

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

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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

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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 (%)					
<i>De novo</i>	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 ^y	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 ^y	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. ^y Median (Q1-Q3). ^y 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

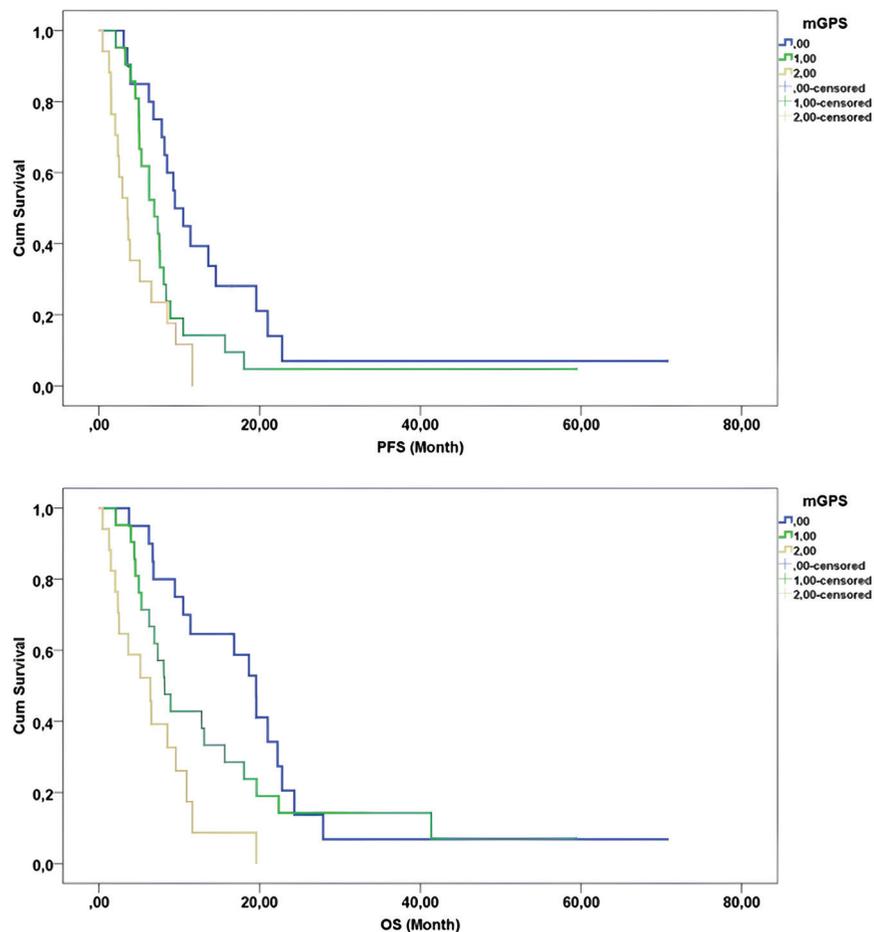


Figure 1. Kaplan-Meier survival curves according to mGPS of the cases.

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/ <i>de novo</i> (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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