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Zekeriya Ülger
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E-mail: zekeriyaulger@yahoo.com
ORCID: 0000-0002-6325-496X

Associate Editor

Volkan Atmış
Ankara University Faculty of Medicine, Department of Internal Diseases, Division of Geriatrics Ankara, Türkiye
volkanatmis@hotmail.com
ORCID: 0000-0002-0080-6448

Gözde Şengül Ayçiçek
Etlik City Hospital, Clinic of Geriatrics, Ankara, Türkiye
E-mail: gzdsengul@gmail.com
ORCID: 0000-0003-0528-8851

Cafer Balcı
Hacettepe University Faculty of Medicine, Department of Internal Diseases, Ankara, Türkiye
E-mail: cafer.balci@hacettepe.edu.tr
ORCID: 0000-0002-1478-1106

Aslı Tufan Çinçin
Marmara University Faculty of Medicine, Department of Internal Diseases, Division of Geriatrics, İstanbul, Türkiye
E-mail: aslitufan@yahoo.com
ORCID: 0000-0002-7522-8275

Muhammet Cemal Kızılarslanoğlu
University of Health Sciences Türkiye, Konya City Hospital, Clinic of Internal Diseases, Division of Geriatrics, Konya, Türkiye
E-mail: drcemalk@yahoo.com.tr
ORCID: 0000-0002-7632-6811

Hacer Doğan Varan
Gazi University Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, Ankara, Türkiye
E-mail: drhacerdogan84@hotmail.com

Vahid Rashedi
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ORCID: 0000-0002-3972-3789

Selahattin Fehmi Akçiçek
Ege University Faculty of Medicine, Department of Geriatrics, İzmir, Türkiye
ORCID: 0000-0003-2583-4709

Sevgi Aras
Ankara University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-5356-303X

Dursun Aras
University of Health Sciences Türkiye, Ankara Training and Research Hospital, Ankara, Türkiye
ORCID: 0000-0001-6020-8098

Güneş Arık
University of Health Sciences Türkiye, Ankara Numune Training and Research Hospital, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-4766-3982

Teslime Atlı
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ORCID: 0000-0001-7359-4856

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ORCID: 0000-0003-1547-8544

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İstanbul University İstanbul Medical Faculty, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0001-5343-9795

Ergün Bozoğlu
University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-9689-9211

Olivier Bruyere
University of Liege Medical Faculty, Department of Public Health, Liège, Belgium
ORCID: 0000-0003-4269-9393

Alessandra Coin
Azienda Ospedale Università, Geriatrics Clinic, Padova, Italy
e-mail: alessandra.coin@unipd.it
ORCID: 0000-0003-1687-4493

Erkan Çoban
Akdeniz University Faculty of Medicine, Department of Geriatrics, Antalya, Türkiye
ORCID: 0000-0001-6281-0541

Aslı Çurgunlu
İstanbul Bilim University Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0001-6281-0541

Ülev Deniz Suna Erdinçler
İstanbul University-Cerrahpaşa Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0003-1208-4750

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr / yayin@galenos.com.tr
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Address for Correspondence
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info@ejgg.org

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Doron Garfinkel
Geriatric-Palliative Consultant, Sheba Medical Center & Deputy Head, Homecare Hospice, Israel Cancer Association
E-mail: dgarfink@netvision.net.il
ORCID: 0000-0002-3171-9881

Kürşat Gündoğan
Erciyes University Faculty of Medicine, Department of Internal Medicine, Kayseri, Türkiye
ORCID: 0000-0002-8433-3480

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Harvard University Medical School, Department of Neurology, Boston, United States
ORCID: 0000-0002-2169-4457

Alfonso J Jentoft
Hospital Universitario Ramón y Cajal (IRYCIS), Department of Geriatrics, Madrid, Spain
ORCID: 0000-0001-7628-4861

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ORCID: 0000-0002-1628-5093

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ORCID: 0000-0002-4936-3705

Nirankar Singh Neki
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ORCID: 0000-0001-6883-1415

Nele Van Den Noortgate
University Hospital Ghent, Department of Geriatrics, Gent, Belgium
ORCID: 0000-0001-5546-5380

Karolina Piotrowicz
Jagiellonian University Faculty of Medicine, Department of Internal Medicine and Gerontology, Kraków, Poland
ORCID: 0000-0002-4760-8588

Cornel Christian Sieber
Friedrich-Alexander University, Department of Geriatrics, Erlangen, Germany
ORCID: 0000-0002-9364-6921

İbrahim Şahin
İnönü University Faculty of Medicine, Department of Endocrinology, Malatya, Türkiye
ORCID: 0000-0002-6231-0034

İlker Taşçı
University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-0936-2476

Mustafa Ender Terzioğlu
Akdeniz University Faculty of Medicine, Department of Geriatrics, Antalya, Türkiye
ORCID: 0000-0002-4614-7185

Eva Topinková
Charles University in Prague Faculty of Medicine, Department of Geriatrics, Staré Město, Czechia
ORCID: 0000-0002-6786-4116

Maurits Vandewoude
University of Antwerp, Department of Geriatrics, Antwerpen, Belgium
ORCID: 0000-0002-5473-6932

Ahmet Yalçın
Ankara University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye

Dilek Gogas Yavuz
Marmara University Faculty of Medicine, Department of Endocrinology, İstanbul, Türkiye
ORCID: 0000-0001-6018-5594

Hakan Yavuzer
İstanbul University-Cerrahpaşa Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0003-2685-6555

Radmila Matijevic
The University of Novi Sad Faculty of Medicine, Novi Sad, Serbia
E-mail: radmilam.ns@gmail.com
ORCID: 0000-0002-4993-9399

Mirko Petrovic
Ghent University, Department of Internal Medicine and Paediatrics, Division of Geriatrics, Belgium
E-mail: Mirko.Petrovic@UGent.be
ORCID: 0000-0002-7506-8646

Graziano Onder
Istituto Superiore di Sanità, Department of Cardiovascular, Endocrine-Metabolic Diseases and Aging, Rome, Italy
E-mail: graziano.onder@iss.it
ORCID: 0000-0003-3400-4491

George Soulis
Outpatient Geriatric Assessment Unit of Henry Dunant Hospital Center, Athens, Greece
E-mail: geosoulis@yahoo.com
ORCID: 0000-0002-2291-5733

Nathalie van der Velde
Amsterdam UMC, Location AMC & Amsterdam Public Health Institute, Department of Internal Medicine, Sub-department of Geriatrics, Amsterdam, Netherlands
E-mail: n.vandervelde@amsterdamumc.nl
ORCID: 0000-0002-6477-6209

Jerzy Gąsowski
Jagiellonian University Medical College, University Hospital, Department of Internal Medicine and Geriatrics, Kraków, Poland
E-mail: jerzy.gasowski@gmail.com
ORCID: 0000-0002-8025-5323

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Selahattin Fehmi Akçiçek
Ege University Faculty of Medicine, Department of Geriatrics, İzmir, Türkiye
ORCID: 0000-0003-2583-4709

Sevgi Aras
Ankara University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-5356-303X

Dursun Aras
University of Health Sciences Türkiye, Ankara Training and Research Hospital, Department of Cardiology Ankara, Türkiye
ORCID: 0000-0001-6020-8098

Güneş Arık
University of Health Sciences Türkiye, Ankara Numune Training and Research Hospital, Clinic of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-4766-3982

Teslime Atlı
Güven Hospital, Clinic of Geriatrics, Ankara, Türkiye
ORCID: 0000-0001-7359-4856

Ayşegül Atmaca
Ondokuz Mayıs University Faculty of Medicine, Department of Endocrinology, Samsun, Türkiye
ORCID: 0000-0003-1547-8544

Zeynep Dilek Aydın
Süleyman Demirel University Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-4462-8970

Gülistan Bahat Öztürk
İstanbul University Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0001-5343-9795

Ergün Bozoğlu
University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-9689-9211

Olivier Bruyère
University of Liege Medical Faculty, Department of Public Health, Liège, Belgium
ORCID: 0000-0003-4269-9393

Mustafa Cankurtaran
Hacettepe University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-8213-7515

Alessandra Coin
Azienda Ospedale Università Padova, Geriatrics Clinic, Padova, Italy
ORCID: 0000-0003-1687-4493

Erkan Çoban
Akdeniz University Faculty of Medicine, Department of Geriatrics, Antalya, Türkiye
ORCID: 0000-0001-6281-0541

Aslı Çurgunlu
İstanbul Bilim University Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0001-6281-0541

Hüseyin Doruk
Başkent University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0003-3534-2628

Alper Döventaş
İstanbul University-Cerrahpaşa Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0001-5509-2625

Ülev Deniz Suna Erdinçler
İstanbul University- Cerrahpaşa Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0003-1208-4750

Doron Garfinkel
Geriatric-Palliative Consultant, Sheba Medical Center & Deputy Head, Homecare Hospice, Israel Cancer Association, Ramat Gan, Israel
ORCID: 0000-0002-3171-9881

Kürşat Gündoğan
Erciyes University Faculty of Medicine, Department of Internal Medicine, Kayseri, Türkiye
ORCID: 0000-0002-8433-3480

Mahmut Edip Gürol
Harvard University Faculty of Medicine, Department of Neurology, Boston, United States
ORCID: 0000-0002-2169-4457

Meltem Gülhan Halil
Hacettepe University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0001-7597-8140

Alfonso J Jentoft
Hospital Universitario Ramón y Cajal (IRYCIS), Department of Geriatrics, Madrid, Spain
ORCID: 0000-0001-7628-4861

Özgür Kara
Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Clinic of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-4204-0014

Berrin Karadağ
ACU University Faculty of Medicine, Kadıköy Acıbadem Hospital, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-6716-112X

Mustafa Kemal Kılıç
University of Health Sciences Türkiye, Ankara Training and Research Hospital, Clinic of Geriatrics, Ankara, Türkiye
ORCID: 0000-0001-7101-0503

Yulia Kotovskaya
Peoples' Friendship University of Russia, Department of Cardiology and Personolized Medicine, Moscow, Russia
ORCID: 0000-0002-1628-5093

Milta Little
Saint Louis University Faculty of Medicine, Department of Geriatrics, St. Louis, United States

Selim Nalbant
Maltepe University Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-4936-3705

Nirankar Singh Neki
Unit Head, Department of Medicine, Govt. Medical College, Amritsar, India
ORCID: 0000-0001-6883-1415

Nele Van Den Noortgate
University Hospital Ghent, Department of Geriatrics, Gent, Belgium
ORCID: 0000-0001-5546-5380

Hasan Öztin
Erzurum Regional Training and Research Hospital, Clinic of Geriatrics, Erzurum, Türkiye
ORCID: 0000-0002-8983-0021

Karolina Piotrowicz
Jagiellonian University Medical Faculty, Department of Internal Medicine and Gerontology, Kraków, Poland
ORCID: 0000-0002-4760-8588

Bülent Saka
İstanbul University Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-4714-4189

Fulden Saraç
Ege University Faculty of Medicine, Department of Geriatrics, İzmir, Türkiye
ORCID: 0000-0001-9281-2492

Cornel Christian Sieber
Friedrich-Alexander University Faculty of Medicine, Department of Geriatrics, Erlangen, Germany
ORCID: 0000-0002-9364-6921

Şevnaz Şahin
Ege University Faculty of Medicine, Department of Geriatrics, İzmir, Türkiye
ORCID: 0000-0001-5457-901X

İbrahim Şahin
İnönü University Faculty of Medicine, Department of Endocrinology, Malatya, Türkiye
ORCID: 0000-0002-6231-0034

İlker Taşçı
University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0002-0936-2476

Mustafa Ender Terzioğlu
Akdeniz University Faculty of Medicine, Department of Geriatrics, Antalya, Türkiye
ORCID: 0000-0002-4614-7185

Eva Topinková
Charles University in Prague Faculty of Medicine, Department of Geriatrics, Staré Město, Czechia
ORCID: 0000-0002-6786-4116

Maurits Vandewoude
University of Antwerp Faculty of Medicine, Department of Geriatrics, Antwerpen, Belgium
ORCID: 0000-0002-5473-6932

Murat Varlı
Ankara University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0003-1176-5255

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Ahmet Yalçın
Ankara University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0001-9472-2212

Pınar Tosun Taşar
Erzurum Atatürk University Faculty of Medicine, Department of Geriatrics, Erzurum, Türkiye
ORCID: 0000-0002-7296-5536

Burcu Balam Yavuz
Hacettepe University Faculty of Medicine, Department of Geriatrics, Ankara, Türkiye
ORCID: 0000-0002-4430-6146

Dilek Gogas Yavuz
Marmara University Faculty of Medicine, Department of Endocrinology, İstanbul, Türkiye
ORCID: 0000-0001-6018-5594

Hakan Yavuzer
İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0003-2685-6555

Mehmet Yürüyen
University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Geriatrics, İstanbul, Türkiye
ORCID: 0000-0001-8678-3090

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CONTENTS

ORIGINAL ARTICLES

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Modified Glasgow Prognostic Score is Associated with Prognosis in Older Adult Patients with Metastatic Melanoma

Mustafa Emre Duygulu[1], Elanur Karaman[2]

[1]Hitit University Erol Olçok Training and Research Hospital, Department of Medical Oncology, Çorum, Türkiye
[2]Karadeniz Technical University Faculty of Medicine, Department of Medical Oncology, Trabzon, Türkiye

Abstract

Objective: Biomarkers are needed to determine risk groups in the treatment plan of geriatric patients diagnosed with cancer. The Modified Glasgow Prognostic Score (mGPS) is an inflammatory scoring system based on measurements of C-reactive protein and albumin in the blood. In our study, the relationships between the mGPS and clinical parameters and the effect of the mGPS on survival were investigated in older adults with metastatic melanoma.

Materials and Methods: Fifty-eight patients aged 65 years and older with a diagnosis of metastatic melanoma were included in the study. The patients were evaluated according to their clinical and pathological features. Overall survival (OS) and progression-free survival (PFS) times and the factors affecting survival were evaluated. Survival relationships by mGPS score were analysed by the Kaplan-Meier method, and prognostic factors for survival were analysed by Cox regression analysis.

Results: The mGPS was higher in patients with brain and/or liver metastases and in those with high serum lactate dehydrogenase levels ($p = 0.015$ and $p = 0.003$, respectively). A high mGPS was associated with decreased survival time (median PFS for mGPS of 0, 1, and 2 were 9.4, 6.9, and 3.5 months, respectively, $p = 0.001$; median OS for mGPSs of 0, 1, and 2 were 19.5, 8.2, and 6.4 months, respectively, $p = 0.001$). In the multivariate analysis, mGPS 2 was found to be an independent risk factor for decreased OS (hazard ratio: 3.26, $p = 0.003$).

Conclusion: A high mGPS was associated with poor survival in metastatic melanoma patients and the mGPS was found to be an independent risk factor for decreased OS.

Keywords: Melanoma, geriatrics, prognosis, survival

Introduction

A substantial proportion of newly diagnosed cancer patients are in the geriatric age group (1). Due to comorbidities among older adult patients, rates of access to standard treatment are lower than those for younger patients. Since the representation of these patients in clinical trials is low, it becomes even more difficult to predict treatment response and prognosis (2).

Systemic inflammation and nutritional status are known to be important for cancer development, angiogenesis, and metastasis (3). In clinical practice, patients' clinical course can be predicted using different inflammation scores. This enables the patient's treatment and follow-up to be more specific. The Modified Glasgow Prognostic Score (mGPS) is an index calculated using serum albumin and C-reactive protein (CRP) levels. The mGPS is an index that combines inflammatory and nutritional status (4). A negative association between a high mGPS and prognosis has been reported for various cancers, such as lung, stomach, and pancreatic cancers (5). The number of studies assessing its clinical significance in patients diagnosed with melanoma is limited.

The association between inflammatory status and prognosis is well established in melanoma. A proinflammatory tumor microenvironment, along with cytokines released by immune cells, contributes to the rapid proliferation, angiogenesis, and metastatic progression of melanoma (6). Elevated levels of

Address for Correspondence: Mustafa Emre Duygulu, Hitit University Erol Olçok Training and Research Hospital, Department of Medical Oncology, Çorum, Türkiye
E-mail: mustafaemreduygulu@gmail.com **ORCID:** orcid.org/0000-0001-5113-6782
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CRP have been correlated with reduced survival in patients (7). Albumin, a negative acute-phase reactant, is often decreased in cancer patients due to reduced synthesis and increased catabolism. Studies have demonstrated significantly lower serum albumin levels in patients with melanoma, particularly among older individuals and those with advanced-stage disease (8). For these reasons, mGPS is a candidate biomarker when CRP and albumin are analyzed together in patients with melanoma.

The incidence of melanoma has been increasing (9,10). Advanced age, high serum lactate dehydrogenase (LDH), and the presence of distant organ metastases adversely affect prognosis (11,12). In our study, we investigated the effect of the mGPS on survival in older adult patients diagnosed with metastatic melanoma.

Materials and Methods

Patients diagnosed with metastatic melanoma at Karadeniz Technical University Farabi Hospital between April 2010 and May 2022 were evaluated retrospectively. The inclusion criteria were as follows: aged ≥65 years; a diagnosis of metastatic melanoma; availability of baseline serum albumin, LDH, and CRP levels at diagnosis; and baseline thoracic and abdominal computed tomography or positron emission tomography imaging. The exclusion criteria were: age under 65 years, presence of non-metastatic disease, diagnosis of a synchronous or metachronous malignancy, or incomplete laboratory or imaging data.

The data were evaluated retrospectively from patient files and electronic data systems. The patients' ages, sex, metastasis status (*de novo*, recurrent), comorbidities, presence of a BRAF mutation, metastasis site, performance status, primary tumor site, and oncological treatment were evaluated. At diagnosis, serum CRP, albumin, and LDH levels were recorded. Units and reference ranges for the biochemical tests were as follows: g/dL (3.5–5.2) for albumin, mg/L (<5) for CRP, and U/L (<248) for LDH.

An mGPS score of 0 was defined as CRP level ≤10 mg/L with any albumin level; mGPS score 1 as CRP level >10 mg/L and albumin level ≥3.5 g/dL, mGPS score 2 as CRP level >10 and albumin level <3.5 g/dL.

Approval from the Karadeniz Technical University Faculty of Medicine Ethics Committee (protocol number: 2023/135, dated: 20.07.2023) was obtained prior to the study. The principles of the Declaration of Helsinki were followed at every stage of the study. Because the patient's identity was not disclosed or compromised and the study was retrospective, patient consent was not required.

Statistics

The categorical variables were examined with the chi-square test. Comparisons of numerical variables in independent groups were made with ANOVA or the Kruskal-Wallis test. Survival times were analyzed using the Kaplan-Meier method. Factors affecting survival were analysed using Cox regression. The variables age, metastasis status, BRAF V600E mutation, metastasis site, comorbid diseases, and mGPS were used in univariate Cox regression analysis. Variables with $p < 0.05$ as a result of univariate analysis were included in multivariate Cox regression analysis. The data were analysed using SPSS version 25.0. Statistical significance was set at $p < 0.05$.

Results

Fifty-eight patients were evaluated in the study. Thirty-two (55.2%) were female, and 26 (44.8%) were male. The mean age was 73.6 ± 6.6 years, *de novo* metastatic patients was 25 (43.1%), and the number of recurrent cases was 33 (56.9%). When the primary tumor location was examined, thirty-four (58.9%) patients were diagnosed with extremity skin melanoma, 15 (25.9%) with trunk and head-and-neck skin melanoma, 5 (8.6%) with mucosal melanoma, and 4 (6.9%) with ocular melanoma. Twenty patients (34.4%) had mGPS 0, 21 (36.2%) had mGPS 1, and 17 (29.3%) had mGPS 2. Elevated mGPS scores were significantly associated with the presence of brain and/or liver metastases, as well as elevated serum LDH levels ($p = 0.015$, and $p = 0.003$, respectively) (Table 1). Chronic disease was present in 40 cases (69%).

Table 1. Clinical and demographic characteristics of patients.

Variable	Total	mGPS score 0 (n = 20)	mGPS score 1 (n = 21)	mGPS score 2 (n = 17)	p
Age‡	73.6 ± 6.6	75.1 ± 6.6	73.2 ± 5.9	72.5 ± 7.4	0.483*
Age, n (%)					
Under 75 years	33 (56.9)ww	8 (40.0)	15 (71.4)	10 (58.8)	0.125**
75 years and older	25 (43.1)	12 (60.0)	6 (28.6)	7 (41.2)	
Gender, n (%)					
Female	32 (55.2)	12 (60.0)	13 (61.9)	7 (41.2)	0.383**
Male	26 (44.8)	8 (40.0)	8 (38.1)	10 (58.8)	
Metastasis, n (%)					
De novo	25 (43.1)	9 (45)	8(38)	8 (47)	0.838**
Recurrent	33 (56.9)	11 (55)	13 (62)	9 (53)	

Table 1. Continued.

Variable	Total	mGPS score 0 (n = 20)	mGPS score 1 (n = 21)	mGPS score 2 (n = 17)	p
Primary tumor localisation, n (%)					
Extremity skin	34 (58.6)	9 (45.0)	13 (61.9)	12 (70.6)	-
Body or head and neck skin	15 (25.9)	8 (40.0)	3 (14.3)	4 (23.5)	
Mucosal	5 (8.6)	2 (10.0)	2 (9.5)	1 (5.9)	
Ocular	4 (6.9)	1 (5.0)	3 (14.3)	-	
Comorbid disease[1]					
Present	40 (69.0)	16 (80.0)	13 (61.9)	11 (64.7)	0.412**
Absent	18 (31.0)	4 (20.0)	8 (38.1)	6 (35.3)	
Diabetes mellitus	12 (20.7)	5 (25.0)	4 (19.0)	3 (17.6)	0.837**
Hypertension	34 (58.6)	13 (65.0)	11 (52.4)	10 (58.8)	0.714**
Hyperlipidemia	16 (27.6)	7 (35.0)	4 (19.0)	5 (29.4)	0.510**
Cardiac disease	11 (19.0)	7 (35.0)	1 (4.8)	3 (17.6)	0.047**
Chronic lung disease	8 (13.8)	5 (25.0)	2 (9.5)	1 (5.9)	0.189**
LDH, n (%)					
High	24 (21.4)	3 (15.0)[a]	9 (42.9)[a, b]	12 (70.6)[b]	0.003**
Normal	34 (58.6)	17 (85.0)[a]	12 (57.1)[a, b]	5 (29.4)[b]	
CRP value[¥]	15.2 (4.7-56.0)	3.4 (1.0-5.6)[a]	18.6 (12.9-58.0)[b]	45.5 (21.1-91.1)[b]	<0.001***
Albumin value[¥]	3.9 (3.4-4.3)	4.1 (3.9-4.3)[a]	4.1 (3.9-4.4)[a]	3.1 (2.8-3.4)[b]	<0.001***
BRAF V600 mutation, n (%)					
Present	5 (14.7)	2 (16.7)	2 (16.7)	1 (10.0)	-
Absent	29 (85.3)	10 (83.3)	10 (83.3)	9 (90.0)	
Brain and/or liver metastasis, n (%)					
Present	28 (48.3)	6 (30.0)[a]	9 (42.9)[a, b]	13 (76.5)[b]	0.015**
Absent	30 (51.7)	14 (70.0)[a]	12 (57.1[a, b]	4 (23.5)[b]	
Lung metastasis, n (%)					
Present	32 (55.2)	11 (55.0)	12 (57.1)	9 (52.9)	0.967**
Absent	26 (44.8)	9 (45.0)	9 (42.9)	8 (47.1)	
Bone metastasis, n (%)					
Present	12 (20.7)	5 (25.0)	2 (9.5)	5 (29.4)	-
Absent	46 (79.3)	15 (75.0)	19 (90.5)	12 (70.6)	
First line therapy, n (%)					
BSC	6 (10.3)	4 (20.0)	2 (9.5)	-	-
Chemotherapy	43 (74.1)	12 (60.0)	17 (81.0)	14 (82.4)	
Immunotherapy	6 (10.3)	3 (15.0)	2 (9.5)	1 (5.9)	
IFN	3 (5.2)	1 (5.0)	-	2 (11.8)	

*ANOVA test. **Chi-square test. ***Kruskal-Wallis test. [¥]Median (Q1-Q3). [ŧ]Mean ± standard deviation.
Statistical significance is indicated by different superscript letters (e.g., a, b). 1 Comorbidities include diabetes, hypertension, hyperlipidemia, chronic heart disease, and chronic lung disease.
LDH: Lactate dehydrogenase, CRP: C-reactive protein, BSC: Best supportive care, IFN: Interferon, OS: Overall survival, PFS: Progression free survival, mGPS: Modified Glasgow Prognostic Score, ECOG: Eastern Cooperative Oncology Group.

