject (2,3). Studies in the COVID-19 pandemic around the world mainly focus on infection control, effective vaccine, and medical treatment; the psychological dimension of the pandemic remains in the background (4,5). It is not known clearly how much the COVID-19 pandemic affects the mental health of the community.

Due to the physiological changes that occur with aging and the increase in the frequency of chronic diseases, the old-aged have a poor prognosis for COVID-19 infection (6). The rate of exposure to the social isolation of the old-aged due to both

physical and social restrictions or individual preferences is higher than that of young people (7,8). For these reasons, the old-aged are one of the most vulnerable groups to the physical and psychological effects of the pandemic (8,9). It is essential to investigate the effects of the pandemic on the mental health of individuals, especially in terms of identifying groups at risk. Thus, an opportunity can be created for early interventions for risk groups. In our country, there is no study comparing the psychological effects of the COVID-19 pandemic on the old-aged with its effects on the young.

We aimed to determine the psychological effects of the COVID-19 pandemic, such as fear, anxiety, stress, depression, and sleep disturbance on the old-aged patients and whether these effects were similar with younger patients.

Materials and Methods

Ethical statement

This study was approved by the İnönü University Turgut Özal Medical Center Scientific Research Ethics Committee (approval number: 102/17) and was conducted by the Helsinki Declaration guidelines. Signed informed consent was obtained from the patients before inclusion in the study.

Study population

This study is a cross-sectional study. A total of 302 patients were included in this study. One-hundred thirty-one patients 65 years who received outpatient treatment in the İnönü University Turgut Özal Medical Center Geriatrics Clinics between July 2021 and October 2021 constituted the "geriatric group". One-hundred seventy-one patients ≥18 years who received the İnönü University Turgut Özal Medical Center Internal Medicine Clinics between the same dates constituted the "young group".

Exclusion criteria

Patients with a current psychiatric illness, those who use psychiatric drugs, and patients with dementia were excluded from the study because; these conditions would affect the results of the scales used in the study. The patients who were diagnosed with a psychiatric illness in the past but were treated were not excluded from the study. In addition, the patients with communication disabilities, severe hearing loss, general condition disorders (such as severe pain, critical shortness of breath, altered consciousness, medical emergency) were excluded from the study because; these conditions would affect the response to the questionnaires and scales.

Data tools

Through the face-to-face data collection form, participants' age, gender, educational status, current diseases, medications they use, and vaccination status were recorded. During the COVID-19 pandemic, it was questioned whether they disrupted their doctor's check-ups for any reason and whether they made changes in their medicines without the knowledge of the doctor. The COVID-19 Fear Scale (FCV-19S) was used to assess the level of participants' COVID-19 fear. The Pitsburg Sleep Quality Index (PSQI) was used to assess their sleep. The Depression Anxiety Stress Scale (DASS-21) was used to assess their emotional distress. All these scales were administered to all participants by the same researcher.

Level of the COVID-19 fear

FCV-19S, validated in Turkish, was used to determine the COVID-19 fear level (10,11). Items in the scale are scored from 1 to 5 as "strongly disagree", "disagree", "neither agree nor disagree", "agree", and "strongly agree". The total score ranges from 7 to 35, as the minimum possible score for each question is one and the maximum is 5. The higher the overall score, the greater the fear of COVID-19.

Emotional distress

The DASS-21 is a shorter version of the DASS-42, a psychometric instrument that measures three dimensions of emotional distress, i.e. depression, anxiety, and stress. In this study, DASS-21, which has Turkish validity, was used to measure the severity of emotional distress (12,13). There are 21 items on the questionnaire that consist of three separate self-reported scales that are designed to assess emotional distress in terms of depression, anxiety, and stress (7 items for each dimension). Each item is rated on a four-point Likert scale ranging from 0 to 3 (0: "Did not apply to me at all," 1: "Applied to me to some degree or some of the time," 2: "Applied to me to a considerable degree or a good part of the time," and 3: "Applied to me very much or most of the time"). If the individual scores 5 points or more from the depression sub-dimension, 4 points or more from the anxiety sub-dimension, and 8 points or more from the stress sub-dimension, it indicates that he/she has a problem in that area.

Sleep quality

The PSQI, validated in Turkish, is used to evaluate sleep quality (14,15). PSQI assesses an individual's sleep quality over the past month. PSQI scores range from 0 to 21, and the sleep quality of those with a total score of 5 and below is "good"; those with a score above five are considered to have "poor" sleep quality.

Statistics

SPSS 22.0 software for Windows is used for statistical analysis. Variables were evaluated for normal distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests. All parameters showed normal distribution. Comparison of normally distributed and independent continuous variables was done with Student's t-test. Continuous variables are shown as mean

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± standard deviation. Pearson correlation coefficient was used to determine the relationship between normally distributed continuous variables, and two-way p<0.05 values were considered statistically significant. Chi-square (or Fisher's Exact test, where appropriate) was used to examine the relationship between categorical variables. Statistical significance level was determined as p<0.05.

Results

The mean age of 302 patients included in the study was 55.9±18.8 (median=61, min=18, max=102). One-hundred thirty-one (45.4%) patients were in the geriatric group. One-hundred seventy-one (53.3%) patients were female (69 old-aged and 92 young) and 131 (46.7%) patients were male (62 old-aged and 79 young). There was no difference between the groups in terms of gender distribution (p=0.155). Geriatric and young groups were compared in terms of demographic data and clinical characteristics, and the findings are summarized in Table 1.

Geriatric and young groups were compared in terms of psychological parameters and sleep quality, and the findings are summarized in Table 2. The mean PSQI score was above the cut-off value of 5 in both groups. When all participants were evaluated, 54.6% of the patients (165/302) had poor sleep quality. The PSQI score of 75 patients (57.3%) in the geriatric group and 90 patients (52.6%) in the young group was above 5, and the difference did not reach the level of statistical significance (p=0.248).

PSQI, FVC-19S, DASS-21 correlation analyses were analyzed separately in the geriatric and younger groups (Tables 3, 4). A positive correlation was found between FVC-19S and DASS-21 and PSQI scores in both the old-aged and the young (r=0.190 p=0.029, r=0.207 p=0.017 in the old-aged r=0.268 p=0.002, r=0.393, p=<0.001 in the young, respectively). There was a positive correlation between PSQI scores and FVC-stress scores in the old-aged and a positive correlation between PSQI scores and depression scores in the young (r=0.378 p=<0.001 and r=0.260 p=<0.001, respectively).

