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Association of the Modified Glasgow Prognostic Score with overall survival in immunotherapy-treated metastatic urothelial carcinoma: A single-center cohort study

mGPS and survival in immunotherapy-treated metastatic bladder cancer

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KEYWORDS: modified Glasgow Prognostic Score (mGPS), metastatic urothelial carcinoma of the bladder (mUC), immunotherapy, checkpoint inhibitors, prognosis, treatment response, prognostic biomarkers

Abstract
Introduction:
Growing evidence suggests that a persistent systemic inflammatory response is associated with poorer survival outcomes in patients with malignant disease. The modified Glasgow Prognostic Score (mGPS), based on elevated C-reactive protein (CRP >10 mg/L) and hypoalbuminemia (<35 g/L), has been established as an independent prognostic marker in various cancers. The aim of this study was to evaluate the prognostic value of the mGPS in patients with metastatic urothelial carcinoma of the bladder (mUC) receiving immunotherapy, with particular focus on treatment response, tolerability, and overall survival.
Methods:
In this retrospective single-center cohort study, 48 patients with mUC treated with immune checkpoint inhibitors were included. Patients received immunotherapy either due to ineligibility for platinum-based chemotherapy or as second-line treatment following disease progression. Pretreatment mGPS was categorized into three groups: mGPS 0 (CRP <10 mg/L), mGPS 1 (CRP >10 mg/L, albumin ≥35 g/L), and mGPS 2 (CRP >10 mg/L, albumin <35 g/L). Overall survival (OS) and disease-free survival (DFS) were analyzed using Kaplan–Meier estimates. Treatment-related toxicity was assessed according to CTCAE criteria. Prognostic factors were evaluated using univariate Cox regression analyses.
Results:
Survival outcomes differed significantly across mGPS categories, with patients classified as mGPS 0 demonstrating the most favorable treatment response and survival. In univariate analysis, both mGPS ($p < 0.0001$) and tumor stage ($p = 0.004$) were significantly associated with prognosis. Response rates to immunotherapy varied markedly between groups (mGPS 0: 71%, mGPS 1: 34%, mGPS 2: 26%; $p < 0.001$). Higher mGPS values were also significantly associated with increased treatment-related and disease-related morbidity.
Conclusion:
Systemic inflammation and nutritional status, as reflected by the mGPS, are independent predictors of treatment response, toxicity, and survival in patients with mUC undergoing immunotherapy. Alongside established pathological markers, the mGPS represents an objective, low-cost, and readily available prognostic tool with potential clinical utility in routine practice.

INTRODUCTION

Bladder cancer is the second most common malignancy of the urinary tract. For patients with locally advanced or metastatic disease who are fit for systemic treatment, platinum-based chemotherapy remains the standard of care. According to the German S3 guideline for bladder cancer, eligibility for platinum-based chemotherapy is defined by an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 or a Karnofsky performance status >70%, a creatinine clearance >60 mL/min, and the absence of relevant comorbidities, including hearing loss (≥ CTCAE grade 2), peripheral neuropathy (≥ CTCAE grade 2), and advanced heart failure (≥ NYHA class III). In patients who are ineligible for platinum-based chemotherapy or who experience disease progression following platinum-based treatment, immune checkpoint inhibitors (ICIs) are recommended as first- or second-line therapy, respectively [1].

Despite advances in systemic therapy, many patients with metastatic urothelial carcinoma (mUC) experience disease progression, local recurrence, or distant metastases. Reliable prognostic biomarkers that allow accurate prediction of treatment response and survival remain limited. Increasing evidence suggests that inflammation plays a central role in cancer development, progression, and treatment resistance [2–4]. In particular, a persistent systemic inflammatory response has been consistently associated with unfavorable outcomes in advanced malignancies [5]. Chronic inflammation has also been identified as a key factor contributing to resistance to immune checkpoint inhibition.

The modified Glasgow Prognostic Score (mGPS) is a well-established marker of systemic inflammation and nutritional status, defined by the combined assessment of serum C-reactive protein (CRP >10 mg/L) and albumin levels (<35 g/L). Elevated CRP reflects an ongoing systemic inflammatory response and has been linked to tumor progression, metastatic spread, and increased cancer-related mortality. In patients undergoing systemic cancer therapy, inflammation is frequently accompanied by weight loss and cancer-associated cachexia, a multifactorial syndrome characterized by increased resting energy expenditure, loss of fat-free muscle mass, and functional decline [6,7]. CRP has been shown to correlate with markers of nutritional impairment and reduced overall survival [8].