The distribution of chronic comorbidities was as follows: diabetes mellitus in 12 patients (20.7%), hypertension in 34 patients (58.6%), hyperlipidemia in 16 patients (27.6%), cardiac disease in 11 patients (19.0%), and chronic lung disease in 8 patients (13.8%).

The median progression-free survival times (mPFS) for patients with mGPS 0, 1, and 2 were 9.4 months [95% confidence interval (CI): 6.8–12.2], 6.9 months (95% CI: 4.6–9.2), and 3.5 months (95% CI: 2.0–5.1), respectively. The median overall survival times (mOS) for mGPS 0, 1, and 2 were 19.5 months (95% CI: 16.0–23.2), 8.2 months (95% CI: 5.8-10.6), and 6.4 months (95% CI: 2.9–9.9), respectively. PFS and OS were significantly shorter in patients with high mGPS values ($p = 0.001$ for both comparisons) (Figure 1).

In the univariate analysis, mGPS of 2 was identified as a risk factor for decreased PFS [hazard ratio: 3.65 (1.779–7.503), $p < 0.001$]. In the multivariate analysis, mGPS 2 remained an independent risk factor for decreased OS times [hazard ratio=3.26 (1.487–7.160), $p = 0.003$] (Table 2).

Discussion

In the current study, the mGPS was associated with a poor prognosis in older adult patients diagnosed with metastatic melanoma. High mGPS was an independent risk factor for decreased OS. Moreover, mGPS levels were higher in patients with brain and/or liver metastases and in those with high serum LDH levels.

Chronic inflammation leads to various types of cancer by inducing cell proliferation and genetic mutations (13). In addition, inflammatory cytokines released by cancer cells and leukocytes promote cancer progression and influence cancer prognosis (14). Age is an important covariate when evaluating associations between inflammatory markers and cancer outcomes. With aging, chronic proinflammatory conditions develop secondary to the increased release of proinflammatory cytokines from immune cells. As a result of chronic inflammation, serum CRP levels increase with age. The increase in inflammation with aging is termed “inflammaging” (15). Therefore, when investigating the relationships of the mGPS score with clinicopathological

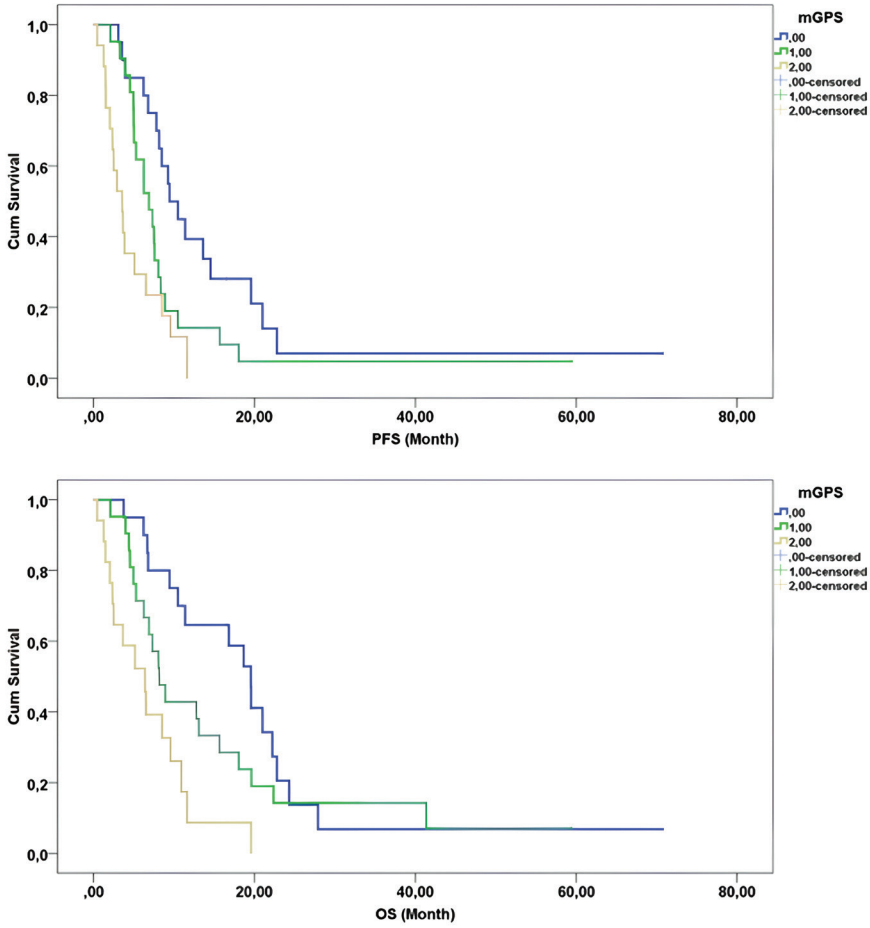

Figure 1. Kaplan-Meier survival curves according to mGPS of the cases.

mGPS: Modified Glasgow Prognostic Score, OS: Overall survival, PFS: Progression-free survival times.

Table 2. Univariate and multivariate cox regression analysis of factors affecting survival.

Variables	Univariate analysis for OS HR (95% CI)	p	Multivariate analysis for OS HR (95% CI)	p	Univariate analysis for PFS HR (95% CI)	p	Multivariate analysis for PFS HR (95% CI)	p
Age (years) ≥75/ <75 (ref)	1.365 (0.779-2.391)	0.277	-	-	1.235 (0.715-2.131)	0.449	-	-
Metastasis status recurrent/*de novo* (ref)	0.826 (0.468-1.457)	0.510	-	-	0.969 (0.557-1.684)	0.910	-	-
BRAF V600E mutation presence/absence (ref)	0.447 (0.104-1.911)	0.277	-	-	0.593 (0.177-1.986)	0.396	-	-
Metastasis site (brain and/ or liver) presence/absence (ref)	1.770 (1.003-3.121)	**0.049**	1.386 (0.753-2.550)	0.295	1.541 (0.892-2.660)	0.121	-	-
Comorbid disease presence/ absence (ref)	0.654 (0.362-1.181)	0.159	-		0.877 (0.493-1.559)	0.654	-	-
Modified Glasgow Prognostic Score								
Modified Glasgow Prognostic Score 0 (ref)	1	-	-	-	1	-	-	-
Modified Glasgow Prognostic Score 1	1.499 (0.767-2.930)	0.237	1.477 (0.754-2.892)	0.256	1.856 (0.962-3.581)	0.065	-	-
Modified Glasgow Prognostic Score 2	3.692 (1.748-7.799)	**0.001**	3.264 (1.487-7.160)	**0.003**	3.653 (1.779-7.503)	**<0.001**	-	-

HR: Hazard ratio, CI: Confidence interval, OS: Overall survival, PFS: Progression-free survival.

features and survival, older adult patients should be analyzed separately from the general population due to age-related clinical differences.

During systemic inflammation, elevated CRP levels are typically accompanied by decreased serum albumin levels; albumin is a negative acute-phase protein (16). The mGPS is a scoring system that incorporates serum CRP and albumin levels. With this scoring system, it is possible to evaluate inflammation and nutritional status together (17). In previous studies, a high mGPS was shown to decrease OS times and affect prognosis in various cancer types, such as breast, lung, pancreas, and colon cancer (18-21). The mGPS also correlates with frailty in geriatric patients (22).

LDH elevation is a predictive marker for melanoma and is used in disease staging (23). Brain metastases develop in approximately 50% of patients diagnosed with metastatic melanoma and are associated with a poor prognosis (24). Advanced age, male sex, elevated LDH levels, distant metastases, and BRAF and NRAS mutations are associated with poorer prognosis in melanoma. Brain metastases, visceral metastases, and treatment modalities, including BRAF/MEK inhibitors and immune checkpoint inhibitors, significantly affect survival outcomes. With advances in treatment, one-year survival rates have improved from 9–19% to 50% (25,26). In our study, the mGPS was high in patients with brain and/or liver metastases and in patients with high LDH. These data suggest that the mGPS can be used as an effective tool for identifying high-risk cases in practice. Thus, it may be possible to implement personalized treatment and follow-up processes.

There are very few studies examining the relationship between mGPS and melanoma. One study conducted in 2021 revealed that PFS and OS times were shorter in patients with metastatic cutaneous melanoma than in those and that the mGPS was an independent risk factor for decreased survival. However, there was no subgroup analysis for the older adult patients in the present study (27). In our study, the relationship between the mGPS and survival in older adult patients with metastatic melanoma was demonstrated for the first time. Thus, this study contributes to filling the knowledge gap in this patient population.

Study Limitations

Our study was retrospective and conducted at a single center evaluated real-life data. The number of patients receiving checkpoint inhibitor therapy and BRAF/MEK inhibitor therapy was small. Therefore, treatment-specific subgroups could not be evaluated. Furthermore, the inability to access and analyze the nutritional status data of the cases is also considered a limitation.

Conclusion

In the current study, mGPS was associated with decreased PFS and OS in geriatric patients with metastatic melanoma; a high mGPS was an independent risk factor for decreased OS. The mGPS score was found to be higher in high-risk patients with elevated serum LDH levels and brain and/or liver metastases. These results indicate that the mGPS can be used in clinical practice as a scoring system to identify high-risk older adult patients diagnosed with metastatic melanoma. In addition, the current study may serve as a resource for future research to identify high-risk cancer patients in the geriatric age group.

Ethics

Ethics Committee Approval: Approval from the Karadeniz Technical University Faculty of Medicine Ethics Committee (protocol number: 2023/135, dated: 20.07.2023) was obtained prior to the study. The principles of the Declaration of Helsinki were followed at every stage of the study.

Informed Consent: The study had a retrospective design; patient consent was not required.

Authorship Contributions

Concept: M.E.D., E.K., Design: M.E.D., E.K., Data Collection or Processing: M.E.D., Analysis or Interpretation: M.E.D., Literature Search: E.K., Writing: M.E.D., E.K.

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

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ORIGINAL RESEARCH

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A Comparison of the Mini-Mental State Examination (MMSE) with the Five-Minute Cognitive Test (FCT) for Community Dwelling Older Adults: A Cross-Sectional Study

Maryam Chehrehgosha[1], Pedram Karimian[2], Fatemeh Mehravar[3], Mohammad Taghi Badeleh Shamushaki[4]

[1]Golestan University of Medical Sciences, Paramedical School, Department of Surgical Technology, Gorgan, Iran
[2]Student Research Committee, Golestan University of Medical Sciences, Gorgan, Iran
[3]Golestan University of Medical Sciences, Ischemic Disorders Research Center, Department of Biostatistics and Epidemiology, Gorgan, Iran
[4]Golestan University of Medical Sciences, Department of Health Psychology, Gorgan, Iran

Abstract

Objective: To assess the prevalence of cognitive disorder in a community setting among older adults with two cognitive scales.

Materials and Methods: A cross-sectional study involving 450 elderly adults from five urban and regional health facilities in Gorgan was conducted. The instruments were the demographic checklist, mini-mental state examination (MMSE), five-minute cognitive test (FCT). Statistical analysis was performed using SPSS software version 18, with a significance level set at $p < 0.05$.

Results: The participants' mean age was 68.44 ± 7.62. Of them, 42 percent are men and 58 percent are women. According to the MMSE, 46.70% of older adults have normal cognition, whereas 50% of them have a healthy cognitive status based on the FCT evaluation. According to the logistic regression analysis for both scales, age and gender were significant influencing factors. Furthermore, the receiver operating characteristic analysis displays the FCT's noteworthy area under the curve (0.91, $p < 0.000$). The diagnostic accuracy, sensitivity, and specificity of the FCT test were found to be 90.00%, 87.50%, and 92.86%, respectively.

Conclusion: An alternative instrument to the MMSE that could be considered is the FCT, which is a valid, rapid, and reliable cognitive screening tool.

Keywords: Cognitive impairment, MMSE, FCT, cross-sectional study, older adults

Introduction

Cognitive impairment (CI) affects about 50 million people globally, and as the population ages, it is predicted that that this number will grow to 75 million by 2030 (1). Dementia has a substantial negative influence on society. It leads to a loss of economic productivity as well as an increased workload for families and caregivers (2).

A substantial number of comorbidities with accompanying functional impairment are common among older adults, and memory problems exacerbate these conditions for some of them (3). Early detection of CI is a crucial step towards enhancing early identification and treatment, lessening the likelihood of dementia and Alzheimer's occurrence, monitoring the prevalence, and lowering the cost of the healthcare system (4,5).

The primary care setting is the first-line centre in which patients with CI can receive medical consultation (6). The American Academy of Neurology a significant provider of healthcare, acknowledged that "early diagnosis can help identify some forms of mild CI (MCI) that may be reversible, including those caused by sleep problems, depression, or medications This early diagnosis leads to treatments that can improve a person's quality of life, such as correcting hearing loss and avoiding social isolation" (7).

Address for Correspondence: Mohammad Taghi Badeleh Shamushaki, Golestan University of Medical Sciences, Department of Health Psychology, Gorgan, Iran
E-mail: badeleh@gmail.com **ORCID:** orcid.org/0000-0001-6440-8054
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There are numerous screening exams available to check for CI. Doctors give patients a battery of tasks designed to evaluate one or more domains of cognition as part of screening tests. Further neuropsychological testing should be conducted in response to a positive screening test result to clarify the dementia subtype (8).

The mini-mental state examination (MMSE) is the most prevalent screening tool in different studies. Additional screening tools consist of the clock drawing test, abbreviated mental test, Montreal Cognitive Assessment (MoCA), telephone instrument for cognitive status, informant questionnaire on cognitive decline in the elderly, and the five-minute cognitive test (FCT). Each of these instruments has a unique indication and set of benefits (9-11).

Globally, the MMSE is the most widely used as a validated cognitive instrument in clinical settings and research (12). Research has revealed that, despite being a widely accepted and validated tool for dementia screening, the MMSE is biased toward patients who are educated and illiterate, and it has a low sensitivity for identifying MCI (13,14).

Early identification of CI and prompt preventive intervention are ensured by a valid cognitive screening test that is quick and easy to administer (15,16). For non-native English speakers or those without formal education, current screening techniques are frequently irrelevant (17). The FCT is another innovative tool for cognitive screening. It has the advantage of being quick and accurate in identifying CI at an early stage (18). Given the growing number of older adults and the significance of early detection of cognitive decline, we need to use cognitive evaluations other than in-person neuropsychological testing (19).

Even though it is widely acknowledged that identifying CI in older adults is crucial, primary care frequently overlooks CI in older adults (20). Therefore, early detection using the appropriate quick test is essential. This study aims to assess the differences between two cognitive assessment scales (FCT, MMSE) among older adults living in the community.

Materials and Methods

A community-based, cross-sectional study was carried out in collaboration with Golestan University of Medical Sciences. The Golestan Research Ethics Committee (approval ID: IR.GOUMS.REC.140, date: 28.11.2023) gave its approval for the study. Every participant or informal caregiver provided written informed consent.

Participants

A representative cohort comprising 450 elderly individuals from the community was assembled from five urban and regional health facilities located in Gorgan, Iran. Based on the relevant study and Morgan's statistical table, the sample size was ascertained to be 379 individuals. In order to enhance the precision of the findings and to facilitate the computation of the sample size, a total of 450 individuals were ultimately surveyed (21). The inclusion criteria were age of 60 years or older, no severe visual or auditory impairments, no documented history of depression or traumatic experiences, the ability to read and write, and providing informed consent to participate in the study. The criteria for exclusion encompassed the incomplete submission of the questionnaire, defined as failing to answer at least two questions, as well as any indication of reluctance to continue participation.

Procedure

This descriptive-analytical cross-sectional study used random sampling to select elderly individuals aged 60 years and above from five health centers in Gorgan city 2023. Providing informed consent, the trained research assistants performed data collection through face-to-face interviews. Data were systematically gathered at the local community health centres.

Participants were recruited for the study according to the inclusion criteria. A demographic checklist was used, including age, gender, marital status, residence, and level of education. The MMSE and the FCT were also used. We performed data collection through face-to-face interviews. The researcher read each question loudly, and the elders filled out the questionnaires.

Initially, the participants underwent a rigorous screening process based on predefined entry and exit criteria, followed by the systematic documentation of their demographic characteristics, which encompassed age, gender, marital status, residential location, and educational attainment, as captured in the researcher's questionnaire. Subsequently, two distinct assessment instruments, namely the MMSE, and the FCT, were employed to ascertain the cognitive functioning of the participants.

Measurements

Mini-Mental State Examination

Generally, the MMSE is frequently employed in a comparative context to evaluate the metric properties and diagnostic efficacy of novel assessment instruments (22). The MMSE encompasses a variety of distinct cognitive domains, which assess orientation to time, orientation to place, free recall, attention and calculation, delayed recall, and linguistic abilities, respectively. The MMSE has a score range of 0 to 30, where a higher score indicates better cognitive functioning (23). The valid and psychometric version of the MMSE for the Iranian older adult population was used for this study (24). This assessment's total scores fall into one of four categories: severe CI is represented by scores 0-10, moderate CI by scores 11-20, mild CI by scores 21-26, and normal cognitive status by scores 27-30 (24,25).

Five-Minute Cognitive Test

The FCT was conceived through a comprehensive multiphase research initiative, culminating in a final iteration designed to assess five distinct cognitive domains, namely episodic memory, linguistic fluency, temporal orientation, visuospatial abilities, and executive functioning (18). A total of eight culturally unbiased images were extracted from the International Picture Naming Project to serve as stimuli for the assessment of episodic memory. The FCT creates scores that range from 0 to 20, where lower scores indicate lower cognitive functioning. A person who scores higher than 16 points is said to have a normal cognitive range, while those who score between 16 and 14 points indicate mild CI, and those who score lower than 14 points indicates CI (26).

Statistics

Statistical analysis was performed using SPSS software version 18, with variables reported as frequencies and percentages. The Shapiro-Wilk test was utilized to assess the distribution of variables. Chi-square and ANOVA tests were conducted to analyse demographic variables and cognitive status. Regression models were used to examine the role of each of these variables. Receiver operating characteristic (ROC) analysis was also used to determine scale thresholds.

Results

Study Cohort Characteristics

The participants' mean age was 68.44 ± 7.62. Fifty-eight percent of them were women and 42% men. The majority of participants in the study had completed primary education (32%). Out of the total, 42% were homemakers and 26% were retirees collecting pensions. Thirty percent of the individuals reported that one of their children resides close to where they live.

Based on the cognitive status evaluation of the MMSE form, 46.70% of the elderly have normal cognition, while based on the FCT evaluation, 50% were healthy in terms of cognitive status (Table 1).

When assessing demographic factors, age and sex have been crucial in assessing cognitive abilities. Female gender and older age are associated with more severe and inappropriate cognitive status (Table 2).

The results of the Pearson correlation test indicated a statistically significant positive relationship between the average MMSE and FCT scores ($r=0.748$, $p < 0.001$). According to the multivariate logistic regression model, only age and sex were found to be statistically significant in the final model. Even though education has been linked to the MMSE this association was not significant for the multivariate model's prediction ($p > 0.05$) (Table 3).

The ROC curve was used to determine sensitivity and specificity. The area under the curve (AUC) for FCT was 0.91 and $p < 0.000$ (Figure 1).

Table 4 reports the diagnostic capabilities of the MMSE in comparison to the FCT for assessing cognitive disorders. The sensitivity and specificity of the FCT test were 87.50% and 92.86%, respectively. The diagnostic accuracy of the FCT test was 90.00% (Table 4).

Discussion

The MMSE and the FCT were compared in this study to see if the new scales could screen for cognitive disorders as accurately as the MMSE. The findings showed that the MMSE and FCT scales discriminate between people with CI and healthy individuals almost identically. Age and sex were identified as influencing factors for cognitive disorders based on the logistic regression for both scales. Furthermore, the ROC analysis shows significant remarkable AUC for FCT.

It is crucial to acknowledge that, in a community setting, the MMSE is the most thoroughly studied scale for detecting dementia in Iran's senior population (27). Individuals with

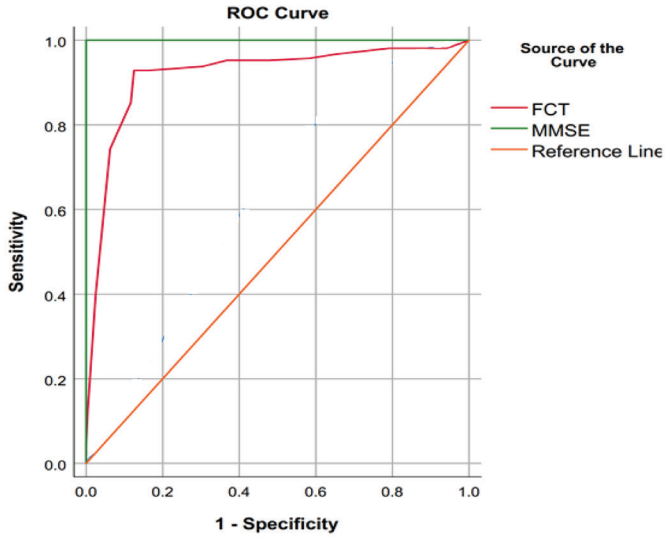

Figure 1. The receiver operating characteristic curves of MMSE, and FCT

FCT: Five-minute cognitive test, MMSE: Mini-mental state examination, ROC: Receiver operating characteristic

Table 1. Mean and frequency of cognitive status based on MMSE, and FCT scale

Cognitive scales		Frequency (%)	Mean ± SD
MMSE	Normal	210 (46.70)	29.33 ± 0.95
	MCI	88 (19.60)	24.90 ± 1.24
	Moderate	143 (31.80)	17.88 ± 2.01
	Severe	9 (2.00)	8.88 ± 1.26
FCT	Normal	225 (50.00)	16.19 ± 3.51
	Moderate	45 (10.00)	9.00 ± 0.00
	Severe	180 (40.0)	6.91 ± 1.50

FCT: Five-minute cognitive test, MCI: Mild cognitive impairment, MMSE: Mini-mental state examination, SD: Standard deviation

Table 2. Cognitive score of the elderly based on demographic variables

Variables		MMSE				FCT		
		Normal	MCI	Moderate	Severe	Normal	Moderate	Severe
Age		66.54 ± 6.32	69.22 ± 8.84	70.02 ± 7.69	80.22 ± 2.94	67.65 ± 7.30	67.42 ± 8.06	69.68 ± 7.76
p-value ANOVA		0.000				0.018		
Sex	Male	111 (52.90)	26 (29.50)	45 (31.50)	3 (33.30)	115 (51.10)	9 (20.00)	61 (33.90)
	Female	99 (47.10)	62 (70.50)	98 (68.50)	6 (66.70)	110 (48.90)	36 (80.00)	119 (66.10)
p-value Pearson chi-square		0.000				0.000		
Marital status	Married	180 (85.70)	65 (73.90)	115 (80.40)	3 (33.30)	187 (83.10)	34 (75.60)	142 (78.90)
	Single/widow/divorce	30 (34.50)	23 (26.40)	28 (32.20)	6 (6.9)	38 (43.70)	11 (12.60)	38 (43.70)
p-value Pearson chi-square		0.000				0.371		
Living arrangement	City	191 (91.00)	71 (80.70)	118 (82.5)	7 (77.80)	198 (88.00)	40 (88.9)	149 (82.8)
	Rural	19 (9.00)	17 (19.30)	25 (17.5)	2 (22.20)	27 (12.00)	5 (11.10)	31 (17.20)
p-value Pearson chi-square		0.040				0.271		
Education	Elementary	70 (33.30)	32 (36.40)	43 (30.10)	2 (22.20)	78 (34.70)	11 (24.40)	58 (32.20)
	Middle	52 (24.80)	26 (29.50)	36 (25.20)	6 (66.70)	56 (24.90)	13 (28.90)	51 (28.30)
	High school	13 (6.20)	9 (10.20)	28 (19.60)	0 (0.00)	16 (7.10)	9 (20.00)	25 (13.90)
	Diploma	57 (27.10)	17 (19.30)	29 (20.30)	1 (11.10)	58 (25.80)	11 (24.40)	35 (19.40)
	Bachlor	18 (8.60)	4 (4.50)	7 (4.90)	0 (0.00)	17 (7.50)	1 (2.20)	11 (6.10)
p-value Pearson chi-square		0.018				0.189		
Child number		3.54 ± 1.93	3.61 ± 2.10	3.58 ± 1.69	3.55 ± 2.12	3.60 ± 1.91	3.80 ± 2.24	3.46 ± 1.78
p-value ANOVA		0.994				0.526		
Drug number		2.98 ± 3.08	2.59 ± 2.80	2.90 ± 2.23	4.66 ± 6.00	2.96 ± 3.19	2.71 ± 2.18	2.90 ± 2.59
p-value ANOVA		0.205				0.862		

FCT: Five-minute cognitive test, MCI: Mild cognitive impairment, MMSE: Mini-mental state examination, ANOVA: Analysis of variance

Table 3. Multivariate logistic regression

Model	Variable	Parameter estimate	Standard error	p-value	Odds ratio (95% CI)
MMSE	Age	0.08	0.01	0.000	1.08 (1.05-1.12)
	Sex	1.11	0.21	0.000	3.04 (2.00-4.61)
	Education	0.13	0.08	0.115	1.13 (0.96-1.33)
FCT	Age	0.03	0.01	0.007	1.03 (1.01-1.06)
	Sex	0.92	0.20	0.000	2.52 (1.69-3.75)
	Education	0.10	0.08	0.203	1.10 (0.94-1.29)

FCT: Five-minute cognitive test, MMSE: Mini-mental state examination, CI: Confidence interval

higher levels of education might gain an unequal advantage from the educational bias in these tests. Regarding the other cognitive tests assessed in this study—MoCA, Addenbrooke's Cognitive Examination III (ACE-III), Assessment of Cognition and Executive function (PEACE), Rey Auditory Verbal Learning Test (AVLT) The lengthy administration times make them unsuitable for regular use in primary care and community care settings (28). In individuals with mild CI, impaired episodic memory has been identified as the initial symptom and has been found to predict the development of Alzheimer's disease (AD) (18). The FCT was

Table 4. Diagnostic properties of the MMSE test compared to the FCT in diagnosing cognitive disorders.