Discussion

This study is the first study to compare the psychological effects of the COVID-19 pandemic on the old-aged and young people in our country. It was concluded that the fear of COVID-19 is higher in old-aged than in young people. It was found that the pandemic caused higher levels of anxiety and depression in the old-aged compared to young people. Additionally, it was seen that half of the old-aged have poor sleep quality, and sleep quality deteriorates as the fear of COVID-19 increases in both the old-aged and young people. The results of this study are very important. Because both emotional distress and sleep disorders in the old-aged can predispose to many geriatric syndromes and have the potential to worsen existing problems.

In the study by Bakioğlu et al. (16), in Turkey with 960 participants (18-76 years old, with a mean age of 29.74±9.64) the mean FVC-19S of the whole group was found to be 19.44±6.07. In the

Table 1. Comparison of geriatric and young groups in terms of demographic data and clinical features			
Parameters	Geriatric group (n=131)	Young group (n=171)	p
Age#	73.07±7.27	42.98±13.83	<0.001
Education level ≥8 years n (%)	20 (15.3)	59 (34.5)	<0.001
Number of chronic diseases#	2.37±1.10	1.67±1.54	<0.001
Number of drugs used#	4.16±1.14	2.25±2.0	<0.001
COVID-19 vaccinated n (%)	118 (90.1)	102 (59.6)	<0.001
Who delay their doctor's appointment n (%)	108 (82.4)	106 (62.0)	<0.001
Who change their medications themselves n (%)	9 (6.9)	8 (4.7)	0.291
# Mean ± standard deviation, COVID-19: Coronavirus disease-2019			

Table 2. Comparison of geriatric and young groups in terms of psychological parameters and sleep quality			
Parameters	Geriatric group (n=131)	Young group (n=171)	p
PSQI#	7.12±4.08	6.78±4.31	0.346
FCV-19S#	26.12±5.54	15.65±7.51	<0.001
DASS 21# (total score)	39.43±9.92	25.66±13.89	<0.001
Depression score of DASS-21#	14.12±4.52	6.10±5.49	0.008
Anxiety score of DASS-21#	16.64±4.61	10.11±6.80	<0.001
Stress score of DASS-21#	8.39±4.01	9.72±5.57	<0.001
# Mean ± standard deviation, PSQI: Pitsburg Sleep Quality Index, DASS-21: Depression Anxiety Stress Scale, FCV-19S: Fear of Coronavirus-19 Scale			

study of Bakioğlu et al. (16), age grouping was not made. In our study, young and geriatric groups were evaluated separately, and the mean FVC-19S in the geriatric group was found to be much higher (26.12±5.54) than in Bakioğlu et al.'s (16) study. This result is quite remarkable in terms of the risks it carries for the old-aged. The high fear of COVID-19 can cause many other situations, such as social isolation, failure to attend chronic disease controls, and postponing applications to health institutions for newly developing symptoms (17). Our study found that four out of every five old-aged patients disrupted their routine doctor control due to the pandemic, and some of the patients themselves made changes in the drugs or drug doses they used. In addition, our results show a positive correlation between FVC-19S and DASS-21 scores, and the emotional distress of individuals increases as the fear of COVID-19 increases. In parallel with the increase in emotional distress in the old-aged, it is expected that the nutritional status, energy level, interest and willingness, and quality of life will deteriorate (18). During the pandemic process, it becomes inevitable for the old-aged to regress in their physical and cognitive abilities and increase the frequency of geriatric syndromes such as malnutrition, sarcopenia, polypharmacy, and falls. Therefore, the results of our study are an indication that the old-aged are more vulnerable

psychologically and will be more vulnerable physically during the pandemic process.

Although some population-based studies were conducted during the pandemic period, the rates of anxiety disorder, depression, and posttraumatic stress disorder were found to be lower in old-aged individuals than in young people; many other studies have found opposite results (19-21). Sepúlveda-Loyola et al. (22), in their study evaluating the effects of the isolation period on the old-aged during the COVID-19 epidemic, found that the old-aged experienced anxiety, depression, poor sleep quality, and physical inactivity problems. In a study conducted by Wang et al. (23), it was found that the old-aged were more stressed, agitated, and overly suspicious during the pandemic process. Differences in the literature may be due to pandemic management practices, cultural differences, and socio-economic factors in the country where the study was conducted. In our study, depression and anxiety scores of the DASS-21 were higher in the old-aged. COVID-19 infection often progresses with a more severe clinical picture and higher mortality in old-aged individuals than in young people (24,25). For this reason, the old-aged have become the focal point of the measures and restrictions (such as going out on the street, using public transport) within the scope of combating the pandemic in our country (26). This situation has

Table 3. PSQI, FVC-19S, DASS-21 correlation analysis results in the geriatric group

	PSQI	FVC-19S	DASS-21	Depression score of DASS-21	Anxiety score of DASS-21	Stress score of DASS-21
PSQI r p	1	0.207** 0.017	0.010 0.909	0.081 0.359	0.145 0.098	0.378** <0.001
FVC-19S r p		1	0.190* 0.029	0.290** <0.001	0.350** <0.001	0.268** 0.002
DASS-21 r p			1	0.750** <0.001	0.798** <0.001	0.321** <0.001

*: <0.05 (correlation is significant at the 0.05 level), **: <0.01 (correlation is significant at the 0.01 level). PSQI: Pitsburg Sleep Quality Index, DASS-21: Depression Anxiety Stress Scale, FCV-19S: Fear of Coronavirus-19 Scale

Table 4. PSQI, FVC-19S, DASS-21 correlation analysis results in the young group

	PSQI	FVC-19S	DASS-21	Depression score of DASS-21	Anxiety score of DASS-21	Stress score of DASS-21
PSQI r p	1	0.393** <0.001	0.095 0.367	0.260** <0.001	0.067 0.383	0.074 0.335
FVC-19S r p		1	0.268** 0.002	0.368** <0.001	0.083 0.278	0.166* 0.030
DASS-21 r p			1	0.716** <0.001	0.870** <0.001	0.718** <0.001