Serum albumin is a negative acute-phase protein, and its concentration decreases in response to inflammatory stimuli. Hypoalbuminemia is therefore closely associated with systemic inflammation, loss of lean body mass, weight loss, increased morbidity, and adverse clinical outcomes in patients with malignant disease [7,9]. Given the close interplay between inflammation and nutritional status, the mGPS provides a biologically plausible composite marker that captures both processes in a single, objective score.

The original Glasgow Prognostic Score (GPS) incorporated elevated CRP and/or hypoalbuminemia; however, subsequent studies demonstrated that hypoalbuminemia alone had limited prognostic value in certain tumor entities, particularly colorectal cancer. Consequently, the score was modified in 2007, resulting in the mGPS, which places greater emphasis on systemic inflammation as the primary determinant of prognosis [7]. Since then, the mGPS has been validated as an independent prognostic factor across a wide range of malignancies, disease stages, and treatment modalities. It is inexpensive, reproducible, and easily applicable in routine clinical practice. However, data on the prognostic relevance of the mGPS in patients with metastatic urothelial carcinoma receiving immunotherapy remain scarce. The present study therefore aimed to evaluate the prognostic value of the mGPS in patients with mUC treated with immune checkpoint inhibitors, with particular emphasis on treatment response, tolerability, and survival outcomes.

METHODS

Study design and patient population

This retrospective single-center cohort study included all patients with metastatic urothelial carcinoma of the bladder (mUC) who received immunotherapy at the Department of Urology, Rostock University Medical Center, between 2016 and 2024. A total of 48 patients were eligible for analysis. The study protocol was approved by the institutional review board (approval number: A 2021-0259).

Inclusion criteria comprised histologically confirmed urothelial carcinoma of the bladder with regional lymph node involvement and/or distant metastases. Patients with concomitant chronic inflammatory diseases or active infections at the time of treatment initiation were excluded to avoid confounding effects on inflammatory markers.

Data collection and treatment

Demographic, clinical, pathological, and laboratory data were retrospectively extracted from electronic medical records. All patients received standard immune checkpoint inhibitors (ICIs), including atezolizumab, pembrolizumab, or nivolumab, with pembrolizumab being the most frequently administered agent. Immunotherapy was initiated either as first-line treatment in patients ineligible for platinum-based chemotherapy or as second-line therapy following disease progression after platinum-based chemotherapy.

Tumor staging was performed according to the 8th edition of the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours. Serum CRP and albumin levels were measured routinely one day prior to the initiation of immunotherapy.

Modified Glasgow Prognostic Score

The modified Glasgow Prognostic Score (mGPS) was calculated as previously described by McMillan et al. [11]. Patients were categorized into three groups based on pretreatment laboratory values:

mGPS 0: CRP <10 mg/L (regardless of albumin level)

mGPS 1: CRP >10 mg/L and albumin ≥35 g/L

mGPS 2: CRP >10 mg/L and albumin <35 g/L

For additional survival analyses, mGPS categories were dichotomized into mGPS 0 versus mGPS 1–2.

Follow-up and outcome measures

Patients were followed at regular intervals every three months during the first and second year after initiation of immunotherapy. Follow-up evaluations included clinical examination and computed tomography (CT) imaging. Follow-up data were obtained during outpatient visits at our institution or, if necessary, by contacting referring physicians.

Overall survival (OS) was defined as the interval between initiation of immunotherapy and cancer-related death. Disease-free survival (DFS) was calculated from the start of immunotherapy to the first documented evidence of disease progression. Median follow-up time was estimated using the reverse Kaplan–Meier method.

Assessment of treatment toxicity

Treatment-related adverse events were documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical Analysis

Overall survival and disease-free survival were estimated using the Kaplan–Meier method, and differences between mGPS groups were assessed using log-rank tests. Univariate Cox proportional hazards regression models were applied to evaluate the impact of individual clinical and pathological variables on OS and DFS. Due to the limited cohort size, multivariate analyses were not performed.