	Criteria	Value	95% CI
FCT	Sensitivity	87.50%	82.64-91.41
	Specificity	92.86%	88.49-95.95
	LR+	12.25	7.50-20.00
	LR-	0.13	0.10-0.19
	PPV	93.32%	89.55-95.80
	NPV	86.68%	82.29-90.11
	Accuracy	90.00%	86.85-92.61

FCT: Five-minute cognitive test, MMSE: Mini-mental state examination, CI: Confidence interval, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value

created to identify deficiencies in a wide range of cognitive domains, such as executive function, language fluency, time orientation, episodic memory, and visuospatial function. Eight culturally impartial images were selected from the International Picture Naming Project to be used as items for episodic memory. As a result, FCT was created with a stronger focus on evaluating episodic memory (8 points) (26).

Cognitive Status

Based on the MMSE and FCT scales, the current study's findings showed that mild to moderate cognitive disorders affected about half of the population. The mean MMSE score for MCI cases was 24.90 ± 1.24, while the mean score for normal older adults was 29.33 ± 0.95. In moderate cases, the mean FCT score was 9.00 ± 0.00, while in normal older adults, it was 16.19 ± 3.51. The mean score of MMSE, for older adults in China was 27.9 ± 1.28 for normal people and 26.3 ± 1.9 for MCI people. The mean score for mild AD, MCI patients, and normal individuals, according to FCT evolution, was 8 ± 3.2, 14.9 ± 2.8, and 17.8 ± 1.2, respectively (26). Additionally, in a different study of the Chinese population, the mean MMSE scores for mild AD, MCI, and normal older adults were 20.11 ± 2.90, 26.25 ± 1.87, and 27.89 ± 1.38, respectively. According to FCT evaluation, the mean scores for MCI patients and healthy individuals were 26.45 ± 4.72 and 30.40 ± 2.91, respectively (18).

Previous research has shown that image-based memory assessments are successful in predicting the transition from MCI to AD. These assessments also accurately differentiate between healthy controls and AD patients. (29,30). Instead of using word recall, the FCT used picture recall to capture episodic memory deficit. In addition to removing any concerns regarding linguistic and educational bias, this design should facilitate the adoption of the FCT by other older adults who lack literacy.

Cognitive Score Based on Demographic Variables

Additionally, based on the results of the logistic regression, age and sex were considered risk factors for cognitive status, aligning with the findings of Pan et al. (18). The mental status was higher in women and worse in older people. However, Zhang et al. (26) found no significant difference in FCT scores between males and females, but they did find a meaningful correlation between FCT scores age and educational year.

According to Jin et al. (31), most multi-cohort studies indicated that women in the oldest age group had a faster rate of cognitive decline than men. These findings were validated by the outcomes of additional multi-cohort research (32). Compared to human males, females exhibit higher lifetime risk, neuropathology, and CI (33). Jeong et al. (34) reported that the cognitive function scores of men were higher than those of women. Men's age, employment status, and depression were linked to dementia, regardless of their cognition. However, for women, the impact of these factors was more pronounced when cognitive function was low (34).

Even though older age and female gender have been identified as significant factors in cognitive status in numerous studies, researchers recommend considering regression models and other variables. Age and sex were the only variables in the final model that were statistically significant in the regression analysis. For the multivariate model's prediction, education was not statistically significant. Although many studies have shown that education contributes to the cognitive status of elders, especially when using the MMSE (35), there is still debate and difficulty in interpreting the role of education. As Laks et al. (36) state, education does not significantly influence delayed recall, memory registration, three-step commands, or naming abilities. Despite the level of education, these factors might still be essential, as memory is crucial for identifying dementia. Furthermore, we note that social and cultural norms, along with environmental influences, affect the outcomes of screening tests, according to the results of several studies. Other aspects besides education must be taken into account when assessing tests (37,38). To rule out the possibility of mild CI, Franco-Marina et al. (39) believe that additional testing may be necessary when using an education-adjusted MMSE test to screen for CI. Additionally, some researchers propose modifying MMSE scores according to educational attainment to lessen this bias; However, there is ongoing discussion regarding the suitability and efficacy of these modifications (39-41).

Receiver Operating Characteristic Curve Analysis

The findings demonstrated that the FCT was suitable for diagnosing CI with an AUC of 0.91, a sensitivity of 87.50, a specificity of 92.86, and a diagnostic accuracy of 90.00 percent for identifying people with mild, moderate, and severe cognitive disorders as well as those with healthy cognitive status. According to Pan et al. (18), the FCT could distinguish between normal cognition and AD with an AUC of 1 (0.972-1), sensitivity of 100% (87.2% to 100%), and specificity of 98.13% (93.4% to 99.8%) (18).

The Zhang et al. (26) study found that the AUC of FCT for measuring CI (MCI and mild AD) was 0.885 (95% CI: 0.838 to 0.922). The FCT test had a sensitivity of 80% and a specificity of 84% for diagnosing CI.

Although Hafızoğlu et al. (42) did not present ROC analysis, their findings showed a considerable correlation between FCT scores and MMSE ($r=0.730$, $p < 0.001$) (42).

According to the findings of a few studies, the FCT is a scale that is acceptable in community settings when compared to the MMSE. Since administering the MMSE necessitates staff training and precise experience in calculation and scoring, and because an inexperienced evaluator may misinterpret a person's cognitive state he FCT can be used as a substitute scale in community settings that is easier to administer and interpret.

Study Limitations

Certain Limitations to This Study Should be Mentioned

This research included only five urban and regional health facilities. Future studies should consider sampling from additional locations or the entire city to improve the generalizability of the findings.

One of the study's limitations has been the high proportion of women, which may be a confounding factor in this field given the influence of demographic factors on MMSE and FCT as well as the study's significant age and gender distribution (more women than men). As a result, we recommend that future research employ the stratification method to better control the confounding variable.

The distribution of participants who were categorized as having moderate dementia by the MMSE form moving toward the severe dementia category when evaluated using the FCT, is another possible confounding factor. This factor is among the restrictions brought about by different cut-off points.

Conclusion

In conclusion, the FCT is a quick, valid, and dependable cognitive screening test. FCT has also been shown in this study to be a rapid, user-friendly, and accurate measure of CI in a community context. It takes ten minutes or longer to finish the majority of widely used screening tools. When used in large-scale epidemiological studies or doctors' offices, Cognitive screening tests with shorter administration times would be preferred. The FCT is an instrument rather than the MMSE that may be taken into consideration. These results could help FCT become more widely used in clinical practice and research.

Ethics

Ethics Committee Approval: The Golestan Research Ethics Committee (approval ID: IR.GOUMS.REC.140, date: 28.11.2023) gave its approval for the study.

Informed Consent: Every participant or informal caregiver provided written informed consent.

Footnotes

Authorship Contributions

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

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ORIGINAL RESEARCH

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G8 Frailty Assessment Tool as a Predictor of Quality of Life in Elderly Patients Receiving Sorafenib for Hepatocellular Carcinoma. A Prospective Cohort

Elham Arif[1], Mohamed Mortada Mohamed Goda[1], Heba Aly[2], Marwa Ahmed Mohamed[3], Dina Fathy[2]

[1]Ain Shams University Faculty of Medicine, Department of Geriatric Medicine, Cairo, Egypt
[2]Ain Shams University Faculty of Medicine, Department of Tropical Medicine, Cairo, Egypt
[3]Ain Shams University Faculty of Medicine, Department of Internal Medicine, Cairo, Egypt

Abstract

Objective: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the fourth most common in Egypt. Studies report a significant age-specific increase in HCC development. Sorafenib is frequently used to treat patients with HCC across all age groups, including the elderly. Assessing treatment tolerability, quality of life (QoL), and symptom burden in older patients is crucial because frailty is more prevalent with advancing age and can lead to poorer outcomes. The G8 has demonstrated superior prediction of complications and symptom burden among older adults with various cancers. Therefore, our primary aim is to assess G8 frailty tool as predictor of QoL in elderly patients with HCC receiving sorafenib. Our secondary aim was to assess the correlation between G8 and side effects and decompensation during sorafenib treatment.

Materials and Methods: The study subjects were elderly patients (aged 60 years or older) presenting to HCC outpatient clinics at Ain Shams University who were eligible for sorafenib. Patients were initiated on sorafenib and followed for three months. G8 was assessed before the first dose of sorafenib. European Organization for Research and Treatment of Cancer Quality of Life 15 items Questionnaire for Palliative Care scores and timed up and go test (TUGT) were assessed before the first dose and repeated after one and three months of treatment. Data were tabulated and statistically analyzed using SPSS version 29 (SPSS Inc., Chicago, IL).

Results: Mean G8 score was 12.98 ± 2.61 (7-17). No statistically significant differences were noted in patients' QoL when assessed before starting sorafenib treatment and during follow-up. A worse G8 score was significantly associated with poorer physical function, as measured by TUGT, in all three encounters. Moreover, lower G8 scores were significantly correlated with worse QoL subscale scores during most follow-up encounters. Additionally, worse G8 scores were correlated with greater side effects after 3 months of treatment.

Conclusion: In elderly patients with HCC, G8 can predict QoL and symptom burden during sorafenib treatment. These findings highlight the importance of incorporating frailty assessments into routine clinical practice to guide personalized care for this vulnerable population.

Keywords: G8, quality of life, EORTC QLQ-C15-PAL, Egyptian elderly, HCC, sorafenib

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most prevalent malignancy and the second leading cause of cancer-related mortality globally (1). It is, in fact, the fourth most prevalent cancer in Egypt (2). Aging is widely recognized as a risk factor for the development of HCC (3). Recent studies indicate a notable age-specific increase in HCC incidence (4). Elderly patients are considered "frail" owing to comorbidities, altered pharmacokinetics, and increased susceptibility to adverse effects of chemotherapy or surgical interventions (5).

Address for Correspondence: Elham Arif, MD, Lecturer in Geriatric Medicine, Department of Geriatric Medicine, Ain Shams University Faculty of Medicine, Cairo, Egypt
E-mail: Elhamarif31@gmail.com **ORCID:** orcid.org/0009-0009-1676-7402
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Curative interventions, including surgery, transplantation, and ablation, are unavailable to most patients with HCC because of their frequent diagnosis at advanced stages. Liver-directed therapy and oral targeted medications are employed in these individuals to extend survival and alleviate symptoms of malignancy and concomitant liver impairment. Consequently, assessing quality of life (QoL) is crucial to ascertain whether the treatment fulfilled its objective of palliation (6).

The most commonly used oral targeted therapy is sorafenib. Vascular endothelial growth factor receptors (-1, -2, and -3) and platelet-derived growth factor receptor-beta are inhibited by sorafenib, an oral multikinase tyrosine kinase inhibitor that targets the rapidly accelerated fibrosarcoma/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway to inhibit tumour cell proliferation and angiogenesis and induce tumour cell apoptosis (7). Patients with intermediate HCC or Barcelona clinic liver cancer (BCLC) stage C who are not candidates for, or have not responded to, locoregional therapies, particularly those with Child-Pugh Class A liver disease, are generally recommended to receive sorafenib (8). International health authorities approved sorafenib after randomised, phase III, multicenter, double-blind, placebo-controlled trials verified its effectiveness in treating HCC. Among patients with well-preserved liver function (Child-Pugh A), these trials showed a statistically significant improvement in overall survival and time to progression compared with placebo. In these studies, sorafenib was well tolerated (9).

However, data on the safety and efficacy of sorafenib in older HCC patients are limited, and current treatment guidelines for the disease do not recommend specific procedures for older patients (10). Recent research indicates a higher prevalence of adverse health effects among older adults, resulting in a diminished QoL (11). Consequently, additional research on the QoL and tolerability of Sorafenib in the older Egyptian population is essential. Furthermore, forecasting the symptom burden in older adults is crucial for preventing adverse outcomes. Comprehensive techniques such as G8 provide a superior assessment of older adults and may predict patients' QoL during cancer therapy (12).

The primary objective of this research was to assess the G8 frailty tool as a predictor of QoL in a sample of Egyptian older patients with HCC receiving sorafenib. Our secondary aim was to assess the correlation between G8 and side effects and decompensation on sorafenib treatment.

Materials and Methods

From February 2023 to April 2024, this prospective cohort study was conducted at the HCC outpatient clinics of Ain Shams University Hospitals. In compliance with the the Declaration of Helsinki, ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Ain Shams University (approval number: FMASU R76/2023, date: 09.04.2024).

Sample Size and Power Calculation

A formal sample size calculation was conducted before the start of the study. A minimum of 51 patients were required to detect a small-to-moderate effect size (0.2) in changes in European Organization for Research and Treatment of Cancer Quality of Life 15 items Questionnaire for Palliative Care scores (EORTC QLQ-C15-PAL) across three time points (baseline, 1 month, and 3 months) using a repeated-measures analysis of variance (ANOVA) with 80% power and a significance level of 0.05. This calculation assumed a correlation among repeated measures of 0.5 and a non-sphericity correction of 1. To account for possible dropouts, the sample size was increased by 20%, resulting in a target of approximately 58 participants.

In addition, the sample size was sufficient to evaluate the discriminatory ability of the G8 score to predict treatment discontinuation of sorafenib treatment, assuming a 20% discontinuation rate and an area under the curve of 0.80, based on a two-sided Z-test with 80% power and α=0.05.

A total of 58 patients were enrolled. Forty patients completed the full 3-month follow-up, which was considered adequate to ensure statistical validity for the study's primary and secondary objectives.

Study Participants

Subjects aged 60 years or older with a verified diagnosis of HCC were included. According to the European Association for the Study of the Liver (EASL) guidelines, the diagnosis of HCC was made using imaging criteria (triphasic computed tomography or dynamic magnetic resonance imaging) or, for cases with atypical imaging results, by hepatic focal lesion biopsy with histopathology (13,14).

To be eligible for systemic therapy (sorafenib), they had preserved liver function (Child-Pugh stage A or B7) and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Regarding their tumor staging on the BCLC staging system, they were classified as either BCLC C (with extrahepatic metastasis and/or portal vein invasion) or BCLC B (diffuse, infiltrative, bilobar HCC), regardless of whether they were treatment-naïve or had progressed/failed on other treatment modalities. In cases of unconfirmed portal vein invasion, abdominal Doppler was performed to confirm it.

Patients were excluded if they had a history of decompensation, hepatic encephalopathy, or neuropsychiatric disorders. Before starting treatment, baseline upper GI endoscopy was performed, with intervention as indicated. One hundred patients were assessed; however, only 58 met the study inclusion criteria (Figure 1).

Treatment Protocol

Our study participants received sorafenib for HCC according to the standard regimen recommended by the EASL (13,14). Sorafenib was prescribed at an initial dose of 400 mg twice daily, with monitoring for side effects and tolerability; liver function tests and enzyme measurements were performed weekly for the first month and then monthly. The dose was reduced to 200 mg twice daily or discontinued in the event of intolerability or side effects (13,14).

Adverse events were monitored throughout the treatment period and classified according to the common terminology criteria for adverse events, version 5.0.

History and Laboratory Investigations

Data collection included a detailed history of disease onset and course, prior viral hepatitis, antiviral therapy received, previous HCC treatments, and comorbidities. Moreover, patients underwent complete blood counts, liver function tests, including liver enzymes, and alpha-fetoprotein (AFP) measurements at the start of treatment and after three months.

Frailty assessment by G8 before the first dose: The G8 screening tool comprises seven components related to dietary intake, weight loss, mobility, neuropsychological issues, body mass index, prescription medications, and self-assessed health. It is derived from the Mini-Nutritional Assessment questionnaire and is designed specifically for older adults with cancer (15). A cut-off value of 14 shows high sensitivity for predicting the need for a complete geriatric assessment and indicates an elevated risk of frailty (15).

Assessment of quality of life before the first dose, after one month, and after three months:

Authorization to use the Arabic version of the EORTC QLQ-C15-PAL was obtained from the EORTC.

A popular, validated, translated, and published measure for assessing symptoms and QoL in cancer patients, the EORTC QLQ-C15-PAL is a reduced, 15-item version of the EORTC QLQ-C30 (16). It includes overall QoL; symptom measures (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, and constipation); and functional scales (including emotional scales) (16). The scale used to quantify the responses ranged from 0 to 100. It can be used in an outpatient setting with high patient volume. Elevated emotional, functional, and overall QoL ratings indicate a favorable QoL, whereas increased symptom and exhaustion scores reflect a greater symptom burden (16).

Assessment of physical function and Gait before the first dose, after one month, and after three months:

Timed up and go test (TUGT) is a straightforward assessment of an individual's mobility, necessitating both static and dynamic balance. It measures the time required for an individual to stand up from a chair, walk three meters, turn 180 degrees, walk back to the chair, and sit down after performing a second 180-degree rotation. During the assessment, the individual is required to wear their customary footwear and use any mobility assistance they typically need (17).

Statistics

• Data were tabulated and statistically analyzed using SPSS, version 20 (SPSS Inc., Chicago, IL).

• Quantitative data were presented as mean ± standard deviation. The independent t-test was used to compare quantitative data between independent groups. Repeated-measures ANOVA and paired t-tests were used to compare quantitative data over time.

• Qualitative data were expressed as frequencies (n) and percentages (%). Fisher's exact test and the chi-square test were used to assess the association between qualitative variables. The McNemar test and the Marginal Homogeneity test were used to compare qualitative data over time.

• The Pearson correlation coefficient (r) test was used to assess the correlation between two quantitative variables greater than zero indicates a positive relationship, while a value less than zero signifies a negative relationship (values were interpreted as follows: 0 no correlation, $0.0 < r < 0.30$ as weak, $0.30 < r < 0.70$ as moderate, $0.70 < r < 1.0$ as strong, and 1.0 as perfect correlation).

• A p-value ≤0.05 was considered significant.

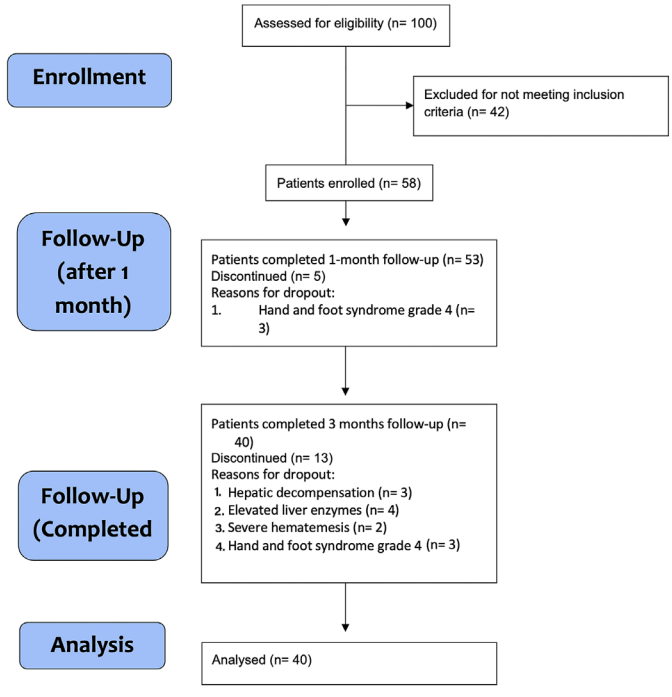

Figure 1. Inclusion of patients.

Results

Demographic Data and Disease Characteristics of the Studied Patients

Patient characteristics are presented in Table 1. Among the 58 included patients, the mean age was 67 years, and approximately 79% (n = 46) were male.

58.6% (n = 34) had comorbidities, with a mean Charlson Comorbidity Index of 11.5.

77.6% (n = 45) had post-hepatitis C cirrhosis, 36.2% (n = 21) were HCC treatment-naïve, and 82.7% (n = 48) were Child-Pugh A. Regarding tumor staging, 82.8% (n = 48) were classified as BCLC C. In addition, 86.2% (n = 50) had a baseline ECOG score of 1. The mean G8 score was 12.98 ± 2.61 (range: 7-17).

Quality of Life by EORTOC QLQ C15 PAL, TUGT, and Tumor Characteristics

As shown in Table 2, among the 58 included patients, 40 completed 3 months of treatment and follow-up. Dropouts were due to severe hematemesis in two patients; three patients developed grade IV hand-foot syndrome. Three patients developed decompensation, four developed elevated liver transaminase levels (>5 times the upper limit of normal), and six missed follow-up visits. A high rate of dropout in studies is expected in elderly with HCC due to a decline in functional reserve and metabolic alterations leading to higher rates of drug interactions and adverse effects (18). Mean TUGT increased significantly after 3 months of treatment, from 9.66 ± 1.75 seconds to 10.3 ± 1.73 seconds (p = 0.000) (Table 2).

Functional scores and overall QoL measured by the EORTC QLQ-C15-PAL were 89.4 ± 17.91 (40-100) and 59.96 ± 19.18 (16-100) at baseline, and increased to 90.88 ± 12.76 (40-100) and 64.58 ± 13.75 (33.3-83) after 3 months; these changes were not statistically significant. Symptom, fatigue, and emotional scores did not differ significantly during the follow-up period. At baseline, the mean AFP level was 26,228.98 ± 177,509.04 ng/mL (range, 2-1,352,775 ng/mL). 60.3% (n = 35) had vascular invasion, involving the main or branch portal vein; 36.2% (n =

Table 1. Demographic data and disease characteristics in the studied patients.

		n	%
Demographics			
Age mean ± SD (min-max)		67.59 ± 7.29 (60–93)	
Sex	Female	12	20.70%
	Male	46	79.30%
Comorbidities	No	24	41.40%
	Yes	34	58.60%
Mean Charlson Index mean ± SD (min-max)		11.55 ± 1.84 (7–15)	
Comorbidities and clinical history			
Duration of chronic hepatitis (years) mean ± SD (min-max)		7.32 ± 4.53 (1-20)	
Past hepatitis C virus treatment	No	13	22.40%
	Yes	45	77.60%
Past hepatitis B virus treatment	No	58	100.00%
	Yes	0	0.00%
Steroid, azathioprine for autoimmune hepatitis		1	1.70%
Unknown (cryptogenic)		12	20.70%
Hepatocellular carcinoma (HCC) status Duration of HCC (months) mean ± SD (min-max)		16.92 ± 21.36 (0–84)	
Previous HCC treatment	No treatment	21	36.20%
	TACE	14	24.10%
	Multiple TACE	11	19.00%
	RFA	2	3.40%
	Combined TACE ± RFA	4	6.90%
	TARE	1	1.70%
	SBRT	2	3.40%
	Liver transplantation	2	3.40%
	Resection	1	1.70%

Table 1. Continued.

		n	%
Demographics			
Symptoms	Asymptomatic	14	24.10%
	Fatigue	14	24.10%
	Abdominal pain	27	46.60%
	Anorexia	1	1.70%
	Nausea and vomiting	0	0.00%
	Weight loss	1	1.70%
	Abdominal distension	1	1.70%
	Jaundice	0	0.00%
	Fever	0	0.00%
Liver function and endoscopy findings			
Child score	A5	35	60.30%
	A6	13	22.40%
	B7	10	17.20%
UGI Findings (OV varices)	No	25	43.10%
	Grade I-II OV	19	32.80%
	Grade III-IV or risky OV	14	24.10%
PHG in UGI	No	22	37.90%
	Yes	36	62.10%
Clinical and performance characteristics			
BCLC	BCLC-0	0	0.00%
	BCLC-A	0	0.00%
	BCLC-B	10	17.20%
	BCLC-C	48	82.80%
ECOG at 0	0	1	1.70%
	1	50	86.20%
	2	7	12.10%
G8 at 0 mean ± SD (min-max)		12.98 ± 2.61 (7–17)	

SD: Standard deviation, min: Minimum, max: Maximum, ECOG: Eastern Cooperative Oncology Group, HCC: Hepatocellular carcinoma, UGI: Upper gastrointestinal endoscopy, BCLC: Barcelona Clinic Liver Cancer, TACE: Trans arterial chemoembolization, TARE: Trans arterial chemoembolization, SBRT: Stereotactic body radiotherapy, RFA: Radiofrequency ablation, OV: Esophageal varices, PHG: Portal hypertensive gastropathy.