*: <0.05 (correlation is significant at the 0.05 level), **: <0.01 (correlation is significant at the 0.01 level) PSQI: Pitsburg Sleep Quality Index, DASS-21: Depression Anxiety Stress Scale, FCV-19S: Fear of Coronavirus-19 Scale

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been frequently brought to the agenda by health authorities and the media since the beginning of the pandemic period, and the old-aged have been exposed to this news every day from all social media channels, especially television. In addition, during the pandemic, we can estimate that the old-aged are more likely to have experienced a loss of ability, status, and closeness than younger peehand, the stress score was higher in the young group in our study. There are understandable reasons why young people have higher stress scores than old-aged. In our country, young people are more active in their work-life compared to the old-aged. Despite the fear of getting sick, they have to work and enter crowded environments when necessary. In addition, the worry of infecting their relatives can also cause stress by putting pressure on them. Although the COVID-19 pandemic has led to significant changes in all individuals' daily routines and lifestyles, young people may have experienced more stress in the face of these changes.

Although the COVID-19 vaccination is reduced to 12 years of age, free of charge, and campaigns that motivate people to be vaccinated in our country, the vaccination rates have still not reached the desired level. In our study, the COVID-19 vaccination rates were significantly higher in the old-aged. The biggest force that drives people to get vaccinated is the fear of catching a disease. The fact that vaccination rates are higher in the old-aged than in the young may be due to the higher fear of COVID-19 and anxiety level in the old-aged compared to the young. In addition, the initiation of COVID-19 vaccination with healthcare professionals and old-aged individuals in our country, and thus the high level of awareness and sensitivity in the geriatric population about vaccine protection, may also play a role (27).

Sleep is closely related to physical and mental health. For this reason, in our study, we evaluated the psychological effects of the COVID-19 pandemic together with the sleep quality of the patients. The literature emphasized that sleep disorders are frequently encountered during the pandemic, and this situation was named "COVID-somnia" (28,29). Our study found that FVC-19S and PSQI scores were correlated in both groups, and sleep quality deteriorated as the fear of COVID-19 increased. The fact that the sleep quality was worse in the old-aged than in the young may be due to the higher fear of COVID-19 in the elderly. In the study conducted by Pekcetin and İnal (30) just before the pandemic in our country, it was found that 44.3% of the old-aged had poor sleep quality, and the mean PSQI was 4.58±2.86. In our study, the PSQI average was even higher due to the effect of the pandemic, and it was observed that the sleep quality was poor in 57.3% of the old-aged. Considering that sleep disorders have severe effects on the old-aged, such as an increase in the risk of accidents and falls, causing depression, and regression in cognitive abilities, this result is quite remarkable.

Two years have passed since the pandemic; known about COVID-19 infection has increased, and vaccines with proven efficacy have been found. Promising drug studies are also ongoing. On the other hand, uncertainty and stress continue at both the individual and social level due to the mutation of the virus and the continuation of new cases and deaths due to COVID-19 infection (31). Our study shows that; even if they are protected from COVID-19 infection or have survived the infection with health, the pandemic has essential effects on the mental health of individuals. Considering that the mental health of the old-aged directly affects their physical health, we can predict that the frequency of geriatric syndromes such as depression, sleep disorders, dementia, malnutrition, sarcopenia, and fragility will secondary increase. Therefore, even if the pandemic ends, the effects of the pandemic will continue for the old-aged.

Study Limitations

Our study is valuable because it shows the magnitude of the psychological effects of the pandemic on the old-aged in our country and is the first study to compare these effects with the young. However, there are some limitations of our study. Our study was designed as cross-sectional, and outpatients admitted to an institution were included in the study. So it is not possible to adapt the study results to the whole society. On the other hand, when comparing the geriatric group and the young group, it is an advantage to conduct the study in a single-center as it will provide similar conditions. Since our study was designed to detect the general psychological effects of the COVID-19 pandemic on the old-aged and determine whether these effects are similar to those of the young, the factors that could affect individuals psychologically were not evaluated separately.

Conclusion

As a result, the rates of experiencing fear, anxiety, and depression due to the COVID-19 pandemic are higher in the old-aged than in the young. More than half of the older adults included in the study have poor sleep quality. Both emotional distress and sleep disorders may predispose to many geriatric syndromes and can worsen existing problems. It is of great importance in terms of public health to investigate the effects of the pandemic on individuals' mental health, identify groups that are especially at risk, and thus make early interventions.

Ethics

Ethics Committee Approval: This study was approved by the İnönü University Turgut Özal Medical Center Scientific Research Ethics Committee (approval number: 102/17) and was conducted by the Helsinki Declaration guidelines.

Informed Consent: Signed informed consent was obtained from patients before inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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How to Treat Osteoporosis in Octogenarians?

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Abstract

Objective: There are few studies investigating the efficacy of anti-osteoporotic drugs in the oldest old. This study aimed to compare the effectiveness of osteoporosis treatment among individuals older and younger than 80 years of age.

Materials and Methods: A total of 257 patients with osteoporosis, aged 65 and over, 234 women and 23 men, were included in the study. Sixty-five of the patients were aged 80 years and older. Seventy-four participants received alendronate, 93 received zoledronic acid, and 90 received denosumab. Dual-energy X-ray absorptiometry scans were performed at baseline and at month 24.

Results: The proportion of the participants receiving glucocorticoid was higher in the under 80-age group. Bone mineral density (BMD) changes were similar between the <80 and ≥80 aged groups. There was no significant difference in the lumbar spine and femoral neck BMD changes between the groups in terms of the anti-osteoporotic agent used. A statistically significant strong positive correlation was found between the femur neck BMD change and fracture risk reduction percentage.

Conclusion: This study showed that osteoporosis treatment in individuals over 80 years of age is as effective as in those under 80 years of age. The results of our study may guide osteoporosis treatment in older individuals.

Keywords: Osteoporosis, oldest old, bisphosphonates, denosumab

Introduction

Osteoporosis is a common chronic disease with a significant global burden characterized by low bone mass, skeletal fragility, and microarchitectural deterioration (1). It is defined as a fragility fracture and/or a T-score of -2.5 or lower and is an important cause of morbidity and mortality among older adults (2).

Pharmacologic agents for the treatment of osteoporosis can be classified as either antiresorptive (alendronate, zoledronate, and denosumab) or anabolic (teriparatide and abaloparatide). Alendronate is an antiresorptive agent commonly used as first-line therapy for osteoporosis and effectively reduces the risk of vertebral, non-vertebral, and hip fractures (3). Zoledronate is administered by intravenous injection at intervals of one year and has anti-fracture efficacy and positive effects on bone mineral density (BMD) in older adults with osteoporosis (4). Denosumab inhibits bone resorption by binding to the receptor

activator of the nuclear factor-κβ ligand, thereby decreasing the differentiation of osteoclasts. Denosumab reduces the risk of hip, non-vertebral, and vertebral fractures (5).

In many countries, the number of patients with osteoporosis is expected to increase with societal aging. In addition, as the number of individuals over 80 years increases, the risk of osteoporotic fractures increases correspondingly (6). Little is known about the efficacy of osteoporosis medication in octogenarians.

Several studies have highlighted a significant association between increasing age and a reduced likelihood of receiving effective osteoporosis treatment (7-9). A large meta-analysis study including patients with a median age of 64 years has showed that denosumab, zoledronic acid, and alendronate had similar fracture risk reduction with small differences in efficacy (10).

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In this study, we aimed to investigate the effect of osteoporosis treatment agents on the BMD change and fracture risk reduction among patients with osteoporosis older and younger than 80 years of age.

Materials and Methods

Participants

A total of 274 patients aged 65 and over who applied to our outpatient clinic and were diagnosed with osteoporosis were included in this retrospective study. Exclusion criteria were renal impairment, primary or metastatic bone tumor, and bone diseases other than osteoporosis. BMD measurement of the lumbar spine and proximal femur was performed by DXA method (using Hologic scanners) before the treatment and at month 24. Seventeen patients without a DXA scan at month 24 were excluded. The percent change from the baseline BMD was calculated at month 24. Alendronate was administered 70 mg/weekly oral, zoledronic acid 5 mg/yearly intravenous, and denosumab 60 mg/every 6 months subcutaneously. All patients were prescribed 1000 mg of calcium and 800 IU of vitamin D per day. Glucocorticoid (GC) use was considered as use of ≥5 mg/day prednisolone or equivalent for 3 months or more. Approval for the study was granted by the Gaziantep University Local Ethics Committee (no: 2020/422 dated 24.02.2021).

Statistics

Statistical analyses were performed with SPSS for Windows version 22.0 (IBM SPSS Statistics, Armonk, NY). The distribution of normality was checked using the Shapiro-Wilk test. We used the independent samples t-test and Mann-Whitney U test to compare two independent groups of variables, the chi-squared test to assess the relationship between categorical variables, and Spearman's rank correlation coefficients between numerical variables. A p-value less than 0.05 was accepted as statistically significant.

Results

The median age of the 257 patients was 69 years, 65 of them were over 80 years old, and 91.1% were women. Eighteen were smokers and none of them had alcohol consumption. The proportion of those receiving GC was higher in the under 80 age group. There was no significant difference between the groups in terms of laboratory analysis results. The proportion of those receiving zoledronic acid and denosumab was higher in the ≥80 age group, although there was no statistically significant difference (Table 1).

Baseline BMD and T-scores of the femoral neck were lower in the ≥80 age group, while BMD changes did not differ between the age groups (Table 2). There was no statistically significant

difference in BMD changes between the groups in terms of the anti-osteoporotic agent used (Table 3).

Age, number of comorbidities, and medications were not correlated with the BMD change and fracture risk reduction. A statistically significant strong positive correlation was found between femur neck BMD change and percentage reductions in major osteoporotic and hip fracture risk. In addition, there was a statistically significant negative correlation between the baseline femur neck BMD and the BMD changes and fracture risk reduction, also between the baseline lumbar spine BMD and lumbar spine BMD changes (Table 4).

Discussion

We aimed to investigate the effectiveness of osteoporosis treatment in individuals over 80 years, who often are not included in clinical trials. Our findings have shown that response to the osteoporosis treatment agents according to the BMD and fracture risk reduction did not differ in individuals younger or older than 80 years.

Senile osteoporosis is characterized by loss of cortical bone and trabecular bone, and hence a decrease in BMD in regions rich in cortical bone such as the proximal femur, pelvis, and humerus. This may explain why the participants over the age of 80 had lower BMDs of the femoral neck than those under the age of 80 in our study (11).

With an increasingly aging population, there is a strong interest in the efficacy of treatment agents in older osteoporotic adults (12,13). However, there is little clinical evidence of the effectiveness of osteoporosis treatment in different age groups. In this study, it was shown that the efficacy of alendronate, zoledronic acid, and denosumab continued in advanced ages.

Multimorbidity and polypharmacy, which are common conditions in older individuals, may complicate compliance with oral antiosteoporotic drugs. In addition, parenteral agents may be preferred more frequently in elderly osteoporosis, since gastrointestinal absorption of oral agents may decrease with age, and zoledronic acid and denosumab have longer dose intervals and can largely eliminate compliance and persistence problems. The relatively higher preference for parenteral treatments in our study may be due to these factors.

A previous study has shown that that alendronate effectively reduces the risk of fractures in vertebral fractures in women aged 55-81 years with low BMD (14). Another study reported that alendronate was effective in reducing the risk of osteoporotic fractures, regardless of age (15).

Zoledronic acid treatment, administered intravenously 5 mg once a year for 3 years, was also effective in patients 75 years of age and older with osteoporosis and significantly reduced the risk of vertebral and nonvertebral fractures (16).