21) had metastatic abdominal lymph nodes; and 27.6% (n = 16) had extrahepatic spread other than to abdominal lymph nodes, indicating that a patient may have more than one site of metastasis (Figure 2, Table 2).

At the third month of treatment, 75% of patients developed grade I or II side effects, compared with 49.1% after the first month; this difference was statistically significant (p = 0.007). The incidence of decompensation was slightly higher at the third month of treatment (17.5%) compared with the first month (10.9%); this difference was not statistically significant (p = 0.063) (Table 3).

At the end of the study (month 3), 69% (n = 40) of patients were evaluated for treatment response. Twenty-three patients (57.5%) had stable disease, five (12.5%) had a partial response, and twelve (30%) progressed during treatment, as shown in Table 3.

Correlation between G8 and Quality of life and TUGT

As shown in Table 4, G8 had a statistically significant negative correlation with TUGT at baseline and at each follow-up through the 3-month treatment period, with p-values of 0.000, 0.000, and 0.003, respectively, indicating that worse G8 scores were associated with poorer physical function.

Regarding QoL, G8 showed a statistically significant positive correlation with functional and emotional scores before treatment and at the first follow-up (1 month).

Symptom scores were negatively correlated with G8 at baseline, at 1 month, and at the final follow-up (3 months). The fatigue subset had a negative correlation with G8 at the start and after 3 months, with p-values of less than 0.001 and 0.042, respectively.

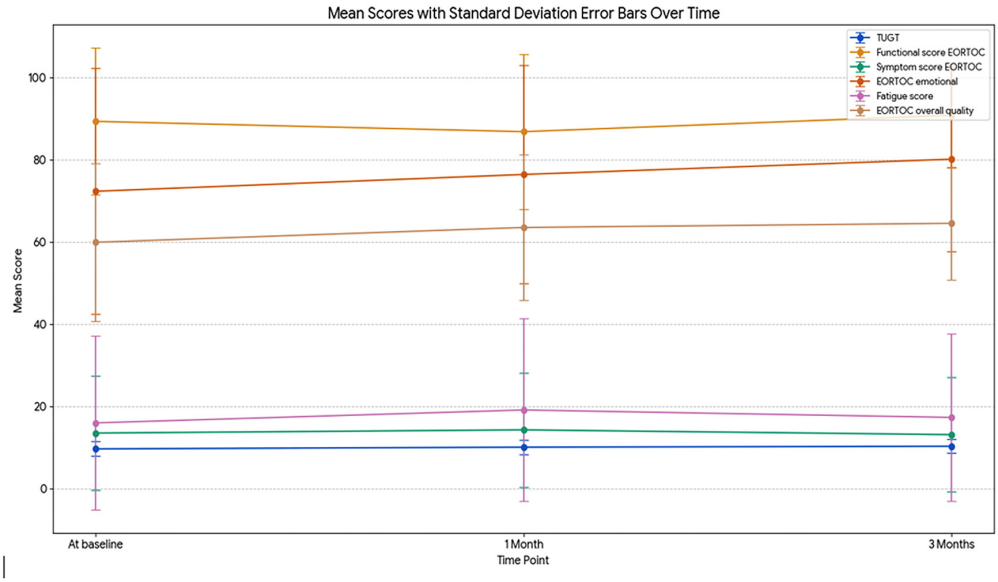

Figure 2. The longitudinal changes in timed up and go test and overall quality-of-life scores over the 3-month period.

TUGT: Timed up and go test, EORTOC: European Organisation for Research and Treatment of Cancer Quality of life questionnaire.

At baseline and at 1 and 3 months of follow-up, there were statistically significant positive associations between overall QoL and G8 (p = 0.000, 0.031, and 0.009, respectively).

G8 and Side Effects, Decompensation, and Treatment Response

In Table 5, patients' baseline G8 was lower in patients who developed side effects and decompensation later, with a statistically significant difference (p-value: 0.052) in patients who developed side effects at the third month of treatment, and therefore, G8 may predict patients' drug tolerability. Baseline G8 was lower in patients who could not continue treatment for 3 months. In contrast, G8 was higher in patients who had partial response and stable disease, with a borderline statistically significant difference (p = 0.054).

In Table 6, patients were classified according to scores of G8.

Patients who scored lower on the G8 (frailer) had higher (worse) symptom and fatigue scores at baseline (p = 0.002 and p = 0.011, respectively). They also had significantly lower emotional and overall well-being scores.

After the first month of treatment, patients with lower baseline G8 scores had significantly worse scores in all EORTC subsets, except for fatigue, which was worse but not statistically significant.

Similarly, after 3 months of treatment, patients with worse G8 scores at baseline showed significantly worse scores in all EORTC subsets, except for the functional score, which was worse but not statistically significant.

Frailty (low G8 score) is associated with poorer QoL, greater symptom burden, and increased fatigue over time. The orange bars, representing patients with higher G8 scores, tend to maintain higher scores and better overall outcomes. This underscores the importance of geriatric assessment tools, such as G8, in oncology: they help identify patients who may need tailored treatment or supportive care (Figure 3).

Discussion

HCC is a serious public health issue in Egypt. The government's mass screening program for HCV identification and treatment may contribute to Egypt's rising rates of HCC detection (19). Moreover, incidence has increased significantly in older age groups. Sorafenib is among the most frequently used agents for treating HCC, particularly in advanced stages; however, its effect on the QoL of older Egyptian adults remains understudied. Moreover, predicting of symptom burden and QoL before treatment in older adults is of utmost importance because frailty is more prevalent in this population. G8 has been evaluated in multiple studies as a predictor of frailty and increased symptom burden (12).

In the current study, the mean age of HCC patients was 67 years. Regarding the main findings of our study, the QoL in study subjects did not show a significant change after 1 and 3 months of treatment. Data on QoL with sorafenib treatment in the literature are scarce. However, Pereira et al. (20) showed worse QoL among patients treated with sorafenib compared with other treatment modalities, whereas Abraham et al. (21) reported better QoL in a relatively younger population (mean age 57 years).

Table 2. Quality of life, TUGT, and tumor characteristics at baseline and during treatment.

		At baseline		1 month		3 months		p-value
Functional and quality of life (QoL) scores								
TUGT		**9.66 ± 1.75 (6–16)**		**10.07 ± 1.72 (6–13)**		**10.3 ± 1.73 (8–14)**		**0.000***
Functional score EORTC		**89.4 ± 17.91 (40–100)**		**86.89 ± 18.84 (40–100)**		**90.88 ± 12.76 (40–100)**		**0.255**
Symptom score EORTC		**13.51 ± 13.85 (0–59)**		**14.29 ± 13.9 (0–59)**		**13.13 ± 13.93 (0–59)**		**0.403**
Emotional score EORTC		**72.38 ± 29.95 (0–100)**		**76.47 ± 26.58 (0–100)**		**80.19 ± 22.52 (17–100)**		**0.776**
Fatigue score EORTC		**15.99 ± 21.15 (0–66.7)**		**19.13 ± 22.22 (0–67)**		**17.32 ± 20.35 (0–66.6)**		**0.177**
The overall quality of life EORTC		**59.96 ± 19.18 (16–100)**		**63.57 ± 17.8 (16–83)**		**64.58 ± 13.75 (33.3–83)**		**0.610**
Laboratory parameters								
Hemoglobin (g/dL)		**12.61 ± 1.95 (8.7–18.7)**		**12.53 ± 2.63 (0–18.6)**		**12.62 ± 2.83 (0–18.3)**		**0.143**
White Blood cell (10^3/µL)		**6833.1 ± 2962.2 (1040–14700)**		**6139.36 ± 2758.57 (19–17700)**		**5394.44 ± 2770.44 (11–11800)**		**0.026***
Platelets (10^3/µL)		**190.55 ± 90.98 (42–495)**		**183.51 ± 93.97 (50–406)**		**168.63 ± 88.41 (58–419)**		**0.112**
AST aspartate aminotransferase (U/L)		**60.16 ± 40.31 (17–187)**		**70.15 ± 50.95 (26–243)**		**72.44 ± 55.03 (14–268)**		**0.289**
ALT alanine transaminase) (U/L)		**45.09 ± 33.63 (9–144)**		**48.51 ± 34.34 (14–200)**		**53 ± 45.53 (12–236)**		**0.495**
S.albumin (g/dL)		**3.73 ± 0.48 (2.76–4.7)**		**3.58 ± 0.44 (2.7–4.5)**		**3.61 ± 0.52 (2.5–4.7)**		**0.022***
S.bilirubin (mg/dL)		**0.95 ± 0.4 (0.34–2.6)**		**1.09 ± 0.54 (0.37–3)**		**1.12 ± 0.57 (0.5–3.8)**		**0.192**
INR		**1.16 ± 0.18 (0.95–1.89)**		**1.16 ± 0.19 (0.96–1.84)**		**0.82 ± 0.62 (0–2.1)**		**0.000***
Alpha feto protein AFP (ng/mL)		**26228.98 ± 177509.04 (2–1352775)**		**-**		**11009.49 ± 37924.21 (3.7–169521)**		**0.310**
Radiological and clinical features								
SLD		7.75 ± 4.98 (1-23.1)		-		6.73 ± 4.86 (1-21)		0.484
n		**At baseline**		**1 month**		**3 months**		**p-value**
		%	**n**	**%**	**n**	**%**		
Focal hepatic lesion number	Single	24	41.4%	-	-	17	42.5%	0.058
	Double	15	25.9%	-	-	6	15.0%	
	3 or more	19	32.8%	-	-	17	42.5%	
Focal hepatic lesion site	Lt lobe	8	13.8%	-	-	7	17.5%	0.317
	Rt lobe	37	63.8%	-	-	25	62.5%	
	Bilobar	13	22.4%	-	-	8	20.0%	
Vascular invasion	No	23	39.7%	-	-	14	35%	0.206
	Main branch	10	17.2%	-	-	11	27.5%	
	Rt or Lt branch	19	32.8%	-	-	13	32.5%	
	Segmental (main and branch)	6	10.3%	-	-	2	5%	

Table 2. Continued.

		At baseline		1 month		3 months		p-value
Lymph nodes	No	37	63.8%	-	-	26	65%	0.625
	Yes	21	36.2%	-	-	14	35%	
Extra hepatic spread (other than lymph. nodes)	No	42	72.4%	-	-	26	65%	1.000
	Yes	16	27.6%	-	-	14	35%	
Side effects	No	-	-	28	50.9%	10	25.0%	0.007*
	Yes	-	-	27	49.1%	30	75.0%	
Decompensation	No	-	-	49	89.1%	33	82.5%	0.063
	Yes	-	-	6	10.9%	7	17.5%	

*Highly significant. AFP: Alpha-fetoprotein, AST: Aspartate aminotransferase, EORTC QLQ-C15-PAL: EORTOC Quality of Life 15 items Questionnaire for Palliative Care.

Table 3. Distribution of treatment response after 3 months among the studied patients (m RECIST criteria).

		n	%
Treatment response	Lost	7	12%
	Stopped	11	19%
	PD	12	20.7%
	PR	5	8.6%
	SD	23	39.7%

PD: Progressive disease, PR: Partial response, SD: Stable disease, RECIST: Modified Response Evaluation Criteria in Solid Tumors.

In the current study, symptom and fatigue scores on the EORTC QLQ-C15-PAL were higher (worse) in patients aged 70 years or older, although the difference was not statistically significant. In a similar context, Marta et al. (22) examined adverse effects and toxicity rates in patients younger than 70 years compared with older patients and found no significant differences.

The correlation between the G8 score and QoL in HCC has not been extensively studied in the literature. In a study of prostate cancer patients, the G8 score showed significant positive correlations with functional score before the start of therapy, with emotional score at the start and after 1 month, with overall QoL at all three encounters. It also showed a negative correlation with symptom scores at the beginning and at every follow-up, and with fatigue scores at the beginning and after three months, according to Hamaya et al. (23). It also concluded that QOL was worse with G8 scores below 14, in line with our study.

According to another study by Ditzel et al. (24), G8 frailty and the QoL of patients with solid tumours were significantly correlated. It was concluded that lower QoL ratings are correlated with lower G8 scores.

Regarding G8 and the risk of adverse effects in elderly patients receiving sorafenib, our study concluded that G8 correlated with decompensation after one month of treatment and with adverse effects after three months. Other studies did not show a significant correlation between G8 scores and adverse events; for example, Sekiguchi et al. (25) concluded that worse G8 scores

Table 4. Correlation between G8 and quality of life and TUGT.

		G8 zero
TUGT 0	Pearson correlation	-0.543**
	Sig. (2-tailed)	0.000
TUGT 1	Pearson correlation	-0.524**
	Sig. (2-tailed)	0.000
TUGT 3	Pearson correlation	-0.462**
	Sig. (2-tailed)	0.003
Functional score EORTC 0	Pearson correlation	0.415**
	Sig. (2-tailed)	0.001
Functional score EORTOC 1	Pearson correlation	0.343*
	Sig. (2-tailed)	0.021
Functional score EORTC 3	Pearson correlation	0.008
	Sig. (2-tailed)	0.959
Symptom score EORTC 0	Pearson correlation	-0.558**
	Sig. (2-tailed)	0.000
Symptom score EORTC 1	Pearson correlation	-0.398**
	Sig. (2-tailed)	0.007
Symptom score EORTC 3	Pearson correlation	-0.454**
	Sig. (2-tailed)	0.003
EORTC emotional 0	Pearson correlation	0.370**
	Sig. (2-tailed)	0.004
EORTC emotional 1	Pearson correlation	0.313*
	Sig. (2-tailed)	0.036
EORTC emotional 3	Pearson correlation	0.253
	Sig. (2-tailed)	0.106
EORTC overall quality 0	Pearson correlation	0.511**
	Sig. (2-tailed)	0.000
EORTC overall quality 1	Pearson correlation	0.322*
	Sig. (2-tailed)	0.031
EORTC overall quality 3	Pearson correlation	0.396**
	Sig. (2-tailed)	0.009
Fatigue score 0	Pearson correlation	-0.454**
	Sig. (2-tailed)	0.000
Fatigue score 1	Pearson correlation	-0.266
	Sig. (2-tailed)	0.077
Fatigue score 3	Pearson correlation	-0.319*
	Sig. (2-tailed)	0.042

*,**Statistically significant, TUGT: Timed up and go test, EORTC: European Organization for Research and treatment of cancer.

did not correlate with survival or with adverse events associated with sorafenib.

While our study demonstrates the G8 tool's predictive value for QoL and toxicity in elderly Egyptian HCC patients, comparisons with international cohorts reveal important nuances. For instance, Williet et al. (11) reported a lower treatment discontinuation rate (15%) in frail European patients receiving sorafenib than our 31% attrition. This may reflect disparities in comorbidities (e.g., higher HCV prevalence in our population) or in access to early supportive interventions.

Table 5. G8 and side effects and decompensation and treatment response.

		G8 zero	p
Side effects 1 month	No	13.2+2.9 (7-17)	0.645
	Yes	12.9+2.3 (8-17)	
Side effects 3 months	No	14.6+2 (10-17)	0.052*
	Yes	13.1+2.1 (8-17)	
Decompensation 1 month	No	13.4+2.5 (7-17)	0.009*
	Yes	10.5+1.4 (9-12)	
Decompensation 3 months	No	13.5+2.2 (8-17)	0.655
	Yes	13.1+2 (11-17)	
Treatment response	Lost	9.7+3.1 (7-13)	0.054*
	Stopped	12+2.7 (8-17)	
	PD	13.4+2.7 (8-17)	
	PR	14.6+1.8 (12-17)	
	SD	13.7+2 (10-17)	

*: Statistically significant, PD:: Progressive disease, PR: Partial response, SD: Stable disease.

Notably, Sekiguchi et al. (25) found that G8 predicted survival but not adverse events in Japanese HCC patients, in contrast to our observed correlation between G8 and toxicity. This discrepancy could stem from variations in frailty cutoffs (e.g., G8 <14 vs. <12) or cultural differences in symptom reporting. However, our findings align closely with Ditzel et al. (24), in whose prospective Danish cohort G8 scores were linked to QoL deterioration across cancer types, reinforcing frailty's transdiagnostic impact.

These comparisons underscore that while G8 is a globally relevant screening tool, its operational thresholds and clinical implications may require regional calibration, particularly in high-burden settings like Egypt, where HCC etiology and healthcare infrastructure differ from high-income countries.

Taken together, these findings align with recent international evidence validating the G8 tool's utility in geriatric oncology. For instance, Sekiguchi et al. (25) demonstrated G8's prognostic value for treatment tolerability and survival in elderly patients with HCC receiving systemic therapy, while Ditzel et al. (24) confirmed its relevance for predicting QoL outcomes. Earlier work by Hamaya et al. (23) in prostate cancer also supported G8's predictive role across multiple QoL domains. Collectively, these studies highlight the G8 tool's global applicability; however, its

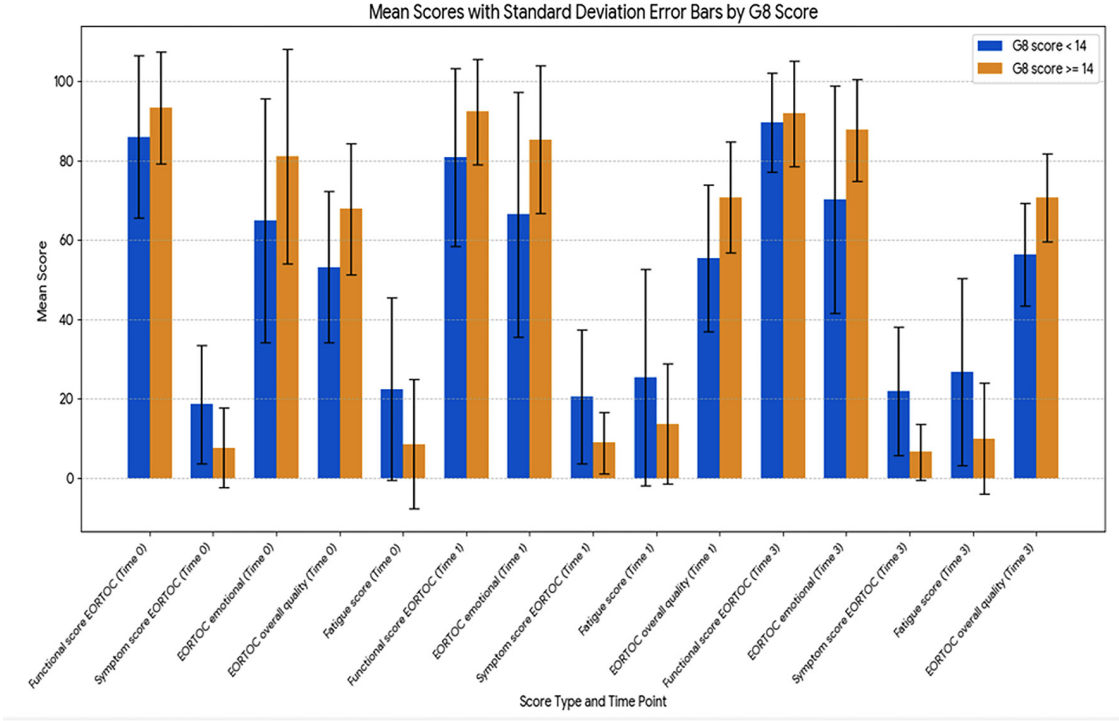

Figure 3. G8 scoring and quality of life domains along study course.

EORTOC: European Organisation for Research and Treatment of Cancer Quality of life questionnaire.

Table 6. Correlation between categories of G8 and quality of life, decompensation, and side effects in the third month.

		Below 14	G8 14 or more	p
		Mean ± SD (min–max)	Mean ± SD (min–max)	
Functional score EORTC 0		86 ± 20.4 (40–100)	93.3 ± 14 (57–100)	0.123
Symptom score EORTC 0		18.6 ± 14.9 (0–59)	7.7 ± 10 (0–33.3)	0.002*
EORTC emotional 0		64.9 ± 30.8 (0–100)	81 ± 27 (0–100)	0.041*
EORTC overall quality 0		53.2 ± 19 (16–83)	67.8 ± 16.5 (33.3–100)	0.003*
Fatigue score 0		22.4 ± 23 (0–66.7)	8.6 ± 16.2 (0–50)	0.011*
Functional score EORTOC 1		80.8 ± 22.4 (40–100)	92.3 ± 13.3 (40–100)	0.049*
EORTC emotional 1		66.4 ± 30.9 (0–100)	85.3 ± 18.6 (40–100)	0.020*
Symptom score EORTC 1		20.5 ± 16.8 (0–59)	8.9 ± 7.7 (0–25)	0.007*
Fatigue score 1		25.4 ± 27.3 (0–67)	13.7 ± 15.2 (0–50)	0.091
EORTC overall quality 1		55.5 ± 18.5 (16–83)	70.7 ± 14 (33.3–83)	0.003*
Functional score EORTC 3		89.6 ± 12.4 (60–100)	91.8 ± 13.2 (40–100)	0.583
EORTC emotional 3		70.2 ± 28.6 (17–100)	87.7 ± 12.8 (67–100)	0.024*
Symptom score EORTC 3		21.9 ± 16.1 (3.3–59)	6.6 ± 7 (0–25)	0.001*
Fatigue score 3		26.7 ± 23.6 (0–66.6)	10 ± 13.9 (0–50)	0.013*
EORTC overall quality 3		56.4 ± 12.9 (33.3–83)	70.7 ± 11.1 (50–83)	0.000*
Side effects at 3 months	No	1 (5.6%)	9 (40.9%)	0.013*
	Yes	17(94.4%)	13(59.1%)	
Decompensation at 3 months	No	13 (72.2%)	20 (90.9%)	0.211
	Yes	5 (27.8%)	2 (9.1%)	

An independent t-test was utilised. A p-value <0.05 was considered statistically significant. *: Statistically significant, SD: Standard deviation, EORTC: European Organization for Research and treatment of cancer, min: Minimum, max: Maximum.

operational thresholds and clinical implications may require local adaptation in high-burden settings, such as Egypt. Sekiguchi et al. (25) on G8's prognostic value in HCC patients receiving systemic therapy (Cancer Rep). Ditzel et al. (24) on G8 and QoL outcomes in geriatric oncology (Lancet Healthy Longevity). Hamaya et al. (23) on frailty and QoL in prostate cancer (Int J Clin Oncol).

Study Limitations

Several factors limit this study. First, although the sample size achieved the estimated statistical power, the relatively small sample may limit the generalizability of the findings. Second, the use of the abbreviated EORTC QLQ-C15-PAL, while practical for palliative settings, may have overlooked key QoL domains—such as social, cognitive, and financial aspects—that are captured by the full EORTC QLQ-C30. Third, due to the limited number of events, multivariable analyses (e.g., logistic regression) were not performed to assess the independent predictive value of the G8, thereby restricting our ability to control for potential confounders such as comorbidities, ECOG performance status, and Child-Pugh class.