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Table 1. Socio-demographic characteristics and laboratory analysis results of the participants

	Aged <80 years (n=192)	Aged ≥80 years (n=65)	p	Total (n=257)
Gender				
Female	176 (91.7%)	58 (89.2%)	0.616	234 (91.1%)
Male	16 (10.8%)	7 (10.8%)		23 (8.9%)
Age (years)#	67	82	<0.001*	69
Treatment agent				
Alendronate	62 (32.3%)	12 (18.5%)		74 (28.8%)
Zoledronic acid	68 (35.4%)	25 (38.5%)	0.084	93 (36.2%)
Denosumab	62 (32.3%)	28 (43.1%)		90 (35.0%)
Other comorbidities				
Hypertension	76 (39.6%)	29 (44.6%)	0.476	105 (40.9%)
Diabetes mellitus	40 (20.8%)	18 (27.7%)	0.253	58 (22.6%)
Coronary artery disease	24 (12.6%)	8 (12.3%)	0.957	32 (12.5%)
Glucocorticoid-user	40 (20.8%)	6 (9.2%)	0.039*	46 (17.9%)
Cancer	11 (5.7%)	4 (6.2%)	0.900	15 (5.8%)
Smoker	15 (7.8%)	3 (4.6%)	0.383	18 (7.0%)
Serum 25-OH vitamin D (nmol/L)†	35.6±6.1	34.0±5.5	0.169	35.2±6.2
Parathyroide hormone (pg/mL) #	58	69	0.941	60
Serum calcium (mg/dL)†‡	9.7±0.6	9.6±0.5	0.640	9.7±0.5
Serum phosphorus (mg/dL)†	3.7±0.6	3.6±0.4	0.601	3.7±0.5
C-reactive protein (mg/dL)#	2.9	3.0	0.828	3.0
Erythrocyte sedimentation rate (mm/hr)#	17	20	0.546	18
Serum creatinine (mg/dL)#	0.65	0.68	0.221	0.66

*p≤0.05, #Data are presented as median, †Data are presented as mean ± standard deviation, ‡Albumin-adjusted calcium

Table 2. Comparison of the DXA scan assessments, BMD changes and fracture risk reduction

	Aged <80 years (n=192)	Aged ≥80 years (n=65)	p	Total (n=257)
Lumbar spine				
Baseline T-score#	-2.83±0.59	-2.74±0.78	0.394	-2.80±0.67
Baseline BMD (g/cm²) #	0.74±0.06	0,75±0.12	0.403	0.74±0.08
24th month BMD (g/cm²) #	0.77±0.07	0,77±0.12	0.765	0.77±0.08
BMD change (%)†	4.35 (-1.27-16.93)	3.00 (-1.35-17.64)	0.116	3.99 (-1.35-17.64)
Baseline T-score#	-2.28±0.64	-2.70±0.81	0.000*	-2.39±0.71
Baseline BMD (g/cm²) #	0.59±0.07	0,55±0.09	0.000*	0.58±0.08
24th month BMD (g/cm²)#	0.61±0.07	0,57±0.09	0.000*	0.60±0.08
BMD change (%)†	2.69 (-1.89-23.25)	3.69 (-1.50-28.93)	0.215	2.81 (-1.89-28.93)
Major osteoporotic fracture risk reduction (%)†	6.67 (-11.24-47.86)	9.09 (-9.09-50.00)	0.734	7.85 (-11.24-50.00)
Hip fracture risk reduction (%)†	12.25 (-3.85-68.66)	10.31 (-4.23-57.28)	0.950	11.76 (-4.23-68.66)

*p≤0.05, BMD: Bone mineral density, #Data are presented as mean ± standard deviation, †Data are presented as median (min-max)

Denosumab has been shown to significantly reduce the risk of hip fracture in elderly patients aged 75 years and older at high risk of fracture (17). In a study involving 3.902 participants receiving denosumab treatment, it was shown that age was not an important factor in terms of treatment effectiveness in individuals under 75 years of age and older (18). Anabolic agents, particularly teriparatide, have also been shown to have similar efficacy in older adults (19,20).

According to the results of our study, it was thought that the similar BMD response in both age groups might be due to the higher number of GC-users. However, there was no

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Table 3. Comparison of the BMD changes between treatment agents

Treatment agent		Lumbar spine BMD change (%)	p	Femur neck BMD change (%)	p
Alendronat (n=74)	Aged <80 years (n=62)	3.63	0.189	1.85	0.509
	Aged ≥80 years (n=12)	1.34		3.27	
Zoledronic acid (n=93)	Aged <80 years (n=68)	4.33	0.469	2.83	0.815
	Aged ≥80 years (n=25)	4.44		3.03	
Denosumab (n=90)	Aged <80 years (n=62)	4.77	0.261	3.00	0.153
	Aged ≥80 years (n=28)	2.83		5.96	
BMD: Bone mineral density, data are presented as median					

Table 4. Correlation analysis results between femur neck and lumbar spine BMD changes and major osteoporotic and hip fracture risk reduction

		Baseline femur neck BMD	Baseline lumbar spine BMD	Femur neck BMD change (%)	Lumbar spine BMD change (%)	Major osteoporotic fracture risk reduction (%)	Hip fracture risk reduction (%)
Baseline femur neck BMD	r p	1.000	0.226 0.000*	-0.292 0.000*	-0.004 0.943	-0.335 0.000*	-0.274 0.000*
Baseline lumbar spine BMD	r p	0.226 0.000*	1.000	-0.043 0.414	-0.232 0.000*	-0.054 0.302	-0.019 0.718
Femur neck BMD change (%)	r p	-0.292 0.000*	-0.043 0.414	1.000	0.109 0.037*	0.962 0.000*	0.961 0.000*
Lumbar spine BMD change (%)	r p	-0.004 0.943	-0.232 0.000*	0.109 0.037*	1.000	0.103 0.050*	0.101 0.053
Major osteoporotic fracture risk reduction (%)	r p	-0.335 0.000*	-0.054 0.302	0.962 0.000*	0.103 0.050*	1.000	0.953 0.000*
Hip fracture risk reduction (%)	r p	-0.274 0.000*	-0.019 0.718	0.961 0.000*	0.101 0.053	0.953 0.000*	1.000
r: Spearman rank correlation coefficient, *Significant at 0.01 level, BMD: Bone mineral density							

significant difference in BMD change between GC-users and non-users, and age groups, according to treatment agents.

Study Limitations

Our study has some limitations. First, there was a lack of bone turnover markers measurement in our study. Second, a longer follow-up with a higher number of patients could better demonstrate the differences in fracture incidence. Despite these limitations our study has some strengths. First, it focuses on individuals 80 years of age and older, who are often excluded from clinical trials, but are at the highest risk of fracture. Second, we compared the effects of treatment agents among themselves, while most previous studies compared the effects of the drugs with placebo. Third, the similarity of comorbidities, inflammatory markers, and other laboratory measurements between the groups was important to compare the treatment agents more transparently.