A dropout rate of 31% was observed by the third month, primarily due to clinical deterioration, treatment intolerance, or loss to follow-up—challenges frequently encountered in elderly patients with advanced HCC. As a result, a per-protocol analysis was conducted, which may introduce attrition bias and further limit generalizability. Although comorbidities were assessed using the Charlson Comorbidity Index, other relevant factors such as socioeconomic status, psychosocial support, and access to care were not fully accounted for and may have influenced both treatment adherence and patient-reported outcomes.

Future studies with larger cohorts, comprehensive multivariable analyses, and the use of intention-to-treat approaches are warranted to validate and expand upon these findings.

While the dropout rate reflects real-world challenges in elderly patients with HCC, our analysis confirmed the validity of the retained cohort. Future work will address confounders such as socioeconomic status.

Conclusion

Worse G8 scores were consistently associated with poorer QoL, slower gait speed, and increased risk of treatment-related toxicity in elderly patients with HCC. These findings highlight the clinical utility of the G8 screening tool in identifying frail patients at higher risk of adverse outcomes during systemic therapy. Incorporating G8 into routine oncologic assessment

may support more individualized treatment strategies, including dose adjustments, enhanced supportive care, and closer monitoring. Additionally, G8 can facilitate informed decision-making by aligning treatment plans with patient frailty status and expectations.

Ethics

Ethics Committee Approval: In compliance with the the Declaration of Helsinki, ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Ain Shams University (approval number: FMASU R76/2023, date: 09.04.2024).

Informed Consent: Non required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.A., Concept: E.A., M.M.M.G., H.A., M.A.M., D.F., Design: E.A., M.M.M.G., H.A., M.A.M., D.F., Data Collection or Processing: E.A., D.F., Analysis or Interpretation: E.A., M.M.M.G., M.A.M., D.F., Literature Search: E.A., D.F., Writing: E.A., M.M.M.G., H.A., M.A.M., D.F.

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ORIGINAL RESEARCH

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Evaluation of C-reactive Protein-Albumin-Lymphocyte (CALLY) Index in the Pathogenesis of Osteoporosis

Emel Sabaz Karakeci[1], Nesibe Aydoğdu[2]

[1]*University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Department of Physical Medicine and Rehabilitation, Elazığ, Türkiye*
[2]*University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Department of Internal Medicine, Elazığ, Türkiye*

Abstract

Objective: To assess the relationship between bone mineral density (BMD) and the C-reactive protein-albumin-lymphocyte (CALLY) index in postmenopausal women.

Materials and Methods: A cross-sectional analysis of 337 postmenopausal women [107 with osteoporosis (OP), 144 with osteopenia, and 86 controls] was conducted from January 2023 to December 2024. Participants were stratified by BMD using DXA T-scores: normal ≥-1, osteopenia -1 to -2.5, OP ≤-2.5. Hematological parameters (C-reactive protein, albumin, lymphocyte counts) were analyzed, and the CALLY index was derived.

Results: No statistically significant difference in CALLY index scores was observed between groups ($p = 0.130$). However, albumin and lymphocyte levels were significantly lower in the OP group than in the normal group ($p = 0.002$).

Conclusion: Low albumin and lymphocyte levels observed in the OP group underscore the significance of these parameters in the pathogenesis of bone loss. However, the CALLY index, which integrates these parameters, does not offer sufficient discrimination for assessing the low-grade systemic inflammation associated with OP. Prospective studies with larger sample sizes may help clarify the role of the CALLY index in the etiology of OP.

Keywords: Bone mineral density, CALLY index, hematological index, inflammation, osteoporosis

Introduction

Osteoporosis (OP) is a systemic skeletal condition marked by a reduction in bone mass and significant changes in the structure of bone tissue. This condition significantly increases bone fragility, resulting in greater susceptibility to fractures. Its prevalence increases with age, making it a significant public health issue for individuals and society because of the fractures it causes. OP often starts insidiously and progresses without symptoms until bone fractures occur. With the extension of human life expectancy worldwide, OP has become a significant medical challenge. A 2010 report indicated that approximately 5 million men and more than 20 million women in European countries were diagnosed with OP. It is more prevalent among individuals of European ancestry and women. The prevalence of OP increases with age, particularly during the first few years after menopause, a period when bone loss accelerates (1).

OP has a complex etiopathogenesis, and recent literature suggests that it is influenced not only by hormonal and mineral imbalances but also by inflammatory processes. Proinflammatory cytokines, especially interleukin-6 and tumor necrosis factor-alpha, have been shown to accelerate bone resorption by increasing osteoclast activity. Furthermore, targeting inflammation in OP treatment has become an important focus for the development of new therapeutic strategies (2). Inflammation-related complex parameters, such as hemoglobin, albumin, lymphocytes, and platelets, the C-reactive protein (CRP)/albumin ratio (CAR), and the systemic immune-inflammation index (SII), have been used as indicators of inflammation (3,4). Recent research has introduced

Address for Correspondence: Emel Sabaz Karakeci, MD, University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital, Department of Physical Medicine and Rehabilitation, Elazığ, Türkiye
E-mail: emelsabaz@gmail.com **ORCID:** orcid.org/0000-0001-7760-4476
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the C-reactive protein-albumin-lymphocyte (CALLY) index, a new composite measure that has demonstrated greater predictive ability for overall survival in patients with colorectal and gastric cancer compared with traditional prediction methods (5). The CALLY index is a non-invasive quantitative measure. A low CALLY index indicates significant active inflammation, which may compromise overall health. A compromised immune system is linked to an increased vulnerability to infections and various diseases. Additionally, a low index often reflects inadequate nutritional intake, leading to deficiencies that can adversely affect physical well-being and recovery.

The relationship between the CALLY index and OP has not been clearly established. This study sought to examine the potential correlation between the CALLY index and the development of OP. If the CALLY index proves to be a reliable predictive marker for OP, it could facilitate the identification of at-risk individuals and enhance measures to prevent its onset.

Materials and Methods

The research was conducted following ethical approval from the University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital Non-interventional Ethics Committee, which was obtained on (approval number: 2025/3-8, dated: 06.02.2025). We retrospectively reviewed the medical records of patients who visited the outpatient clinics of the departments of internal medicine and physical medicine and rehabilitation from January 2023 to December 2024. The selection criteria included a detailed anamnesis, physical examination findings, and demographic information such as age and gender, alongside laboratory parameters including albumin level, CRP, complete blood count, and T-scores. Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry (DEXA) in all subjects. The research was conducted in the Nuclear Medicine Department at University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital. This study measured BMD at the lumbar spine (L1–L4 and L2–L4) and at the proximal femur (total femur, femoral trochanter, and Ward's triangle). These measurements were obtained in the anteroposterior view using the Lunar GE device (MDL DPX Prodigy-tech. 150070, Madison, USA). The study employed a scanning voltage of 67 kV and a current of 1500 mA, resulting in a delivered dose of 20.0 µGy over approximately 3 minutes. The evaluation of results centered on BMD, measured in g/cm2, and associated T-scores for both examined regions. The diagnosis of OP adhered to the World Health Organization's classification criteria. Individuals with T-scores ≥-1.0 were categorized as normal; those with T-scores between -1.0 and -2.5 were classified as osteopenic; and individuals with T-scores ≤-2.5 were diagnosed with OP. This classification system underscores the importance of precise measurement in assessing bone health and the risk of OP.

Inclusion Criteria

- Patients who underwent bone measurement in the outpatient clinic with suspected OP
- Postmenopausal women diagnosed with OP
- Patients who had been followed or treated at our institution within the last two years
- Patients who underwent a DEXA scan at our institution within the last year

Exclusion Criteria

- History of inflammatory diseases
- Compression fractures
- Inability to mobilize independently
- Active malignancy, organ failure, critical illness, or pacemaker
- Diseases affecting bone metabolism (hyperparathyroidism, thyrotoxicosis, chronic renal failure, and malabsorption syndromes etc.)
- Secondary causes of OP (chronic systemic corticosteroid use, anticonvulsant use, and long-term alcohol and tobacco consumption.)
- Infection within the last 3 months
- Incomplete diagnostic or treatment information
- History of ischemic or hemorrhagic cerebrovascular disease
- Cognitive dysfunction diagnoses such as dementia, Alzheimer's disease, known organic brain damage such as Parkinson's disease (the ability to move independently can be significantly impaired in individuals with Alzheimer's disease or Parkinson's disease. This impairment can complicate accurate positioning during DEXA scanning, which may lead to less reliable measurements of BMD. Patients with advanced Parkinson's disease and dementia are particularly at risk for developing secondary OP or osteomalacia due to an increased risk of falls and nutritional deficiencies. Additionally, these neurological diseases are often associated with chronic low-grade systemic inflammation, which may impact certain components of the CALLY index, especially CRP and albumin levels).

Laboratory Measurements

Blood samples from all patients were collected during their initial evaluation upon presentation to our clinic, prior to the diagnosis of OP or the initiation of any specific anti-osteoporotic treatment. The samples were analyzed by complete blood count using the Sysmex XN-3000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). CRP and serum albumin levels were quantified using a Roche Cobas 8000 biochemistry analyzer (Roche Diagnostics, Basel, Switzerland). In our

laboratory, reference ranges for these biomarkers were defined as follows: serum albumin, 3.5–5.2 g/dL; lymphocyte counts, 1000–4000 cells/μL; and CRP, 0–5 mg/dL. These parameters offer essential information regarding the physiological and inflammatory conditions of the subjects studied.

CALLY Index

The CALLY index was determined using a specific formula that takes into account the serum albumin level (in g/dL), lymphocyte count (in cells/μL), and CRP level (in mg/dL). The formula is expressed as follows: [serum albumin level (g/dL) × lymphocyte count (cells/μL)/CRP (mg/dL) × 10^4.

Statistics

Statistical analyses were performed using IBM SPSS version 27 (IBM, Chicago, IL, USA) to ensure a comprehensive examination of the data. The Shapiro-Wilk test was used to assess whether the data follow a normal distribution. For quantitative data that did not follow a normal distribution, descriptive statistics were presented as median values, along with their corresponding minimum and maximum values. Categorical variables were reported as n (%). The Kruskal–Wallis test was used to analyze non-normally distributed data from two or more independent groups, followed by post hoc Dunn-Bonferroni tests to identify significant pairwise differences between groups. Spearman's rank correlation test was used to assess correlations in non-parametric data. A significance level of $\alpha = 0.05$ was set for all statistical tests conducted.

Results

The study included 337 female patients, all of whom underwent bone measurements. The participants were categorized into three distinct groups based on their bone health: 86 patients were classified as having normal bone density, 144 were identified as having osteopenia and 107 patients were diagnosed with OP, The mean ages of the OP, osteopenia, and control groups were 67.4 ± 10.1, 59.8 ± 11.2, and 55.2 ± 10.3, respectively ($p < 0.001$) (Table 1). In the normal group, 18 patients (20.9%) had no comorbidities. In the osteopenia group, 29 patients (20.1%) had no comorbidities, compared with 14 patients (13.1%) in the OP group. Patients in the study presented with various comorbid conditions, including diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and asthma. Statistical analysis indicated that lymphocyte levels, age, urea, T-score, and albumin levels were significantly reduced in the groups studied ($p < 0.05$). When comparing CALLY index scores, "no statistically significant difference was found in the CALLY index between the groups ($p = 0.130$) (Figure 1). T-scores, the standard measures derived from BMD assessments, play a crucial role in diagnosing and staging OP. In this context, we found low, non-significant correlation between the CALLY index and T scores ($r = 0.063$, $p = 0.251$).

Discussion

The current paradigm of OP pathogenesis has evolved beyond mechanical considerations to encompass complex inflammatory interactions. While traditionally associated with aging, this systemic skeletal disorder demonstrates variable onset patterns, which are influenced by a complex interplay among metabolic, endocrine, and inflammatory factors (6,7). Particularly compelling is the growing evidence implicating chronic low-grade inflammation as a key driver of accelerated bone remodeling and microarchitectural deterioration (8). Clinical observations consistently reveal spatial associations between inflammatory states and bone loss patterns, where systemic

Table 1. Distribution of variables by group

	Normal	Osteopenia	Osteoporosis	Total	p-value
Age (year)	55.2 ± 10.3	59.8 ± 11.2	67.4 ± 10.1	62.0 ± 12.1	**p < 0.001**
Urea (mg/dL)	30.43 ± 11.11	35.47 ± 15.47	38.94 ± 14.60	35.24 ± 14.51	**p < 0.001**
Creatinine (mg/dL)	0.71 ± 0.18	0.76 ± 0.34	0.72 ± 0.26	0.73 ± 0.28	0.728
Ca (mg/dL)	9.49 ± 0.42	9.44 ± 0.48	10.34 ± 9.64	9.74 ± 5.45	0.534
Vitamin D (ng/mL)	19.31 ± 8.78	21.53 ± 10.21	21.24 ± 11.10	20.87 ± 10.18	0.378
Height (meter)	1.55 ± 0.6	1.54 ± 0.5	1.53 ± 0.6	1.54 ± 0.6	0.328
Weight (kg)	78.90 ± 13.55	76.47 ± 12.03	74.45 ± 13.77	76.45 ± 13.07	0.148
BMI (kg/m^2)	32.90 ± 6.94	32.34 ± 5.26	31.94 ± 5.90	32.35 ± 5.93	0.812
T-score	-0.01 ± 0.7	-1.6 ± 0.6	-3.1 ± 0.9	-1.7 ± 1.4	**p < 0.001**
Kymphocyte (cells/μL)	2.60 ± 2.62	2.28 ± 0.76	1.96 ± 0.73	2.26 ± 1.48	**0.001**
CRP (mg/L)	7.28 ± 13.22	5.53 ± 6.60	7.83 ± 19.02	6.71 ± 13.34	0.771
Albumin (g/dL)	4.15 ± 0.26	4.03 ± 0.34	3.97 ± 0.38	4.04 ± 0.34	**0.003**
CALLY index	0.38 ± 0.49	0.34 ± 0.31	0.33 ± 0.38	0.35 ± 0.38	0.130
Comorbid diseases, n (%)	68 (79.9%)	115 (79.1%)	93 (86.9%)	336 (81.9%)	

BMI: Body mass index, Ca: Calcium, CRP: C-reactive protein, CALLY: C-reactive protein-albumin-lymphocyte

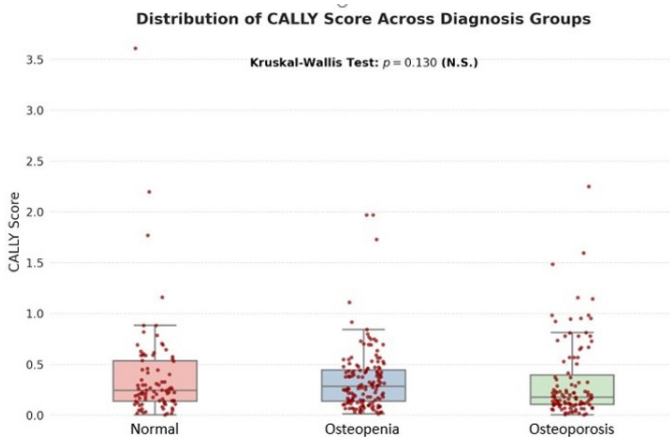

Figure 1: Relationship of CALLY index values between the groups

CALLY: C-reactive protein-albumin-lymphocyte

inflammation is associated with generalized OP, while localized inflammatory processes are associated with regional reductions in bone density (7).

Among the investigated inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) provides unique insights by simultaneously reflecting two immune pathways: neutrophilia, indicating active inflammation, and lymphopenia, suggesting an impaired stress response. Multiple research groups have reported significantly elevated NLR in osteoporotic patients compared with both osteopenic individuals and healthy controls, lending credence to the inflammation-OP hypothesis (9). However, the inflammatory landscape appears more complex when examining other hematological indices. Kim et al. (10) and colleagues identified a positive correlation between platelet count and BMD specifically in postmenopausal women, while Fang et al. (11) team observed concurrent elevations in the platelet-to-lymphocyte (PLR), monocyte-to-lymphocyte (MLR), and NLR ratios in patients with OP. These findings were extended by Zhang et al.(12) who demonstrated negative correlations of PLR, SII, MLR, and NLR with BMD measurements.

Not all studies support these associations, however. Eroglu et al. (13) reported a significantly increased PLR but an unchanged NLR in their OP cohort, while Dost Sürücü et al. (14) found no meaningful differences in either NLR or PLR between the study groups. Similarly, SII failed to show significant discriminatory value in assessing OP risk (15). These inconsistent findings have driven the search for more reliable inflammatory biomarkers in bone health evaluation.

The CRP-albumin axis has emerged as particularly promising in this context. Multiple lines of evidence confirm that elevated CRP levels not only correlate with reduced bone density but also independently predict osteoporotic fracture risk (16). Concurrently, research demonstrates that decreased serum albumin levels are significantly associated with reduced BMD (17,18). When combined to form the CAR, these markers show an enhanced predictive capacity for bone loss, with particularly strong negative correlations observed in postmenopausal women undergoing DXA assessment (19). Collectively, these findings strongly support the involvement of subclinical systemic inflammation in the development of OP (20).

Building on this evidence, our study investigated the novel CALLY index in postmenopausal OP. To our knowledge, this represents the first evaluation of this inflammatory marker in bone health assessment. Our analysis found no statistically significant difference in the CALLY index between the OP and control groups. However, we identified significant differences in other parameters, including age, urea levels, albumin levels, lymphocyte counts, and T-score. Several factors may explain the lack of a significant difference in the CALLY index. These include the presence of a low-grade, subclinical inflammatory process associated with OP, the limited discriminative ability of the index components (especially CRP) in this context, and the potential impact of various comorbid conditions on inflammatory processes and, consequently, on the CALLY index. Additionally, OP is recognized not only as an inflammatory condition but also as one affected by hormonal and mineral imbalances. The CALLY index may have limited diagnostic value in non-inflammatory subtypes of OP.

The older age of the OP group indicates that the prevalence of OP increases with age. Additionally, the lower T score validates the study's diagnostic criteria and confirms the reliability of the grouping.

We observed significant differences in albumin and lymphocyte levels between the groups. Notably, the OP group had the lowest median values for both parameters. Low albumin levels indicate the presence of subclinical inflammation and suggest metabolic and inflammatory interactions that contribute to the development of OP linked to malnutrition. Additionally, the significantly lower lymphocyte count observed in the OP group, which tends to decrease during chronic inflammation, reflects the influence of inflammatory and immunological processes on bone metabolism.

Study Limitations

The limitations of our study include its single-center, retrospective design and relatively small sample size. Additionally, we were unable to control for all potential confounding factors, such as medication use and comorbidities. We also did not conduct parallel assessments of other inflammatory markers, including NLR, PLR, SII, and CAR. Furthermore, the lack of a comprehensive correlation analysis between the CALLY index and T scores at various anatomical sites represents a significant limitation of the study.

Conclusion

Significantly lower levels of albumin and lymphocytes in the OP groupcompared with the normal groupunderscore the importance of these parameters in bone loss. However, the CALLY index, which combines these parameters, does not seem to provide adequate differentiation for assessing the low-grade systemic inflammation associated with OP. Prospective studies with larger sample sizes will help clarify the role of the CALLY index with respect to subclinical inflammation in the etiology of OP.

Ethics

Ethics Committee Approval: The research was conducted following ethical approval from the University of Health Sciences Türkiye, Elazığ Fethi Sekin City Hospital Non-interventional Ethics Committee, which was obtained on (approval number: 2025/3-8, dated: 06.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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ORIGINAL RESEARCH

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Atrial Fibrillation Doesn't Come Alone: The Geriatric Syndromes Behind the Arrhythmia

Huzeyfe Arıcı, Serdar Özkök, Tuğba Erdoğan, Denizler Sezer, Neslihan Hazel Önür, Deniz Seyithanoğlu, Cihan Kılıç, Hümeyra Özalp, Gülistan Bahat, Mehmet Akif Karan

İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, İstanbul, Türkiye

Abstract

Objective: Atrial fibrillation (AF) is a frequent arrhythmia in older adults; geriatric syndromes, which are prevalent in this population, may influence AF outcomes. This study aimed to uncover the independent associations between AF and key geriatric syndromes in a real-world outpatient population.

Materials and Methods: This retrospective cross-sectional study examined patients aged 65 years or older who underwent comprehensive geriatric assessment at a tertiary-care outpatient clinic between 2012 and 2024. Univariate and multivariate analyses were performed to examine the associations between AF and geriatric syndromes.

Results: In 1251 patients the mean age was 75.7 ± 6.8 years, and 68.5% were female. AF prevalence was 11.5% (n = 145). Patients with AF (those whohad a current diagnosis of AF or in whom AF was newly detected during routine annual ECG screening) were older (mean age 77.9 ± 7.4 years) andwere predominantly female (73.1%). AF was significantly more prevalent in patients with frailty ($p < 0.001$), polypharmacy (defined as ≥5 drugs;$p < 0.001$), and constipation ($p = 0.039$). In multivariate analysis, advanced age [odds ratio (OR): 1.041, 95% confidence interval (CI): 1.011–1.072; $p = 0.007$], frailty (OR: 2.029, 95% CI: 1.337–3.080; $p < 0.001$), and polypharmacy (OR: 2.961, 95% CI: 1.789–4.900; $p < 0.001$) were independently associated with AF.

Conclusion: AF in older adults is not an isolated cardiac event but an indicator of broader geriatric vulnerability. Our findings indicate important associations between frailty, polypharmacy, and AF. These results underscore the critical need to shift from rhythm-focused care to a holistic, geriatric-centered approach in managing older adults with AF.

Keywords: Geriatric syndromes, atrial fibrillation, disability, polypharmacy

Introduction

Atrial fibrillation (AF) is the predominant sustained cardiac arrhythmia in clinical practice, characterized by disorganized atrial electrical activity leading to an irregular ventricular response and the loss of effective atrial contraction. The frequency of AF increases significantly with age, affecting approximately 4.2% of individuals aged 60–70 years and 17% of individuals aged 80 years or older (1,2). Community- and hospital-based studies confirm a prevalence of >25% among the very old (3). A large retrospective cohort study found that nearly one-third (29.8%) of older adults had documented AF, highlighting its substantial burden in geriatric populations (4). Importantly, AF is associated with significant morbidity and mortality in older adults, including increased risk of ischemic stroke, heart failure, functional decline, and diminished quality of life (3,5).

The management of AF in older adults is particularly challenging due to the high prevalence of multimorbidity, polypharmacy, and a constellation of age-related vulnerabilities collectively known as geriatric syndromes. Geriatric syndromes are multifactorial clinical conditions not attributable to discrete diseases but resulting from cumulative deficits in multiple organ systems. Epidemiological studies reveal that over 90% of community-dwelling older adults have at least one geriatric syndrome, and approximately 70–75% have two or more concurrent geriatric

Address for Correspondence: Huzeyfe Arıcı, MD, İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, İstanbul, Türkiye
E-mail: huzeyfearicii@gmail.com **ORCID:** orcid.org/0000-0003-4128-8533
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syndromes (6,7). The burden of geriatric syndromes increases with age and is strongly linked to negative consequences such as hospitalization, institutionalization, poor quality of life, and increased mortality (8,9).

Despite their clinical importance, few studies have investigated the relationship between geriatric syndromes and AF. Most contemporary guidelines address rhythm and rate control, anticoagulation, and risk stratification, but they do not adequately address how geriatric syndromes may impact clinical presentation, treatment decisions, and outcomes.

It is essential to determine the prevalence of AF and of the geriatric syndromes independently associated with AF among older adults to raise AF awareness and promote a more comprehensive AF management approach. Notably, this aligns with the recent shift emphasized by geriatric guidelines from a disease-based to a patient-centered approach. In this context, the purpose of our study is to assess the prevalence of AF in the older population and to identify the conditions and geriatric syndromes associated with AF.

Materials and Methods

Study Population

The study population consisted of community-dwelling older adults aged ≥65 years who underwent a comprehensive geriatric assessment between January 2012 and December 2024. Exclusion criteria were as follows: (i) being under 65 years of age; (ii) refusing to participate; (iii) any condition that might impair valid communication or data collection (e.g., profound hearing loss, severe depression, or psychosis); (iv) severe edema, metal implants, or cardiac pacemakers that would interfere with BIA measurement; and (v) conditions such as osteoarthritis, peripheral arterial disease, or stroke that would interfere with HGS measurement. Patients with complete documentation regarding AF status and geriatric syndrome variables were included in the analysis. The diagnosis of AF was based on physician-confirmed documentation or electrocardiographic evidence recorded in patient files. Patients with missing key clinical variables or with uncertain rhythm status were excluded. Informed consent was obtained from all participants. The study was approved by the İstanbul Faculty of Medicine Clinical Research Ethics Committee (reference number: 3580336, decision number: 18, date: 05.09.2025).

Geriatric Syndromes

All participants were assessed using standard comprehensive geriatric assessment tools. The selection of geriatric syndromes for this study was guided by their clinical relevance and the presence of robust diagnostic criteria:

Basic and instrumental functional status were evaluated using the Katz Activities of Daily living (ADL) scale and the Lawton instrumental ADL (IADL) scale, respectively. For ADL, a score of 1 was assigned if the participant was able to perform it independently, and 0 if assistance was required or if the participant was totally unable to perform it, yielding a total score between 0 (complete dependence) and 6 (full independence) (10). For IADL, each item was scored 1 (independence) or 0 (dependence), producing a total score ranging from 0 (complete dependence) to 8 (full independence) (11). Participants' ADL and IADL scores were evaluated separately; failure to obtain full scores on either assessment was interpreted as dependency.

The FRAIL scale is a simple 5-item questionnaire used to screen for frailty in older adults. It covers fatigue, resistance, ambulation, illness, and weight loss. Scores ≥3 were considered frail, scores of 1–2 were considered pre-frail, and scores of 0 were considered robust (12). In our study, patients with a score of 3 or higher were considered frail. Polypharmacy is defined as the regular use of five or more prescribed medications. (13).

The mini-mental state examination (MMSE) is a commonly employed cognitive screening instrument designed to evaluate cognitive status and identify potential impairments in older adults. It assesses orientation, attention, memory, language, and visuospatial skills and has a maximum possible score of 30. A score of 24 is interpreted as "cognitive impairment" (14).

The geriatric depression scale (GDS-30) is a 30-item self-report assessment tool developed to screen older adults as part of preventive measures. Questions are answered with "Yes" or "No", and 20 of the 30 questions examine depressive feelings; each depressive response is assigned 1 point. The total score ranges from 0 to 30. Patients scoring 14 or higher were included in the study (15,16).

Sarcopenia is characterized by the presence of both reduced skeletal muscle mass index (SMMI) and diminished handgrip strength (HGS). HGS was measured with a Jamar hydraulic dynamometer following a standardized protocol: participants were seated with the elbow flexed to 90° and the wrist in a neutral position. Each participant completed three maximal efforts with each hand, and the measurements were averaged. Cut-off values for HGS were taken from a study conducted by Bahat et al. (17) (32 kg for men and 22 kg for women). BIA assessments were performed using the Tanita BC-532. Measurements were taken with the patients fasting, with their bladders emptied, and with no metal objects (e.g., earrings, rings, watches, belts) on their bodies; patients were in the supine position with their extremities not touching the body. Fat-free mass (FFM) in the patients was assessed using the bioelectrical impedance analysis (BIA). Skeletal muscle mass (SMM) was calculated using the formula FFM × 0.566. The equation SMM (kg)=0.566×FFM was validated using both individual and group data obtained from

a cohort of healthy subjects (18). SMMI was calculated using the formula: SMMI (%) = [SMM (kg)/body mass (kg)] × 100 (19). Cut-off values for SMMI were also taken from a study conducted by Bahat et al. (20) (%37.4 for men and %33.6 for women).

The mini nutritional assessment–short form (MNA-SF) is a validated 6-item screening tool designed to identify malnutrition or the risk of malnutrition in older adults. Standard cut-offs were applied: 12–14 normal, 8–11 at risk, and 0–7 malnourished. In this study, patients with scores of 7 or less were evaluated (21).

Patients were considered to have urinary incontinence if they reported involuntary urine loss that occurred at least once weekly, persisted over time, and affected their daily functioning or well-being (22).

Patients with involuntary loss of solid or liquid stool or gas, occurring more than once per week and causing functional or psychological impairment, were considered to have fecal incontinence (23). For study eligibility, constipation was defined according to the Rome IV criteria (24).

Statistical Analysis

Descriptive statistics were applied to characterize the study population. Continuous variables were presented as mean ± standard deviation or as median with interquartile range according to their distribution, whereas categorical variables were reported as frequencies and percentages.

Comparisons of categorical variables between patients with and without AF were performed using the Pearson chi-square ($\chi 2$) test to determine whether AF was significantly associated with each geriatric syndrome.

Variables that were significant in the univariate analysis were subsequently entered into a binary logistic regression model to identify independent predictors of AF. Multicollinearity among the potential confounders was assessed before their inclusion in the same model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. For all analyses, a p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 2,320 older adults who underwent comprehensive geriatric assessment between January 2012 and December 2024 were screened for study eligibility. After excluding cases with missing or incomplete data, 1,251 patients were included in the final analysis. Of these participants, 857 (68.5%) were female and 394 (31.5%) were male. The overall prevalence of AF in the study population was 11.5% (n = 145). Among individuals with AF, the mean age was 77.9 ± 7.4 years, and 106 patients (73.1%) were predominantly female. Other demographic data for the patients are presented in Table 1.

Descriptive statistics of geriatric syndromes showed that, among 1,251 participants with complete data the prevalence of frailty (38.9% vs. 18.8%; $p < 0.0001$), polypharmacy (84.7% vs. 61.4%; $p < 0.0001$), ADL (37.2% vs. 26.7%; $p = 0.0076$), and IADL (51.7% vs. 35.2%; $p = 0.0001$) in the group with AF were higher than in patients without AF. All detailed counts, percentages, and p-values for these variables are provided in Table 2.

Bivariate analyses using Pearson's chi-square test identified the following geriatric syndromes as significantly associated with AF: frailty ($p < 0.001$), polypharmacy ($p < 0.001$), disability ($p = 0.001$) and constipation ($p = 0.039$). Other chi-square analyses and p-values are shown in Table 3. A binary logistic regression was conducted to identify the independent predictors of AF, with age, female sex, frailty, polypharmacy, and constipation included as covariates. The regression model showed that age, polypharmacy, and frailty were significantly associated with AF ($p = 0.007$, $p < 0.001$, and $p < 0.001$). Neither female sex nor constipation was not significantly associated with AF ($p = 0.504$ and $p = 0.408$). P-values and other statistical data for all parameters are presented in Table 4.

Discussion

Table 1. Demographics of patient with and without atrial fibrillation.

Overall	Without AF	With AF
Total, n = 1251	1106	145
Age	75.4 ± 6.8	77.9 ± 7.4
Sex		
Women	67.9%	73.1%
Men	32.1%	26.9%
Marital status		
Married	54.6%	48.6%
Widow	40.1%	49.3%
Single	2.7%	%0.7%
Number of chronic diseases	3.7 ± 1.9	5.0 ± 1.9
Number of medications used	5.9 ± 3.4	7.4 ± 3.0
DM	33.2%	34.5%
MI	1%	2.8%
HT	71.7%	80.0%
CAD	19.5%	29.7%
CHF	4.5%	23.4%
CKD	5.3%	9.0%
COPD	5.3%	10.3%

n: number, AF: Atrial fibrillation, DM: Diabetes mellitus, MI: Myocardial infarction, HT: Hypertension, CAD: Coronary artery Disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease.

AF represents the most frequent sustained cardiac arrhythmia among older adults, with prevalence increasing significantly with age. Additionally, AF contributes substantially to morbidity and mortality through thromboembolic events, heart failure, and functional decline (25). In parallel, geriatric syndromes are increasingly recognized as predictors of adverse outcomes in older adults, including hospitalization, institutionalization, and death (8,9). However, few studies have addressed the prevalence of these geriatric syndromes in older adults and their association with AF.

Table 2. Frequency of geriatric syndromes in the study population.

Geriatric syndrome AF	With AF	Without AF
ADL	37.2%	26.7%
IADL	51.7%	35.2%
Frailty	38.9%	18.8%
Polypharmacy	84.7%	61.4%
Sarcopenia	45.9%	48.0%
Depression	40.0%	31.7%
Cognitive impairment	22.7%	17.9%
Malnutrition	1.4%	4.5%
Urinary incontinence	50.3%	42.2%
Fecal incontinence	8.3%	5.2%
Constipation	38.6%	30.2%

AF: Atrial fibrillation, ADL: Activities of daily living, IADL: Instrumental activities of daily living.

Table 3. Univariate logistic regression analyses regarding the factors associated with AF.

Geriatric syndrome p-value	OR	95% CI
Frailty <0.001	2.76	1.91–3.98
ADL 0.007	1.63	1.14–2.34
IADL <0.001	1.97	1.39–2.80
Polypharmacy <0.001	3.48	2.17–5.57
Constipation 0.039	1.45	1.02–2.08
Depression 0.09	1.44	0.94–2.18
Cognitive impairment 0.242	1.31	0.83–2.06
Malnutrition 0.074	0.29	0.07–1.22
Urinary incontinence 0.068	1.38	0.98–1.95
Fecal incontinence 0.136	1.63	0.85–3.11
Sarcopenia 0.931	0.92	0.64–1.32

n: number, ADL: Activities of daily living, IADL: Instrumental activities of daily living, OR: Odds ratio, CI: Confidence interval, AF: Atrial fibrillation.

In our analysis, frailty was independently associated with AF. This is consistent with multiple studies demonstrating that frailty is a key correlate of AF in older populations. Similarly, Shah et al. (26) performed a national cross-sectional analysis in the United States using Medicare data and found that frailty was present in 38% of patients with AF, significantly higher than among those without AF. They showed that each additional syndrome was associated with decreased anticoagulant use. However, that work did not test the AF–frailty association but rather examined how the syndrome burden modifies treatment patterns in an AF population. Our data complement these findings by demonstrating that in a real-world geriatric referral sample with substantial multimorbidity and high medication burden, frailty co-occurs with AF. This observation is clinically consistent with Shah et al.'s (26) emphasis on the complex intersection between geriatric syndromes and AF management. Differences in study population (community-dwelling, survey-weighted vs. specialty clinic), outcome focus (treatment use vs. AF–frailty link), and case selection likely explain the divergent emphases. In the Framingham Heart Study, Orkaby et al. (27) conducted a prospective analysis of 1,163 community-dwelling older adults and found no significant association between baseline frailty and incident AF over approximately 9.2 years, nor any link between prevalent AF and subsequent frailty. Their patients were younger and healthier on average (mean age approximately 70 years; lower multimorbidity) than our sample (mean age approximately 78 years; higher multimorbidity). Frailty was defined using the Fried phenotype, whereas we used the FRAIL score. The study designs also differed: Framingham used a longitudinal, incidence-based design with competing-risk modeling, whereas our analysis used a cross-sectional, prevalence-based design. Finally, community sampling may introduce survivor or selection effects, while a tertiary geriatric clinic concentrates patients with accumulated deficits, polypharmacy, and functional loss. Together, these factors tend to dilute frailty–AF associations in Framingham but amplify them in our setting. In another study, Shim et al. (28) examined cross-sectional and longitudinal data from a cohort of more than 4,000 older Japanese adults and reported that reduced gait speed and grip strength were associated with both prevalent and incident AF. In contrast, Koca et al. (5) observed higher, although non-significant, frequencies of frailty in AF compared to sinus rhythm when using the Fried and FRAIL scales; FRAIL scores were positively correlated with AF symptom severity. This pattern is reflected in our data. Although categorical frailty may not always distinguish between groups, AF tends to be concentrated among individuals with functional frailty. These findings underscore frailty as both a risk marker

Table 4. Multivariate logistic regression analyses regarding factors independently associated with AF.

Variable	p-value	Odds ratio	95% CI lower	95% CI upper
Frailty	0.001	2.029	1.337	3.08
Polypharmacy	<0.001	2.961	1.789	4.9
Constipation	0.408	1.173	0.804	1.712
Female sex	0.504	1.151	0.762	1.738
Age	0.007	1.041	1.011	1.072

CI: Confidence interval, AF: Atrial fibrillation.

and a potential consequence of AF-associated deconditioning.

Polypharmacy (≥5 medications) was highly prevalent in our cohort and independently associated with AF. In a retrospective study of approximately 340,000 patients over the age of 75, conducted by Chen et al. (29), the prevalence of polypharmacy was found to be high in patients with AF, similar to our study. They showed that patient with ≥5 drugs at diagnosis and polypharmacy predicted more major bleeding and heart-failure hospitalization. We examined the co-occurrence of AF and polypharmacy in a CGA context, whereas Chen et al. (29) examined prognosis and treatment response after AF using claims-based exposure windows. Taken together, both perspectives argue for medication review and consideration of polypharmacy to improve safety in older adults with AF. These findings suggest that polypharmacy may not only be a marker of comorbidity but also a contributor to AF progression or complications.

Our study found that disability was significantly associated with AF. The prevalence of AF was greater among participants with disabilities than among those without, reinforcing the notion that AF is linked to functional decline in later life. Our findings are consistent with previous studies assessing functional status in older adults with AF. Wallace et al. (30) showed that incident AF shortened disability-free survival and increased the risk of subsequent ADL disability, even after accounting for interim stroke and heart failure. In our study, we observed a higher prevalence of disability and a stronger cross-sectional association, particularly for IADL. This difference is plausibly explained by case mix: our AF group has greater multimorbidity and polypharmacy, which likely depresses instrumental function first. Wallace et al. (30) provide longitudinal evidence that AF independently accelerates ADL disability; our data extend this gradient into IADL. This supports the clinical imperative to integrate decisions regarding rhythm and rate control and anticoagulation into function-focused, multimorbidity-aware care plans. Parks et al.'s (31) cohort analysis of approximately 3,500 patients found that new-onset AF was associated with an accelerated annual decline in ADL independence and walking speed, even after multivariable adjustment. In a longitudinal analysis of the ILSA study by Noale et al. (32) they followed patients for over eight years and showed that, during follow-up, baseline cardiac arrhythmia was significantly associated with an increased risk of developing ADL disability. They used a time-to-event model for any new ADL, whereas we used a full-independence-only approach. While they pooled arrhythmias, we studied only patients with AF. Their study supports arrhythmia as a longitudinal driver of ADL disability, while our data extend the functional burden to IADL, suggesting that function-oriented management is warranted. In a cross-sectional study conducted by Koca et al. (5) 123 patients were examined: 64 had AF and 56 were in sinus rhythm. In this study, patients with AF had significantly lower IADL scores. Our study demonstrated a higher disability burden in both domains, with a stronger signal for IADL dependence. In Koca et al. (5) patients with AF were older than controls, exhibited greater multimorbidity, and had a markedly higher prevalence of coronary artery disease and heart failure. Similarly, in our study, AF patients were even older on average and—relative to our non-AF group—had more chronic diseases and used more medications; coronary artery disease and congestive heart failure were also more frequent among AF patients. Thus, Koca et al. (5) map an "instrumental-first" disability phenotype in AF, and our data extend this by showing a higher absolute prevalence in both ADL and IADL among an older, polypharmacy-laden clinic population. These findings highlight the need to incorporate function-focused goals (especially IADL support) into AF management from the outset. In another cohort study conducted by Piacenza et al. (33) with approximately 3,400 patients, cluster analysis was performed on two large disease groups. They showed that functional dependence is strongly associated with AF.

Study Limitations

One of the limiting factors of our study is its retrospective nature. Furthermore, because patients presented to a tertiary healthcare facility, they had more comorbidities and more complex conditions. This makes it difficult for the study population to be representative of the general population.

Conclusion

Our study adds to the growing evidence that geriatric syndromes, particularly frailty, polypharmacy, and disability, are closely associated with AF in older adults. Incorporating comprehensive geriatric assessment into the routine clinical management of AF

may enhance risk stratification, improve therapeutic decision-making, and ultimately optimize outcomes. Future longitudinal studies are needed to better characterize the causal pathways linking specific geriatric syndromes to AF incidence, progression, and prognosis.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Faculty of Medicine Clinical Research Ethics Committee (reference number: 3580336, decision number: 18, date: 05.09.2025).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.K., H.Ö., Concept: S.Ö., G.B., M.A.K., Design: T.E., M.A.K., Analysis or Interpretation: H.A., D.S., N.H.Ö., Literature Search: H.A., D.S., Writing: H.A., S.Ö.

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ORIGINAL RESEARCH

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Handgrip Strength Thresholds for Predicting Independent Walking Ability After Hip Fracture Surgery in Mexican Elderly: A Prospective Cohort Study

Andrea Maria Fuentes Sanchez[1], Wendy Valenzuela Sanchez[1], Hector Eduardo García Cavazos[1], Michael R. McClung[2], Hugo Gutierrez Hermosillo[3], Enrique Diaz de Leon Gonzalez[1]

[1]Unidad Médica de Alta Especialidad Hospital de Traumatología y Ortopedia No. 21, Instituto Mexicano del Seguro Social, Monterrey, Nuevo León, México
[2]Oregon Osteoporosis Center, Oregon, United States
[3]Escuela Nacional de Estudios Superiores, Unidad León, Universidad Nacional Autónoma de México, Guanajuato, Mexico

Abstract

Objective: Hip fractures are commonly associated with disability, and muscle strength is an independent prognostic factor for functionality and walking ability. Handgrip strength (HGS) measurement represents an easy and economical strategy for estimating muscle strength and establishing a functional prognosis in elderly patients with hip fractures. Currently, there are no HGS thresholds in the Mexican population to ascertain functional outcomes, such as independent walking ability. The objective was to determine a cut-off point associated with independent walking ability.

Materials and Methods: Prospective cohort study that included hospitalized patients older than 60 years for hip fracture. HGS was measured next day of surgery. Cognitive, functional, and nutritional status were also assessed, as well as comorbidities and walking ability. Logistic regression was employed to confirm the association with independent walking.

Results: We included 185 patients, 61 men and 124 women, with 34 individuals (18.3%) capable of independent walking. Participants with high HGS were younger, had lower comorbidity scores, and displayed higher functional pre-fracture scores. The thresholds for predicting independent walking were ≥12 kg for women and ≥19 kg for men. High HGS and lower comorbidity scores were independently associated with independent walking.

Conclusion: HGS in the Mexican population predicts independent walking after hip fracture surgery.

Keywords: Clinical geriatrics, elderly, falls, frailty, gait, geriatric trauma, handgrip strength, hip fracture, sarcopenia

Introduction

Hip fractures in older adults represent a significant public health issue owing to a marked increase in incidence over the past two decades, resulting from aging populations, increased longevity, and a higher prevalence of osteoporosis (1). This trend is expected to continue globally in the coming years, placing pressure on healthcare systems and families due to the challenges of demographic shifts and resource limitations, thereby imposing a substantial economic burden (2). Hip fractures significantly impair patients' functional status. For instance, up to 80% of patients who survive an initial hospitalization for a hip fracture experience permanent disability (3), and 40% do not regain the ability to walk independently (4).

Several factors influence functional outcomes following a hip fracture (2,5), with muscle strength being one of the most critical for physical recovery (6). Handgrip strength (HGS) is a measurable indicator of overall muscular strength and physical capability and has prognostic value for survival (7) and for functionality (8–13).

Address for Correspondence: Enrique Diaz de Leon Gonzalez, Unidad Médica de Alta Especialidad Hospital de Traumatología y Ortopedia No. 21, Instituto Mexicano del Seguro Social, Monterrey, Nuevo León, México.
E-mail: edleon20@hotmail.com **ORCID:** orcid.org/0000-0002-8567-2206
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However, there are notable ethnic differences in HGS (14), suggesting that prognostic cut-off points may vary depending on the population investigated. In Mexico, studies have examined the associations among HGS, functionality, and complications in hospitalized elderly patients (15,16). Although evidence suggests that higher HGS is associated with independent walking, no specific cut-off points have been established in the Mexican population because of a lack of prognostic studies. Therefore, this study aimed to determine an HGS cut-off point associated with independent walking recovery in Mexican subjects with hip fracture.

Materials and Methods

Study Design

The current cohort study was conducted in the Hip and Pelvic Surgery Department at the Unidad Médica de Alta Especialidad Hospital de Traumatología y Ortopedia No. 21, from the Mexican Institute of Social Security (IMSS), located in Monterrey, Mexico. Ambulatory adults aged ≥60 years who were hospitalized for hip fracture surgery between February and June 2022 were invited to participate; those who accepted and signed informed consent were included in the study. Patients with pathological fractures and those lost to follow-up were excluded. The study was reviewed and approved by the Local Health Research Committee No. 1903 of the IMSS (institutional registration number: R-2022-1903-001, date: 01.03.2022).

Variables

Data pertaining to social and demographic characteristics, such as age and sex, were extracted from medical records. Functional capacity before the fracture, mental status, and nutritional status were evaluated using the Barthel index (17), the short portable mental status questionnaire (18), and the mini nutritional assessment (MNA) scale, respectively (19). Finally, Charlson's comorbidity index (20), the FRAIL (21), and SARCF (22) scales were employed to measure comorbidity, frailty, and probable sarcopenia risk. The body mass index (BMI) was calculated from self-reported weight and height.

Handgrip Strength

HGS assessments were performed by a qualified physician on the first day following hip fracture surgery, with measurements documented for both hands while the patient was in bed and the elbow flexed at 90 degrees. The evaluation utilized a Jamar® Electronic Hand Dynamometer, following the method outlined by Gumieiro et al. (23). For the analysis, the maximum grip strength value was used, as indicated by the Asian Working Group for sarcopenia (24).

Walking Recovery

Walking recovery was assessed primarily via standardized telephone interviews with participants or caregivers. When telephone contact was unsuccessful after three attempts, electronic medical records were reviewed. Independent walking was defined as the ability to ambulate without personal assistance, six months after discharge (11). The same operational definition was applied to both telephone- and record-based assessments. Patients lost to follow-up were excluded from the analysis.

Statistical Analysis

Descriptive statistics were employed to characterize the study population. Qualitative variables were summarized as absolute frequencies and percentages, whereas quantitative variables were expressed as medians and interquartile ranges, because most did not follow a normal distribution (Kolmogorov–Smirnov and Shapiro–Wilk tests, $p < 0.05$). Group comparisons were performed using the Mann–Whitney U test for quantitative variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of HGS to predict recovery of independent walking. The Youden index was used to determine the optimal cut-off point. We conducted a binary logistic regression analysis, incorporating predictors such as age, gender, BMI, nutritional status, frailty, multimorbidity, and probable sarcopenia. These predictors were selected a priori based on their clinical relevance and were entered simultaneously into the multivariable logistic regression using the ENTER method. Goodness-of-fit was assessed with the Hosmer–Lemeshow test and pseudo-R^2 indices. Multicollinearity was assessed using the variance inflation factor (VIF) and the condition index. VIF values <2.5 and condition index values <30 were considered acceptable thresholds. All predictors met these criteria, indicating no relevant collinearity. Associations between HGS and other variables were reported as odds ratios derived from logistic regression models.

The sample size was calculated assuming an alpha level of 0.05, statistical power of 0.80, proportion one of 0.10, and proportion two of 0.40, yielding a minimum of 32 participants per group. A p-value <0.05 was considered statistically significant. All analyses were conducted using Stata/SE version 18 (Stata Corporation, College Station, TX, USA).

Results

Results of the Receiver Operating Characteristic Area Analysis

The study included 185 participants (61 men and 124 women), with 34 individuals (18.3%) capable of independent walking. ROC analysis demonstrated that maximal HGS had significant

discriminatory power in identifying individuals capable of independent ambulation in both male and female participants (Figure 1 and Table 1). The optimal cut-off values, as determined by the Youden index, were 19.5 kg for men and 12.05 kg for women. For practical application in clinical settings, these values were rounded to 19 kg and 12 kg, respectively, as fractional thresholds are not typically used at the bedside. This rounding did not significantly impact sensitivity, specificity, or likelihood ratios, which remained consistent with the Youden-derived cut-offs. In this cohort, the optimal thresholds derived from the Youden Index effectively distinguished participants who regained independent walking ability. When these values were applied, men with higher HGS exhibited excellent sensitivity and acceptable specificity, while women demonstrated moderate sensitivity and specificity. The likelihood ratios indicated a clinically meaningful increase in the probability of independent walking for those exceeding the cut-off, with consistent performance observed across both sexes.

General Characteristics and Grip Strength Measures

Individuals with lower HGS tended to be older and to have higher Charlson's Comorbidity Index scores and lower pre-fracture Barthel Index scores. These individuals also exhibited poorer cognitive and nutritional status, and a higher prevalence of probable sarcopenia and frailty (Table 2).