Conclusion

The current study showed that different osteoporosis treatment agents are effective in reducing BMD and fracture risk in elderly individuals with osteoporosis aged 80 years and over. Age has not been found to affect the effectiveness of osteoporosis treatment in elderly individuals with osteoporosis. This study provides information that can guide future studies of the treatment of osteoporotic adults 80 years of age and older.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Local Ethics Committee (Gaziantep University, no: 2020/522, date: 24.02.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

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Authorship Contributions

Concept: A.Ç., E.M.E., Design: Z.A.Ö., Data Collection or Processing: A.Ç., E.Ö., Analysis or Interpretation: A.Ç., Z.A.Ö., Literature Search: E.Ö., E.M.E., Writing: A.Ç., E.Ö.

Conflict of Interest: The authors have no conflicts of interest to report.

Financial Disclosure: The authors declared that this study received no financial support

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CASE REPORT

A Rare Synchronous Tumor Association in a Geriatric Patient: Lung Adenocarcinoma and Colon Carcinoma

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Abstract

The incidence of synchronous colorectal and lung cancer is very low and rare. We present the case of a geriatric patient with tumors in the transverse colon and right pulmonary hilum. This case report aims to draw attention to the rare synchronous colon and lung cancer. Treatment of synchronous tumors is different from the treatment of other primary cancers. If possible, radical resection of both tumors should be performed when synchrony is detected. Since our patient was metastatic, a chemotherapy protocol that is effective on both tumors was started. Chemotherapy regimens are also quite different in these patients. Therefore, effectively differentiating synchronous cancers from colorectal cancer with pulmonary metastases has important therapeutic implications for these patients.

Keywords: Synchronous, cancer, elderly

Introduction

The liver is the first and most common site of colorectal cancer metastases. The second most common organ for metastases is the lung (1). Lee et al. (2) reported that 10-20% of patients with colorectal cancer develop lung metastases. Pulmonary metastasis of colorectal cancer usually occurs as multiple lesions in both lungs due to the distribution of the primary tumor through the circulation. However, approximately 10% of pulmonary metastases consist of a single solitary pulmonary nodule (2). A solitary pulmonary nodule in a patient with current or pre-existing colorectal cancer should initially suggest a metastasis of colorectal cancer. However, in some rare cases, patients may develop synchronous colorectal and lung cancer. In fact, lung cancer appears to be one of the most common second primary cancers in patients with colon cancer (3). In these patients, not only surgical resection but also chemotherapy regimens are quite different from those for patients with colorectal cancer with pulmonary metastases. Hence, effectively distinguishing synchronous cancers from colorectal cancer with pulmonary metastases has important therapeutic implications for these patients.

This case report aims to draw attention to synchronous tumors by presenting a case of rare synchronous colon and lung cancer.

Case Report

A 73-year-old female patient was admitted to our polyclinic with loss of appetite, weakness, and weight loss for the last three months. On the physical examination, her general condition was moderate, body temperature was 36.8 °C, pulse was 90/min, respiratory rate was 21/min, and blood pressure was 110/70 mmHg. Head and neck examination revealed painless lymphadenopathy (LAP) of approximately 2 cm in the left cervical region. Other system examinations were normal. She had a 15-year history of type 2 diabetes mellitus. There was no feature in her family history. The patient, who had a shortness of breath in the system query and a 15 pack-year smoking history, was admitted to the geriatric service with a preliminary diagnosis of malignancy.

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In her inpatient laboratory tests, sedimentation was 55 mm/hour, hemoglobin: 13.9 g/dL, white blood cell: 7.97 10³/μL, PLT: 283 10³/μL, and C-reactive protein: 2.3 mg/dL. Superficial tissue ultrasonography (USG) revealed 20 mm LAP in the left cervical region and multiple LAPs, the largest of which was 24x15 mm, in the periportal, paraaortic, and peripancreatic areas. On abdominal USG, up to 30 mm of free fluid was detected in the pelvic region. Thoracic and abdominal computed tomography detected fluid up to 48 mm in the right hemithorax, 52 mm in the left hemithorax, multiple LAPs of 26x17 mm in the paraaortic, paracaval, subcarinal, paraesophageal, peripancreatic, and portal hilum, and free fluid in the pelvis.

The lymph nodes in the left cervical region of the patient were excised, and the pathology report indicated lymph node metastasis of mucinous adenocarcinoma. Sections of the metastatic lymph node revealed a neoplastic formation by glandular structures and occasional distribution of atypical cells with hyperchromatic nuclei, large cytoplasm, and a monotonous morphology in places within large mucin pools that have destroyed the lymph node structure. The tumor has the morphology of a mucinous adenocarcinoma (Figure 1). Pathologically, systematic screening of the case, primarily the digestive system, has been suggested to find the primary site of origin.

In the systemic evaluation of the patient, tumor markers were found as CA-125:124 U/mL, CA 19-9: 18.1 U/Ml, and CEA: 359 ng/mL. Positron emission tomography revealed a hypermetabolic lesion with irregular borders in the right pulmonary hilar region (SUV$_{max}$:4.63); several hypermetabolic nodular lesions in both lungs, 9 mm in the upper lobe of the left lung and 12 mm in the upper lobe of the right lung; hypermetabolic lymph nodes

in bilateral supraclavicular, right hilar, right paratracheal, aortopulmonary, subcarinal and bilateral bronchovascular areas (SUV$_{max}$:4.61); pleural effusion up to 46 mm in the left lung and 50 mm in the right lung; hyperipermetabolic lesion in the 5 cm long segment in the transverse colon (SUV$_{max}$:12,35); celiac, gastrohepatic, paracaval, paraaortic, aortocaval, peripancreatic, hypermetabolic lymph nodes in the left common iliac area (SUV$_{max}$: 4.60) and hypermetabolic bone lesions in the right scapula, right acromion, right proximal humerus and left proximal humerus proximal (SUV$_{max}$: 3.13) Figure 2.