Factors Associated with Independent Walking

At six months following surgery, participants exhibiting high HGS demonstrated a significantly greater likelihood of regaining independent ambulation (Table 3). Multivariate analysis identified high HGS and lower scores on the Charlson's comorbidity index as independent predictors of walking ability. The Hosmer–Lemeshow test confirmed an adequate model fit ($\chi^2 = 8.322$, df = 8, p = 0.403), and the Nagelkerke R^2 was 0.314. Multicollinearity diagnostics revealed variance inflation factor (VIF) values <2.5 and a condition index <30, indicating the absence of problematic collinearity.

Discussion

This study aimed to establish HGS thresholds associated with independent walking. As anticipated, grip strength was correlated with age, comorbidities, and functional, cognitive, and nutritional status, all of which are associated with sarcopenia, frailty, and muscle strength. These results align with findings from previous studies (1,9,11–13).

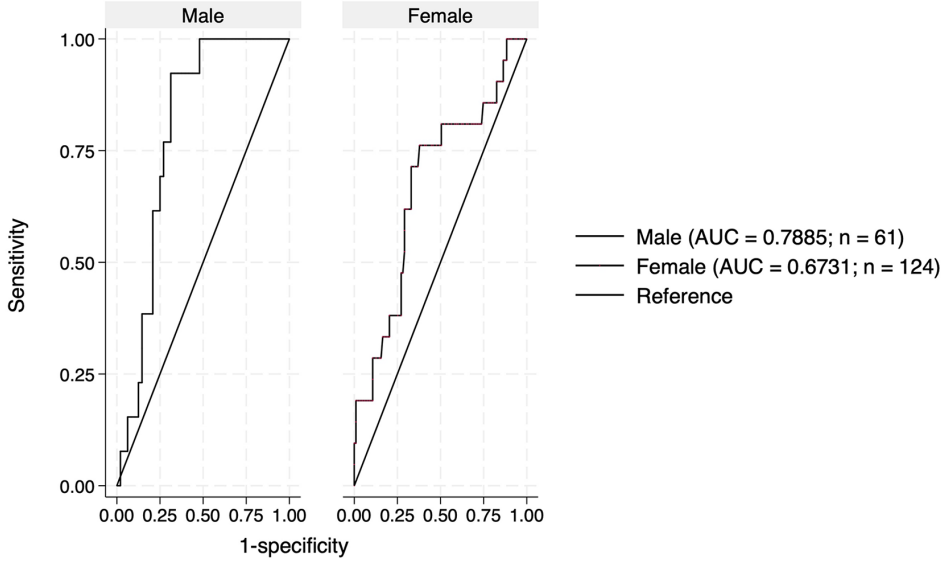

Figure 1. Sex-stratified ROC curves for maximal postoperative HGS predicting independent walking at 6 months after hip fracture surgery. AUC values and sample sizes for each sex are displayed within the figure.

ROC: Receiver operating characteristic, HGS: Handgrip strength, AUC: Area under the curve.

Table 1. Receiver operating characteristic analysis results for handgrip strength predicting independent walking recovery.

Group	Cut-off (kg)	AUC (95% CI)	Sensitivity (%)	Specificity (%)	LR+	LR-
Male	19.50	0.785 (0.683–0.886)	92.31	64.58	2.606	0.119
Female	12.05	0.682 (0.573–0.792)	71.43	65.05	2.044	0.439

Cut-off values are the Youden-optimal thresholds estimated from the continuous maximal handgrip strength analysis. Sensitivity, specificity, and AUC shown here correspond to the dichotomous predictor defined by those thresholds. For operational use in models and prospective estimates, integer thresholds were applied (19 kg in men; 12 kg in women).
AUC: Area under the curve, CI: Confidence interval; LR+: Positive likelihood ratio, LR-: Negative likelihood ratio.

Table 2. Clinical characteristics of participants according to grip strength values by sex.

Variable	Male		p	Female		p
	Low HGS n = 32	High HGS n = 29		Low HGS n = 73	High HGS n = 51	
Age in years	79 (76–84)	77 (65–79)	0.024	81 (75–87)	78 (68–83)	0.005
Type of fracture			1.0			0.552
Intracapsular	12 (37.5%)	10 (34.5%)		24 (32.9%)	13 (25.5%)	
Trochanteric	18 (56.3%)	17 (58.6%)		46 (63%)	34 (66.7%)	
Subtrochanteric	2 (6.3%)	2 (6.9%)		3 (4.1%)	4 (7.8%)	
Type of surgery			0.972			0.232
Hip replacement	12 (37.5%)	11 (37.9%)		26 (35.6%)	13 (25.5%)	
Open reduction with internal fixation	20 (62.5%)	18 (62.1%)		47 (64.4%)	38 (74.5%)	
Length of stay (days)	12 (10–16)	12 (10–14)	0.983	12 (9–14)	10 (8–14)	0.222
Days before surgery	10 (8–13)	9 (8–12)	0.954	9 (7–12)	8 (6–11)	0.189
Body mass index	24.1 (22.1–26.0)	24.3 (22.6–27.7)	0.618	23.8 (21.1–27.2)	25.8 (24.0–28.9)	0.004
Mini Nutrition Assessment (score)	22.8 (18.3–24.0)	22.5 (19.5–24.5)	0.591	21.0 (17.0–23.5)	22.5 (19.5–24.0)	0.017
Short portable mental status questionnaire	6 (3–8)	3 (1–4)	<0.001	4 (3–7)	2 (1–5)	<0.001
Pre-fracture Barthel index	90 (78–95)	95 (85–100)	0.021	80 (65–90)	95 (85–100)	<0.001
Charlson comorbidity index (score)	3 (3–4)	3 (2–3)	0.002	3 (3–4)	3 (3–4)	0.096
Sarcopenia	14 (43.8%)	7 (24.1%)	0.107 0.177	51 (69.9%)	19 (37.3%)	<0.001
Frailty status			0.012			<0.001
Frail	7 (21.9%)	1 (3.4%)		26 (35.6%)	6 (11.8%)	
Prefrail	17 (53.1%)	11 (37.9%)		43 (58.9%)	30 (58.8%)	
Robust	8 (25%)	17 (58.6%)		4 (5.5%)	15 (29.4%)	
Death	7 (21.9%)	2 (6.9%)	0.151	10 (13.7%)	2 (3.9%)	0.120
Walk without help	1 (3.1%)	12 (41.4%)	<0.001	6 (8.2%)	15 (29.4%)	0.002

Data are presented as median (interquartile range) or absolute frequencies (%).
Comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables.
Low handgrip strength was defined as <19 kg in men and <12 kg in women; high handgrip strength as ≥19 kg in men and ≥12 kg in women.
HGS: Handgrip strength.

Table 3. Logistic regression analysis for independent walking.

Variable	p-value	OR (95% CI)
High handgrip strength (ref = low HGS)	0.003	5.236 (1.788–15.331)
Age (years)	0.158	0.971 (0.933–1.011)
Female sex (ref = male)	0.774	1.152 (0.438–3.032)
Mini nutritional assessment (score)	0.135	0.896 (0.775–1.035)
Body mass index	0.158	0.922 (0.824–1.032)
Charlson Comorbidity Index (score)	0.034	0.541 (0.306–0.955)
Short portable mental status (score)	0.901	1.013 (0.821–1.251)
Pre-fracture Barthel index (score)	0.496	1.017 (0.968–1.069)
Frailty status		
-Prefrail (ref = frail)	0.630	1.544 (0.264–9.025)
-Robust (ref = frail)	0.905	1.143 (0.129–10.150)
Not sarcopenic (ref = sarcopenia)	0.325	1.906 (0.528–6.889)

All p-values were obtained through logistic regression analysis. Scores are shown as continuous variables for mini nutritional assessment, Charlson comorbidity index, short portable mental status questionnaire, and pre-fracture Barthel index. Reference categories: frail for frailty status; sarcopenia for sarcopenia status; male for sex; low HGS for handgrip strength.
OR: Odds ratio, CI: Confidence interval, HGS: Handgrip strength.

The results indicated that high HGS was positively correlated with independent walking recovery. Consistent with Savino et al. (11), our results suggest that functional capacity, measurable through HGS, has predictive value for walking outcomes. While the methodology differed—Savino et al. (11) used terciles—our thresholds closely resemble those reported by Chang et al. (20.5 kg for men and 11.5 kg for women) (13). Similarly, Hashida et al. (25) reported a cut-off of 13.2 kg in a Japanese population, supporting the robustness of our findings. According to the results obtained by Pérez-Rodríguez et al. (12), thresholds of 23 kg for men and 13 kg for women yielded comparable outcomes, albeit with slight variations attributable to population differences. García-Peña et al. (15) identified a cut-off of 20.65 kg for men in the Mexican population, consistent with our findings.

Evidence from other settings further reinforces our results. In Colombia, Toro et al. (26) demonstrated that HGS was a strong predictor of one-year mortality after hip fracture, underscoring its prognostic value in Latin American populations exposed to similar socioeconomic and healthcare constraints. Selakovic et al. (6) showed that early postoperative HGS strongly predicted functional recovery at 3 and 6 months, supporting the validity of our methodological choice to measure HGS soon after surgery. Conversely, Steihaug et al. (27) found that sarcopenia defined using combined criteria did not predict changes in mobility after hip fracture, suggesting that HGS may provide a more robust and clinically actionable indicator. Likewise, Milman et al. (28) reported that HGS independently predicted successful rehabilitation, confirming its clinical utility as a simple, low-cost tool in hip fracture care.

In contrast, the thresholds for diagnosing sarcopenia (27 kg for men and 16 kg for women) (29) are higher than our cut-off points, which reflects the frailty of our cohort, in which 75% were frail or pre-frail and 49% were sarcopenic. This vulnerability is consistent with observations made by Menéndez et al. (30). Despite numerous known predictors of functional recovery (5), this study found that only high HGS and lower comorbidity scores were significantly associated with independent walking. Although age, nutritional status (MNA), and frailty are recognized predictors of recovery after hip fracture, they did not remain independent predictors in our multivariable model (Table 3). This should be interpreted in light of methodological constraints: the limited number of outcome events reduced statistical power and widened confidence intervals, and conceptual overlap among geriatric constructs (e.g., MNA includes BMI; frailty intersects with comorbidity and functional status) may have attenuated their apparent effects when modeled simultaneously. Importantly, HGS may act as an integrative marker of overall physiological reserve, thereby capturing variance otherwise attributable to age, nutrition, or frailty. Accordingly, the absence of statistical significance for these domains likely reflects limited precision rather than a lack of clinical relevance.

Measuring HGS early post-surgery may enhance its predictive utility, as noted by Savino et al. (11). In our study, HGS was measured postoperatively, allowing the exclusion of strength loss due to bed rest (6,11) and reflecting real-world rehabilitation conditions. It is noteworthy that the cut-off values identified in this cohort were lower than those proposed by international sarcopenia criteria (27 kg for men and 16 kg for women) (29). This likely reflects the clinical vulnerability of our population—characterized by high rates of frailty and probable sarcopenia—and highlights the importance of developing population-specific thresholds. From a clinical perspective, using locally validated cut-offs may improve the identification of patients at risk of poor functional recovery, guiding earlier physiotherapy, tailored nutritional interventions, and optimized discharge planning.

HGS has proven useful for the early identification of older adults at risk of adverse outcomes, including mortality (7), functional decline (6), and pressure ulcers (1) and is a trustworthy and cost-effective tool (9,11).

This study has several strengths. First, it provides sex-specific cut-off values for HGS associated with independent walking recovery in a Mexican cohort, addressing a critical gap in evidence from Latin America. Second, it is among the few studies that combine HGS thresholds with comprehensive geriatric variables (nutritional status, cognition, comorbidity, and frailty). Third, standardized and validated tools were used for key constructs, enhancing methodological rigor. Finally, the study provides actionable thresholds that can be directly implemented during bedside assessments to support rehabilitation planning in routine clinical practice.

Study Limitations

This study has several limitations. First, the self-reported nature of height and weight data may have introduced non-differential measurement error in the calculation of BMI, potentially attenuating the effect estimates. In addition, comorbidities and health status were self-reported; however, previous research supports the reliability of these self-reports (31). Second, occupational history, which could influence grip strength, was not considered (32). Third, HGS measurement depends on participant cooperation and on proper positioning of the shoulder, elbow, and wrist (23,32). Although delirium was not systematically assessed with a dedicated tool, cognitive status was evaluated with the Pfeiffer (18) short portable mental status Questionnaire to ensure adequate participation. Nonetheless, results may still have been influenced by acute postoperative factors such as pain or sedation. While this could attenuate the accuracy of HGS as a pure measure of muscle strength, its predictive validity in this real-world context supports its role as a pragmatic, clinically applicable tool. Fourth, independent walking outcomes were assessed primarily via standardized telephone interviews and, when participants could not be reached, through review of

medical records; the same operational definition (independent ambulation without personal assistance) was applied. Although this approach was consistent, the lack of a formal validation study between telephone-based and record-based classifications introduces the possibility of misclassification bias. Fifth, five participants (2.7%) were lost to follow-up. This relatively small attrition could still introduce bias (33), particularly if losses occurred disproportionately among frailer or less-mobile patients, although this could not be formally assessed. Sixth, some confidence intervals were wide, reflecting the relatively small sample size in certain subgroups; this limits the precision of the estimates and warrants cautious interpretation. In particular, sex-specific ROC analyses were based on a limited number of positive outcomes, resulting in less stable AUC estimates and wider confidence intervals; therefore, these thresholds should be regarded as exploratory until they are validated in larger cohorts. Another important limitation is the relatively low number of events (independent walkers) compared to the number of predictors included in the logistic regression model, yielding an events-per-variable ratio below the recommended threshold. Although predictors were pre-specified based on clinical relevance and collinearity diagnostics supported model stability, limited EPV may have led to model overfitting, inflated odds ratios, and wide confidence intervals. Additionally, sarcopenia was assessed only with the SARC-F screening tool, without objective measures of muscle mass or physical performance, and thus, results should be interpreted as indicating probable sarcopenia risk rather than confirmed sarcopenia. Finally, this single-center study, conducted in Monterrey, Mexico, had local rehabilitation resources and social support structures, which may limit the generalizability of our findings to other populations and healthcare systems. Therefore, new multicenter studies are warranted to validate the proposed cut-off points and to adapt them to diverse clinical contexts.

Conclusion

HGS obtained shortly after hip-fracture surgery provides a practical indicator of 6-month independent ambulation. Using simple, sex-specific thresholds, clinicians can flag patients who may benefit from earlier, more intensive rehabilitation, potentially reducing the substantial burden of persistent mobility loss on patients, families, and the healthcare system. Future work should validate these thresholds and assess their impact on care pathways.

Ethics

Ethics Committee Approval: The study was reviewed and approved by the Local Health Research Committee No. 1903 of the Mexican Social Security Institute (IMSS) (institutional registration number: R-2022-1903-001, date: 01.03.2022).

Informed Consent: Informed consent was obtained from all participants prior to their inclusion in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.F.S., H.E.G.C., M.R.M., H.G.H., E.D.d.L.G., Concept: A.M.F.S., W.V.S., H.E.G.C., M.R.M., Design: A.M.F.S., W.V.S., H.E.G.C., M.R.M., E.D.d.L.G., Data Collection or Processing: H.E.G.C., M.R.M., Analysis or Interpretation: A.M.F.S., W.V.S., H.E.G.C., M.R.M., H.G.H., E.D.d.L.G., Literature Search: A.M.F.S., W.V.S., H.E.G.C., M.R.M., H.G.H., Writing: A.M.F.S., W.V.S., H.E.G.C., M.R.M., H.G.H., E.D.d.L.G.

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ORIGINAL RESEARCH

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Mortality Prediction of C-Reactive Protein/Albumin Ratio in Non-Cancer Patients in Palliative Care

İbrahim İleri

Ordu State Hospital, Department of Internal Medicine, Division of Geriatric Medicine, Ordu, Türkiye

Abstract

Objective: The C-reactive protein/albumin ratio (CAR) is used to assess the severity of inflammation. It can provide prognostic information for many diseases. CAR is a more sensitive predictor of systemic inflammatory status than the separate evaluation of these 2 parameters. In this study, we investigated the ability of CAR to predict mortality in non-cancer patients followed in the palliative care service.

Materials and Methods: Patients admitted to the palliative service between November 1, 2024, and May 1, 2025 were included. Patients with active rheumatological disease, active infection, cancer, or those transferred to other units during the study were excluded. It was a prospective study involving 200 patients.

Results: The median CAR value in the non-survivor group was 4.04 [interquartile range (IQR) 5.05]. This value was 1.89 (2.99) IQR in the survivor group ($p \leq 0.001$). Logistic regression analysis showed that a high CAR value and a diagnosis of cerebrovascular disease (CVD) are risk factors affecting palliative care mortality in non-cancer patients [respectively; odds ratio (OR) = 1.310, $p \leq 0.001$, confidence interval (CI) = 1.121–1.531; OR = 3.359, $p = 0.043$, CI = 1.042–10.832].

Conclusion: A high CAR value and a CVD diagnosis were risk factors for mortality in non-cancer palliative care patients.

Keywords: CAR index, cerebrovascular disease, mortality, non-cancer, palliative care

Introduction

C-reactive protein (CRP) is a biomarker that increases in circulation during inflammation and is detected by blood tests (1). CRP, synthesized in the liver, may be elevated in bacterial, fungal and parasitic infections, trauma, and progressive cancers. CRP values increase within 6–8 hours in proportion to the severity of inflammation (2).

Albumin is an important indicator of nutritional status (3). Albumin is one of the most frequently examined proteins in the diagnosis of malnutrition, and hypoalbuminemia is generally accepted as an indicator of malnutrition (4). Older patients with low albumin levels also experience significant loss of muscle mass. Hypoalbuminemia is associated with poor recovery and high mortality among older individuals who are living in the community, hospitalized, or residing in nursing homes (5).

The CRP/albumin ratio (CAR) increases in inflammatory states. It can predict prognosis in many diseases (6). High CAR levels are indicative of systemic inflammation and adverse cardiovascular events (7). CAR value is a more sensitive predictor of systemic inflammatory status than the separate evaluation of these 2 parameters (8). The CAR value can predict prognosis and disease progression in cancer patients (9).

In addition to cancer patients, many older and debilitated patients receive palliative care. Mortality is high in these patients due to their general condition, advanced age, and underlying comorbidities.

In this study, we investigated the mortality prediction ability of CAR in non-cancer patients followed in the palliative care service. Additionally, the cut-off value of CAR for predicting mortality was investigated.

Address for Correspondence: İbrahim İleri, Ordu State Hospital, Department of Internal Medicine, Division of Geriatric Medicine, Ordu, Türkiye
E-mail: ibrahimileri60@hotmail.com **ORCID:** orcid.org/0000-0002-7237-5261
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Materials and Methods

Study Participants

Patients admitted to the palliative service between November 1, 2024 and May 1, 2025 were included. Patients transferred to other units during the study, those with active rheumatological disease, those with an active infection, and those diagnosed with cancer were excluded from the study. During the study period, 240 patients were admitted; 40 patients were excluded, and the study continued with the remaining 200 patients. Two hundred patients were followed prospectively in the palliative care unit until discharge or death.

Data Collection

Patients' age, gender, medical information, medical history, number of days of hospitalization, and laboratory values were recorded. Laboratory values of the patients during the first 24 hours in the palliative care service were recorded. Patients were followed up prospectively and divided into 2 groups as surviving or non-surviving patients according to their final status. The survivor group consisted of patients who were discharged from the palliative care service, and the non-survivor group consisted of patients who died in the palliative care service. The causes of death among our patients who died in the palliative care service were generally infections (e.g., pneumonia, bacteremia, infected decubitus ulcers) or other conditions such as heart failure, renal failure, and pulmonary edema. The CAR value was calculated as the ratio of CRP (mg/dL) to albumin (g/dL) from laboratory results obtained within the first 24 hours (10). The Nutrition Risk Screening 2002 (NRS-2002) was used to assess the nutritional status of patients. The NRS-2002 is a malnutrition assessment system developed by the European Society of Clinical Nutrition and Metabolism in 2002 and is frequently used among hospitalized patients. According to the NRS 2002 scoring system, patients with a score of ≥3 are classified as at higher risk for malnutrition, and those with a score of <3 are classified as normal (11). According to NRS 2002, patients at risk of malnutrition were given oral, enteral, and parenteral nutritional support depending on the patients' conditions.

Ethical Statement

Informed consent was obtained from the patient's relatives. An application was submitted to the Ordu University Non-Commercial Scientific Research Ethics Committee, and study approval was obtained (decision number: 2024/139, date: 11.10.2024).

Statistics

IBM SPSS version 23 was used for statistical analysis. In the text, normally distributed numerical variables were expressed as mean ± standard deviation (SD). Non-normally distributed numerical variables were expressed as median [interquartile range (IQR)]. Categorical variables were expressed as numbers (percentages). Comparisons of normally distributed numerical variables were performed with the Student's t-test, and comparisons of non-normally distributed numerical variables were performed with the Mann-Whitney U test. Comparisons of categorical variables were performed using the chi-square (χ^2) test or Fisher's exact test. The sample size for the study was determined using G*Power analysis. The α coefficient was 0.05, and the sample size was calculated to be 184 when the effect size was assumed to be 0.5. Risk factors affecting mortality in non-cancer palliative care patients were determined by logistic regression analysis. Parameters with p-values in Table 1 were included in the regression analysis. If any parameters were highly correlated, only one was included in the regression analysis. The cut-off value of CAR for predicting mortality was determined using receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, and area under the curve were calculated. Youden's index was used to determine the optimal cut-off value. p-value ≤ 0.05 was considered as statistically significant.

Results

The median age of the patients was 83 years (IQR 12). Fifty-two percent of the patients were women. The median CRP value was 10.9 (9.5) IQR in the non-surviving group and 4.7 (7.7) IQR in the surviving group (p ≤ 0.001). The median procalcitonin value was 0.2 (IQR 0.59) in the non-survivor group and 0.13 (IQR 0.13) in the survivor group (p = 0.009). The median CAR value was 4.04 (5.05) IQR in the non-survivor group and 1.89 (2.99) IQR in the survivor group (p ≤ 0.001). A diagnosis of CVD was present in 82% of the non-survivor group versus 57% of the survivor group (p = 0.024). The general characteristics of the patients are presented in Table 1.

Risk factors affecting mortality in non-cancer palliative care patients were investigated using logistic regression analysis. The parameters that have a p-value of <0.200 in Table 1 were included in the regression analysis. Logistic regression analysis showed that having a high CAR value and CVD diagnosis were risk factors affecting palliative care mortality in non-cancer patients (respectively; OR = 1.310, p = ≤0.001, CI = 1.121–1.531; OR = 3.359, p = 0.043, CI = 1.042–10.832). Due to the high correlation of CRP, albumin, and albumin/procalcitonin valueswith other parameters, these parameters were not included in the regression analysis. The results are presented in Table 2.

ROC curve analysis showed that the CAR cut-off point for predicting mortality in non-cancer palliative care patients was 3.25 (sensitivity = 68%, specificity = 71%) (Figure 1).

Discussion

Our study showed that a high CAR value and a diagnosis of CVD were risk factors for palliative care mortality among non-cancer. patients. The cut-off point of CAR for predicting

Table 1. Characteristics of the patients.