Colonoscopy performed for the primary site investigation revealed a suspicious lesion in the transverse colon and biopsy was performed. Pathological examination of the colon biopsy revealed tubulovillous adenoma fragments containing areas of invasive carcinoma (Figure 3). However, mucinous areas were not observed morphologically, and therefore, it was predicted that the case may have a second primary malignancy in the morphology of mucinous adenocarcinoma.
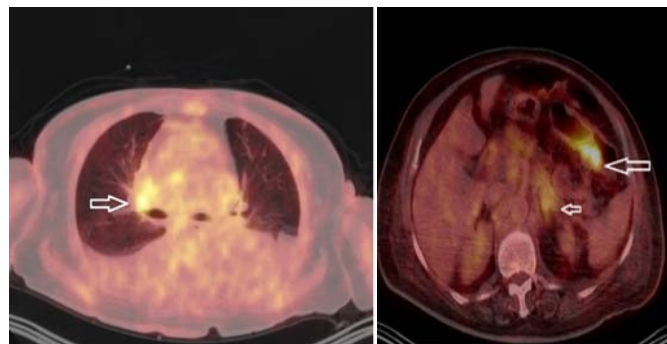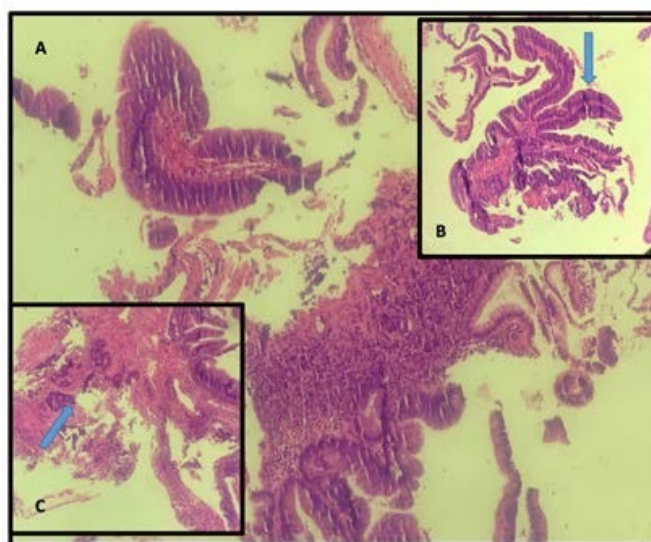

Figure 2. PET CT: Synchronous tumor involvement in the transverse colon and right pulmonary hilar region

PET: Positron emission tomography, CT: Computed tomography
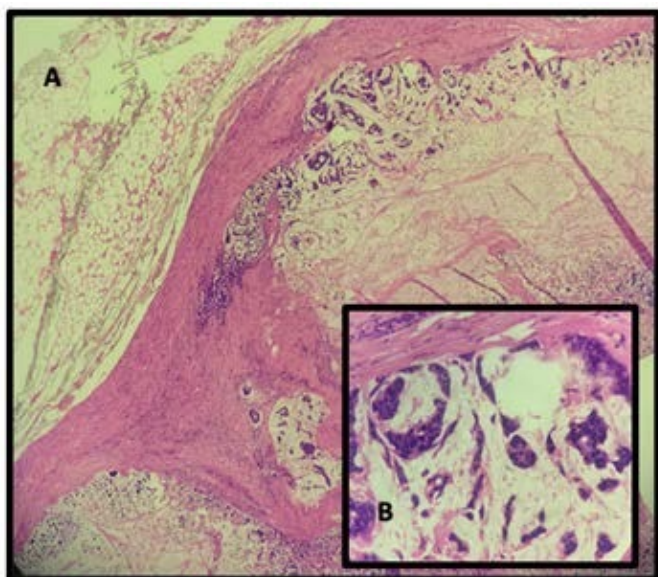
Figure 1. Mucinous adenocarcinoma metastasis positive lymph node

Figure 3. A-Tubulovillous adenoma fragents containing areas of invasive carcinoma, B- villous structure, C-Invasive areas (H&t)

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Endobronchial USG was performed because the patient had a suspicious lesion with SUV$_{max}$: 4.63 in the lung. Biopsy was performed from the lap reaching 40 mm in size in the lower right paratracheal area. Histomorphological examination revealed atypical pleomorphic neoplastic cells with large hyperchromatic nuclei within mucin pools, occasionally containing intracytoplasmic mucin. Its pathology was reported as mucinous adenocarcinoma metastasis (Figure 4). In the immunohistochemical analysis of the case, immune expression

was monitored with ck20 and cdx-2 (Figure 3), but no immune expression of ck20 and cdx-2 (Figure 5). No reactivity was observed with immunohistochemical CK7, TTF-1 and napsin A (Figure 6). The patient was diagnosed with lung mucinous adenocarcinoma and colon adenocarcinoma synchronously.

The patient was referred to the medical oncology clinic with the diagnosis of metastatic synchronous lung and colon cancer, and chemotherapy (3 cycles of paclitaxel d1, d8, d15, and carboplatin d1, d8, d15 every 28 days) was started. The outpatient follow-up of the patient, who is in the first month of treatment, continues.

Discussion

Colorectal cancer is one of the most common types of cancer, it tends to metastasize by the hematogenous route. The liver and lung are the organs that it metastasizes most frequently. Approximately 50% of patients develop liver metastases and approximately 20% develop lung metastases. Therefore, when a patient with colorectal cancer has multiple pulmonary lesions, most clinicians consider them to be lung metastases. However, sometimes pulmonary metastases may occur as a single solitary lesion. In addition, as presented in our case, it can be seen in rare patients with primary lung cancer and synchronous colorectal cancer as a type of multiple primary malignant neoplasms.