	Total n = 200	Non-survivor n = 22 (11%)	Survivor n = 178 (89%)	p
Sex				
Women, n (%)	104 (52%)	11 (50%)	93 (52%)	0.842
Age (IQR)	83 (12)	83 (16)	83 (12)	0.527
Follow-up days, n (IQR)	13 (13)	18 (15)	12 (13)	0.073
Pressure ulcer, n (%)	160 (80%)	21 (96%)	139 (78%)	0.085
NRS-2002 score (IQR)	5 (2)	5 (1)	5 (2)	0.332
Laboratory findings				
Hemoglobin, g/dL (IQR)	9.9 (2.3)	9.8 (2.6)	9.9 (2.3)	0.403
CRP, mg/dL (IQR)	5.35 (8.1)	10.90 (9.5)	4.70 (7.7)	**≤0.001**
Albumin, g/dL ± SD	2.76 ± 0.48	2.58 ± 0.41	2.78 ± 0.48	0.063
Prealbumin, mg/dL (IQR)	12.6 (7.4)	12.15 (9.8)	12.6 (7.3)	0.214
Procalcitonin, µg/L (IQR)	0.14 (0.21)	0.2 (0.59)	0.13 (0.13)	**0.009**
CAR (IQR)	2.02 (3.21)	4.04 (5.05)	1.89 (2.99)	**≤0.001**
CRP/prealbumin (IQR)	0.47 (1.01)	0.84 (1.34)	0.40 (0.91)	**≤0.001**
Albumin/procalcitonin (IQR)	21 (21)	13 (19)	22 (23)	**0.006**
Prealbumin/procalcitonin (IQR)	80 (120)	50 (71)	86 (131)	**0.005**
Comorbidities				
Dementia, n (%)	119 (60%)	12 (55%)	107 (60%)	1.000
CVD, n (%)	119 (60%)	18 (82%)	101 (57%)	**0.024**
DM, n (%)	58 (29%)	5 (23%)	53 (30%)	0.492
HT, n (%)	98 (49%)	13 (59%)	85 (48%)	0.316

n: Number; IQR: Interquartile range, NRS-2002: Nutritional risk screening 2002, SD: Standard deviation, CRP: C-reactive protein, CAR: CRP/albumin ratio, CVD: Cerebrovascular disease, DM: Diabetes mellitus, HT: Hypertension.

Table 2. Logistic regression analysis results*.

	OR	p	CI
CAR	1.310	≤0.001	1.121–1.531
CVD	3.359	0.043	1.042–10.832

*Age, sex, follow-up days, CVD, pressure ulcer, CAR, CRP/prealbumin, prealbumin/procalcitonin, procalcitonin.
CI: Confidence interval, OR: Odds ratio, CRP: C-reactive protein, CAR: CRP/albumin ratio, CVD: Cerebrovascular disease.

mortality in non-cancer patients in palliative care was determined to be 3.25.

Many studies have investigated CAR and demonstrated its relationship with mortality and morbidity in various diseases. Piñerúa-Gonsálvez et al. (12) found that a high CAR value was a risk factor for severe acute pancreatitis. In their study, Aydın and Kaçmaz (13) showed that a high CAR is a risk factor for postoperative intensive care unit admission and 1-year postoperative mortality among older patients undergoing hip fracture surgery. In their study, Yildirim et al. (14) showed that high CAR values are risk factors for severe carotid artery stenosis. Arakawa et al. (15) found that high CAR levels were associated with advanced T stage in patients with resectable pancreatic cancer. The studies we have exemplified show that CAR can provide information on mortality and morbidity across different diseases. Many patients without cancer are followed in palliative care services. Many of these patients may be older and diagnosed with dementia or CVD. The mortality rate is high in this patient group. Multiple risk factors for mortality exist in these patient groups. Hsieh et al. (16) showed that pneumonia, severe decubitus ulcers, a 25% or greater reduction in food intake, treatment for electrolyte imbalance, oxygen requirement, and long-term urinary catheters were 6-month prognostic indicators in patients with advanced dementia living in long-term care facilities. Sakai et al. (17) showed that complete dependence on oral feeding and hypoalbuminemia were risk factors for mortality among patients with advanced dementia receiving palliative care. van Voorden et al. (18) showed that deaths in patients with dementia are most often due to dehydration and

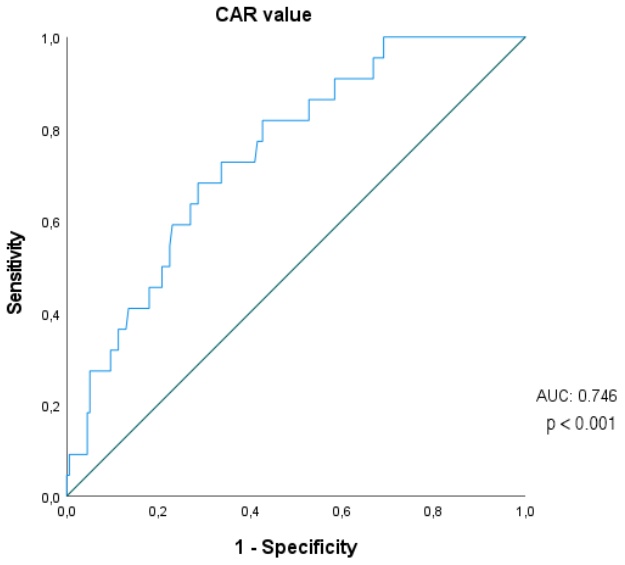

Figure 1. ROC curve analysis examining the cut-off point of CAR* [AUC (95 % CI): 0.746 (0.649–0.843), cut-off: 3.25, p < 0.001, sensitivity: 68%, specifity: 71%, Youden's Index: 0.395].

*: Cut-off value that corresponded to the highest Youden's index in the ROC curve analysis.

ROC: Receiver operating characteristic, CAR: C-reactive protein/albumin ratio, CI: Confidence interval, AUC: Area under the curve.

pneumonia. They showed that mortality was most accurately predicted by being aged 80 and above and by the number of medications used (18). In our study, we showed that mortality in these patients can be predicted by examining the CAR index. We used the CRP and albumin values of the patients examined within the first 24 hours in the palliative care service. CRP and albumin are parameters that are easily and routinely measured in many hospital laboratories. The CAR index is an simple test that can guide us in prognostication of non-cancer patients followed in the palliative service. Additionally, this study showed that the CAR cut-off value for predicting mortality in non-cancer patients receiving palliative care was 3.25. In the study, the CRP/prealbumin, prealbumin/procalcitonin, and albumin/procalcitonin ratios were also investigated for their effects on mortality, but their effects were not demonstrated.

A diagnosis of CVD was also a risk factor for mortality among palliative care patients. Stroke can lead to high rates of mortality and morbidity. This may be due to medical complications related to the neurological disorder, direct effects of severe brain injury, or underlying diseases that caused the stroke. Palliative care may be needed in stroke patients for reasons such as respiratory distress, pain, and respiratory tract secretions (19). In the study by Saricam et al. (20), palliative care mortality among stroke patients was 20.5%. In this study, stroke patients were classified into 3 groups: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. In this study, we did not divide CVD patients into subgroups. Mortality among CVD patients receiving palliative care was 15%. However, in our study, 82% of the non-survivors had a diagnosis of CVD. We have shown that the diagnosis of CVD increases mortality risk in non-cancer patients receiving palliative care.

Our study had several strengths. In this study, 200 patients were followed prospectively for 6 months. Furthermore, palliative care studies in the literature generally focus on cancer patients. Another key strength of this study is its focus on non-cancer patients in palliative care.

Study Limitatons

Our study had limitations. First, we observed only patients in palliative care, so follow-up periods were short. Studies can be conducted that include patients who were discharged and transferred to other units and that provide longer-term follow-up. Second, we conducted this study at a single center; studies involving multiple centers can be conducted to increase the generalizability of the results.

Conclusion

This study showed that a high CAR value and a diagnosis of CVD are risk factors for mortality in non-cancer patients in palliative care. The cut-off value of the CAR to predict mortality was found to be 3.25.

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

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

Ethics

Ethics Committee Approval: An application was submitted to the Ordu University Non-Commercial Scientific Research Ethics Committee, and study approval was obtained (decision number: 2024/139, date: 11.10.2024).

Informed Consent: Informed consent was obtained from the patient's relatives.

Footnotes

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

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ORIGINAL RESEARCH

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Associations Between Variability of Serum Uric Acid Level and Comprehensive Geriatric Assessment Outcomes in Older Adults

Funda Yıldırım Borazan, Çağatay Çavuşoğlu, İbrahim İleri, Berna Göker

Gazi University Faculty of Medicine, Division of Geriatrics, Department of Internal Medicine, Ankara, Türkiye

Abstract

Objective: Serum uric acid (SUA) is a marker with both antioxidant and prooxidant properties. While abnormal SUA levels have been linked to adverse outcomes, the effects of long-term intra-individual SUA fluctuations, particularly in older adults, remain unclear. This study examined the relationship between SUA variability and various components of the comprehensive geriatric assessment (CGA), including functional status, cognition, nutrition, and mood.

Materials and Methods: The study population consisted of 102 patients aged 65 years and older who were evaluated in a geriatric outpatient clinic. Uric acid coefficient of variation (SUA-CV) was calculated using four SUA measurements over a 12-year period. Participants were classified into low and high SUA-CV groups. All participants underwent CGA.

Results: Higher SUA-CV was significantly associated with lower activities of daily living, instrumental activities of daily living, mini-mental state examination, and mini nutritional assessment-short form scores, and with higher GDS scores, polypharmacy, and comorbidities ($p < 0.05$). Correlation analysis revealed significant associations between SUA-CV and various CGA parameters, particularly those reflecting functional and nutritional decline.

Conclusion: Increased variability in SUA levels is associated with poor functional, cognitive, nutritional, and mood status in older adults. SUA-CV may be a novel and cost-effective biomarker for systemic vulnerability in aging and may help guide individualized geriatric care.

Keywords: Uric acid, comprehensive geriatric assessment, variability, older adults

Introduction

Uric acid is the end product of purine metabolism. It has been increasingly recognized for its dual role in human physiology — acting both as a powerful antioxidant and, paradoxically, as a pro-oxidant under certain pathological conditions (1). The normal reference range for serum uric acid (SUA) in humans is between 3.0 and 6.8 mg/dL. However, these values are influenced by demographic factors such as age and sex, as well as various pathological conditions (2). High SUA levels have been associated with many age-related diseases, including cardiovascular disease, hypertension, metabolic syndrome, and neurodegenerative disorders such as Alzheimer's disease (3,4). Although the pathophysiological role of uric acid has been extensively investigated across a broad spectrum of disease processes, a comprehensive and definitive understanding remains elusive. Additionally, recent investigations have increasingly focused on the pathophysiological consequences of hypouricemia, and it has been suggested that both elevated and low SUA levels may be risk factors for comorbidities and all-cause mortality (2,5,6). Findings from small-sample studies suggest that mortality risk follows a U-shaped pattern in relation to SUA levels (5,6). However, beyond absolute uric acid levels, the variability of SUA over time has emerged as a potentially essential but underexplored marker of systemic homeostasis and metabolic resilience, particularly in older adults. In a recent large prospective study, greater variability in SUA levels was associated with an increased risk of cardiovascular disease during a six-year follow-up (7).

Comprehensive geriatric assessment (CGA) is an interdisciplinary and multidimensional approach aimed at assessing the medical,

Address for Correspondence: Funda Yıldırım Borazan, Division of Geriatrics, Department of Internal Medicine, Aydın State Hospital, Aydın, Türkiye
E-mail: dryildirimfunda@gmail.com **ORCID:** orcid.org/0000-0003-0232-2081
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psychosocial, functional, and nutritional conditions of older adults (8). CGA helps predict health outcomes, guide therapeutic decisions, and optimize individualized care plans for older adults. Identifying novel, easily measurable biomarkers that correlate with CGA parameters could enhance early risk stratification and management strategies in geriatric care.

Recent studies have suggested that fluctuations in specific metabolic markers, such as glucose and cholesterol, may provide prognostic information beyond static values (9,10). In this context, SUA variability may reflect underlying inflammatory activity, fluctuations in renal function, or oxidative stress—all of which are relevant to geriatric syndromes such as frailty, cognitive decline, and functional impairment. There are no studies in the literature that have examined this subject in older adults.

The study investigates, in a cohort of older adults, the link between SUA variability and various domains of CGA, including functional status, cognitive function, nutritional status, and mood. We hypothesize that greater variability in uric acid levels may be associated with poorer outcomes in CGA parameters, suggesting its potential role as a surrogate biomarker in geriatric assessment.

Materials and Methods

Study Population

The study population consisted of individuals aged 65 years and older who were evaluated in the geriatric outpatient clinic of (Gazi University) Hospital from January to March 2021. Patients with stage 4 or 5 chronic kidney failure, malignancy, chronic liver disease, or systemic inflammatory disease were excluded from the study. Baseline data on participants' age, sex, educational level, comorbid conditions, and number of prescribed medications were collected. Each participant also underwent a CGA.

Comprehensive Geriatric Assessment

Participants' dependence in performing daily activities was evaluated using the Katz et al. (11) activities of daily living (ADL) and the Lawton instrumental ADL (IADL) scales (12,13). Mood was assessed using the geriatric depression scale—short form (GDS); a score of ≥5 was considered indicative of depression (14). Cognitive impairment was detected by the standardized mini-mental state examination (MMSE) and defined as an MMSE score of <24 and recall of ≤2 words in the three-word recall test (15). Nutritional risk status was assessed using the mini nutritional assessment-short form (MNA-SF) and malnutrition was defined as an MNA-SF score <8 (16,17). Polypharmacy was defined as the regular use of five or more medications.

Participants' height and weight were measured. To measure height, participants stood upright with their back and legs straight against the wall, and a pencil was placed on top of their heads to mark the height on a wall-mounted ruler. Body weight was measured using a Tanita BC 418 device. Body mass index was determined as body weight (kg) divided by the square of height (m^2).

SUA values were retrieved from the hospital records of patients included in the study. The study included 102 patients whose four uric acid measurements were available in the hospital records between 2008 and 2020. There is at least a two-year gap between each SUA. The variability of SUA was calculated from four different values for each patient. The following parameter was calculated for uric acid variability: the uric acid coefficient of variation (uric acid-CV).

Ethical approval for this study was obtained from the Gazi University Ethics Committee (decision number: 682, date: 02.11.2020), and the research was conducted in accordance with the ethical standards of the Declaration of Helsinki. Each participant provided written informed consent before participation.

Statistics

The categorical were reported as numbers and percentages (n,%). The Statistical Package for the Social Sciences (SPSS) version 22.0 was used for the statistical analyses. The Kolmogorov-Smirnov test and histograms were used to verify the normality of the distribution of numeric variables. Data were presented as numbers and percentages for categorical variables, mean ± standard deviation (SD) for normally distributed continuous variables, and median (minimum-maximum) for non-normally distributed continuous variables. The comparison of numerical parameters that followed a normal distribution between two independent groups was performed using the Student's t-test. The intergroup comparisons of numeric variables with non-normal distributions were performed using the Mann-Whitney U test. Spearman's rank correlation coefficient was used for parameters that were not normally distributed. The variability of SUA was calculated with four different values for each patient. The CV is a statistical measure that describes the relative dispersion of parameter values. CV is calculated by dividing the SD of the parameters by their mean value. The following parameter was calculated for uric acid variability: the uric acid-CV. Uric acid variability was categorized into low- and high-variability groups based on the median of the variability distribution in our study population. The median-based cut-off approach has commonly been used in previous studies evaluating biological variability indices and is therefore considered appropriate for the current analysis. We performed a post-hoc power analysis using G*Power version 3.1.9.4. Based on the observed effect size and sample size, the G*Power output yielded a non-centrality parameter (δ) of 3.87, a critical value of 1.98, degrees of freedom (df) of 95, and an estimated statistical power (1–β) of 0.96.

Results

A total of 102 patients (mean age 74.2 years; 64.7% female) were included in the study. When participants were stratified into low- and high-CV groups, significant differences were observed between the groups in ADL, IADL, MNA-SF, GDS, number of medications, and comorbidity count (Table 1).

Geriatric syndromes differed significantly between groups with low and high uric acid variability. Polypharmacy was more common in the high-variability group (78.4%) than in the low-variability group (52.9%) ($p = 0.011$). Similarly, malnutrition (13.7% vs. 2.0%, $p = 0.032$) and depression (43.1% vs. 23.5%, $p = 0.029$) were more frequent among participants with greater variability in uric acid levels. Cognitive impairment also differed markedly, with 39.2% in the high-variability group vs. 5.9% in the low-variability group ($p < 0.001$) (Table 1).

In the correlation analysis, negative correlations were found between SUA-CV and ADL, IADL, MNA-SF, and the number of comorbidities. In contrast, a positive correlation was found among the number of medications, GDS, and SUA-CV (Table 2).

Discussion

In this study, we observed significant correlations between SUA-CV and several CGA parameters, including ADL, IADL, MNA-SF, GDS, and the number of medications and comorbidities. The present study suggests that SUA-CV might serve as an informative biomarker for assessing both general health and functional capacity in older individuals.

Previous studies have primarily focused on hyperuricemia and its associations with adverse geriatric outcomes. For instance, observational cohort studies in older adults have linked elevated SUA levels with an increased risk of frailty (18,19). Conversely, in another cohort, hyperuricemia has paradoxically been associated with greater muscle mass and strength, suggesting a protective role against sarcopenia under certain conditions (20,21).

Table 1. Baseline demographic and clinical characteristics of groups defined by serum uric acid variability (CV).

Characteristics	Total (n = 102)	Low CV (n = 51)	High CV (n = 51)	p-value
Age, years	74.2 ± 6.3	73.4 ± 5.8	75 ± 6.7	0.204
Female, n (%)	66 (64.7%)	28 (54.9%)	38 (74.5%)	0.006
BMI, kg/m^2	27.9 (19.8–39.7)	27.7 (20–35.5)	28.5 (19.8–39.7)	0.434
High school or above, n (%)	25 (24.5%)	11 (21.5%)	14 (27.5%)	0.396
HTN, n (%)	66 (64.7%)	33 (64.7%)	33 (64.7%)	0.528
DM, n (%)	43 (42.1%)	22 (43.1%)	21 (41.2%)	0.500
COPD, n (%)	11 (10.8%)	4 (7.8%)	7 (13.7%)	0.262
CAD, n (%)	24 (23.5%)	10 (19.6%)	14 (27.5%)	0.241
Dyslipidemia, n (%)	19 (18.6%)	6 (11.8%)	13 (25.4%)	0.062
ADL	6 (1–6)	6 (1–6)	5 (2–6)	**0.000**
IADL	8 (1–8)	8 (1–8)	7 (1–8)	**0.000**
MNA-SF	12 (5–14)	13 (7–14)	11 (5–14)	**0.000**
MMSE	28 (10–30)	28 (18–30)	26 (10–30)	**0.005**
GDS	3 (0–14)	2 (0–10)	4 (0–14)	**0.001**
Number of medications	5 (0–14)	4 (0–14)	6 (0–12)	**0.002**
Polypharmacy, n (%)	67 (65.7%)	27 (52.9%)	40 (78.4%)	**0.011**
Malnutrition, n (%)	8 (7.8%)	1 (2%)	7 (13.7%)	**0.032**
Depression, n (%)	34 (33.3%)	12 (23.5%)	22 (43.1%)	**0.029**
Cognitive impairment, n (%)	23 (22.5%)	3 (5.9%)	20 (39.2%)	**0.000**
Fall, n (%)	23 (22.5%)	10 (19.6%)	13 (25.4%)	0.318
Urinary incontinence, n (%)	33 (32.3%)	14 (27.5%)	19 (37.3%)	0.211
Number of comorbidities	3 (0–7)	2 (0–5)	3 (0–7)	**0.007**
Sleep duration	6 (3–10)	7 (4–10)	6 (3–10)	0.908
SUA-CV	0.18 (0.04–0.57)	0.13 (0.04–0.18)	0.29 (0.19–0.57)	**0.000**

Categorical variables are presented as counts and percentages, normally distributed continuous variables as mean ± SD, and non-normally distributed continuous variables as median (range).
SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, ADL: Activities of daily living, IADL: Instrumental activities of daily living, MNA-SF: Mini nutritional assessment-short form, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, SUA-CV: Serum uric acid-coefficient of variation.

Table 2. The results of the correlation analysis between the parameters and SUA-CV.

		SUA-CV	Number of medications	Number of comorbidities	ADL	IADL	MMSE	MNA-SF	GDS
SUA-CV	Rho coefficient	1							
	p								
Number of medications	Rho coefficient	0.266	1						
	p	**0.008**							
Number of comorbidities	Rho coefficient	-0.102	-0.222	1					
	p	0.321	**0.029**						
ADL	Rho coefficient	-0.365	-0.283	0.415	1				
	p	**0.000**	**0.004**	**0.000**					
IADL	Rho coefficient	-0.333	-0.013	-0.442	0.353	1			
	p	**0.001**	0.898	**0.000**	0.000				
MMSE	Rho coefficient	-0.097	0.217	-0.754	-0.151	0.648	1		
	p	0.330	**0.030**	**0.000**	0.130	**0.000**			
MNA-SF	Rho coefficient	-0.240	-0.117	-0.512	0.076	0.422	0.433	1	
	p	**0.017**	0.255	**0.000**	0.457	**0.000**	**0.000**		
GDS	Rho coefficient	0.413	0.361	-0.271	-0.475	-0.196	0.045	-0.352	1
	p	**0.000**	**0.000**	**0.007**	**0.000**	**0.048**	0.651	**0.000**	

ADL: Activities of daily living, IADL: Instrumental activities of daily living, MNA-SF: Mini nutritional assessment-short form, MMSE: Mini-mental state examination, GDS: Geriatric depression scale, SUA-CV: Serum uric acid-coefficient of variation.

With regard to cognitive outcomes, elevated SUA appears to confer neuroprotective effects in conditions like. Alzheimer's or Parkinson-related dementia; however, findings remain inconsistent across subtypes, and some evidence suggests potential harm in vascular dementia (22,23). While most previous studies have relied on a single-time-point SUA measurement, our study considered intra-individual variability in SUA levels over a 12-year period. Although we did not control for potential confounding factors such as medication use or comorbidities, and we did not perform regression analyses, our descriptive findings may reflect potential associations between long-term SUA fluctuations and geriatric assessment outcomes.

Tian et al. (24) investigated the impact of visit-to-visit variability in SUA on all-cause mortality in a large general-population cohort and reported that greater SUA variability was independently associated with an increased risk of all-cause mortality. Their findings underscore the clinical relevance of longitudinal SUA fluctuations beyond single-time-point measurements. Although our study does not focus on mortality outcomes, it examines long-term SUA variability and explores its potential associations with CGA parameters.

From a geriatric clinical perspective, asymptomatic or non-specific hyperuricemia generally does not require pharmacological treatment. Current guidelines highlight that starting urate-lowering therapy in older adults solely based on elevated SUA levels—without gout, nephrolithiasis, or urate-related complications—offers no clear benefit and may increase the risk of medication-related adverse events, especially in individuals with multimorbidity and polypharmacy (25,26). This conservative approach underscores the importance of avoiding unnecessary treatment in geriatric practice. In this context, focusing on SUA variability rather than absolute SUA elevations may provide a more nuanced understanding of physiological instability without prompting unwarranted interventions. Our findings, therefore, complement existing clinical perspectives by suggesting that long-term fluctuations in SUA may be more relevant than isolated hyperuricemia in older adults.

Hypouricemia may reduce antioxidant capacity and is often associated with insufficient dietary intake of protein and purine-rich nutrients, as seen in malnourished individuals, and has been suggested in several studies to be a nutritional marker (6,27). This is particularly relevant in the geriatric population, where reduced appetite, chronic illness, and functional decline may limit adequate dietary intake (28). In our study, the observed association between higher SUA variability and lower MNA-SF scores supports the hypothesis that fluctuations in SUA levels—especially those trending toward hypouricemia—may serve as indirect markers of malnutrition or nutritional instability. Further research is needed to determine whether SUA variability precedes or follows nutritional decline.

This is the first study to examine the relationship between SUA variability and CGA domains in older adults. SUA is a low-cost biomarker commonly measured in clinical biochemical assays. Therefore, we believe that these findings are clinically relevant. Monitoring SUA variability may serve as an additional, readily available tool for risk assessment and early identification of vulnerable individuals among older adults.

Study Limitations

Nevertheless, our study has several limitations. First, the retrospective design and the relatively small sample size of this study may restrict the generalizability of the findings. Second, although we used four SUA measurements over a long period, these measurements were infrequent and unevenly distributed, which may have led to the omission of short-term fluctuations or acute changes. Third, dietary habits, hydration status, and medication use influence uric acid levels; however, these factors were not assessed in the study participants. Future research involving larger prospective cohorts is necessary to both verify these findings and examine the mechanisms underlying them.

Conclusion

Increased SUA variability is associated with negative geriatric outcomes, including functional decline, malnutrition, and depressive symptoms. SUA variability may serve as an underrecognized biomarker of systemic instability and aging-related vulnerability. Incorporating dynamic biochemical markers such as SUA-CV into routine geriatric assessments may improve the identification of at-risk individuals and support personalized interventions.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Gazi University Ethics Committee (decision number: 682, date: 02.11.2020), and the research was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Informed Consent: Each participant provided written informed consent before participation.

Footnotes

Authorship Contributions

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

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