Evans et al. (4) investigated the incidence of primary lung cancer in 127,281 patients with colorectal cancer and found the incidence of primary lung cancer to be 0.6% (801 cases), whereas the incidence of synchronous colorectal and lung cancer was much lower. The pathogenesis, biological behavior, and treatment of synchronous colorectal and lung cancer are
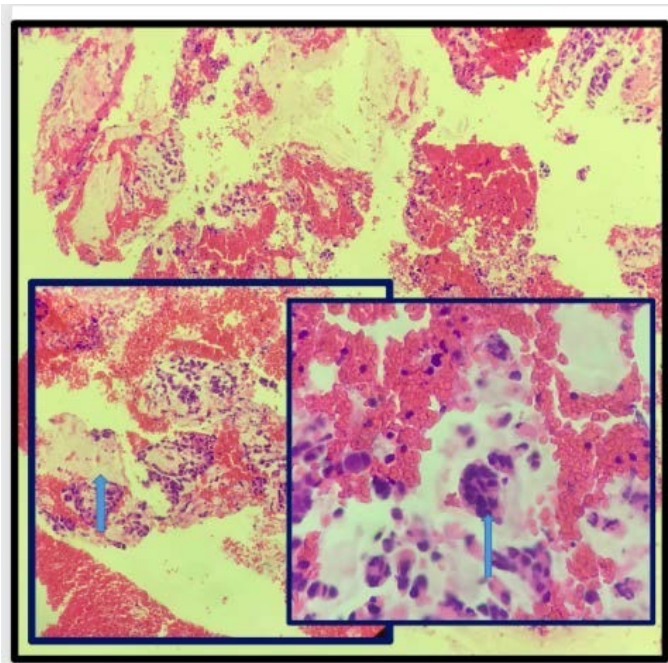

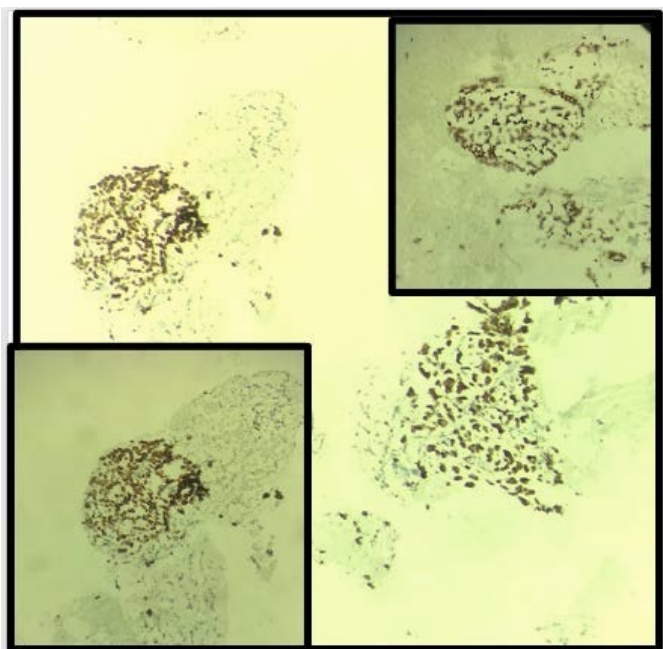**Figure 4.** EBUS material from 4R lymph node (H&E)

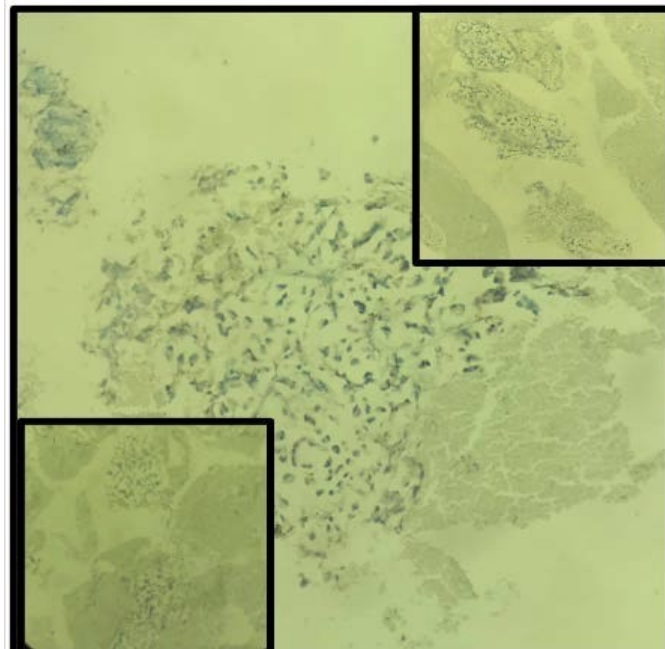**Figure 5.** CK20 and CDX-2 immunoexpression in an immunohistochemical study

Figure 6. No immunohistochemical reactivity was observed with CK7, TTF-1, and napsin A

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quite different from that of colorectal cancer with pulmonary metastases. Therefore, when a single solitary pulmonary lesion is detected in a colorectal cancer patient, it is crucial to distinguish between these two possibilities for appropriate surgical treatment or appropriate chemotherapy. Due to the low incidence, physicians do not have much experience in synchronous colorectal and lung cancer. This may lead to misdiagnosis and delay in treatment. For instance, if a patient with synchronous colorectal and lung cancer is misdiagnosed as colorectal cancer with lung metastases, the chemotherapy given may not be effective for the patient. For these reasons, cancer patients should be carefully examined. If synchronous cancers are detected in the early period, these patients may have better treatment options. Since the incidence of synchronous colorectal and lung cancer is relatively low, each organ should be carefully examined when the first primary cancer is found, and it should be kept in mind that there may be another malignant neoplasm. When suspicious lesions are found, further investigation should be performed immediately. Biopsy if necessary, can reduce the possibility of misdiagnosis and will make it easier for physicians to detect synchronous lesions.

When the patient's condition allows, radical resection of synchronous tumor foci should be performed. After radical resection, appropriate adjuvant chemotherapy should be given according to the pathological type and stage of the tumors. If surgical resection is not feasible, an appropriate chemotherapy protocol that can affect both tumor foci should be chosen.

In conclusion, lung cancer and colon cancer are two very common types of malignancies and are among the leading causes of cancer-related deaths. Especially in developed countries, these cancers constitute a significant public health burden (5). It is generally accepted that smoking plays an important role in lung carcinogenesis (6). In addition, epidemiological data suggest that obesity is associated with an increased risk of colon cancer (7). Diabetes and high dietary meat intake are also associated with an increased risk of colon cancer (7). Although the incidence of synchronous lung and colon cancers is low, future genetic and epidemiological studies are needed to elucidate the potential link between these two types of cancer.

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