All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 48 patients with histologically confirmed metastatic urothelial carcinoma of the bladder were included in the analysis. All patients presented with regional lymph node involvement and/or distant metastases and received immune checkpoint inhibitor therapy (atezolizumab, pembrolizumab, or nivolumab), with pembrolizumab being the most frequently administered agent.

Most patients received immunotherapy as second-line treatment following disease progression after cisplatin-based chemotherapy with gemcitabine. All patients had previously undergone radical cystectomy, and none had received neoadjuvant therapy prior to immunotherapy. Patients treated with first-line immunotherapy were PD-L1 positive, whereas among those receiving second-line immunotherapy, 48% demonstrated PD-L1 positivity. The mean age at initiation of immunotherapy was 64.9 years (±14.1). All primary tumors were high grade (G3), and 40 of 48 patients (85%) had a primary tumor stage of T2. Lymph node metastases were present in all patients, and 24 patients (50%) additionally had distant metastatic disease. The majority of patients had an ECOG performance status of 0 or 1. Baseline mGPS parameters were assessed prior to the initiation of immunotherapy. Detailed patient characteristics are summarized in Table 1.

Follow-up and survival outcomes

The median follow-up time was 11.8 months (range: 6.5–21.9) for overall survival (OS) and 9.1 months (range: 3.0–19.5) for disease-free survival (DFS). At 12 months, 26 patients (54%) were alive, and 32% remained progression-free. Although all patients died within 24 months after treatment initiation, patients with lower mGPS values demonstrated significantly prolonged survival.

Kaplan–Meier survival analysis revealed significant differences in OS and DFS across mGPS categories. Patients classified as mGPS 0 showed a significantly higher cumulative survival rate compared with those in mGPS groups 1 and 2 (Table 2). When dichotomized, mGPS 0 was associated with significantly longer OS ($p < 0.016$) and DFS ($p < 0.02$) compared with mGPS 1–2.

Prognostic factors

Univariate Cox proportional hazards regression analysis identified hypoalbuminemia and mGPS as significant prognostic factors for OS. For DFS, hypoalbuminemia, mGPS, and tumor T stage were significantly associated with outcome. Elevated mGPS was strongly associated with poorer prognosis ($p < 0.0001$), and higher tumor stage was also significantly correlated with reduced survival ($p = 0.004$). Detailed results of the univariate analyses are presented in Table 2 and 3.

Treatment response

The response to immunotherapy differed significantly across mGPS groups. An objective response was observed in 11 of 16 patients (71%) in the mGPS 0 group, compared with 7 of 22 patients (34%) in the mGPS 1 group and 3 of 10 patients (26%) in the mGPS 2 group. This difference was statistically significant ($p < 0.01$) (Table 4).

Treatment-related toxicity

The mGPS was also significantly associated with treatment-related and disease-related morbidity. Immune-mediated adverse events were more frequent and more pronounced in patients with higher mGPS values (Table 5). However, immunotherapy was generally well tolerated across all groups. No treatment modifications or treatment-related deaths were observed.

DISCUSSION

Immunotherapy has become an established treatment option for patients with metastatic urothelial carcinoma of the bladder, either as first-line therapy in individuals who are ineligible for platinum-based chemotherapy or as second-line treatment following disease progression after platinum-based therapy [1]. Despite these therapeutic advances, clinical outcomes remain heterogeneous, and reliable biomarkers capable of predicting treatment response and survival are still limited. Identifying robust and easily accessible prognostic indicators is therefore of considerable clinical importance.

The present study demonstrates that the modified Glasgow Prognostic Score (mGPS), a composite marker reflecting systemic inflammation and nutritional status, is significantly associated with treatment response, morbidity, and survival in patients with metastatic urothelial carcinoma receiving immune checkpoint inhibitor therapy. Patients with lower baseline mGPS values experienced superior survival outcomes, higher response rates to immunotherapy, and fewer treatment-related complications compared with those with elevated mGPS. These findings further support the concept that systemic inflammation is a key determinant of prognosis in advanced malignancies [5].

Systemic inflammatory responses have long been recognized as contributors to cancer progression, immune dysregulation, and resistance to anticancer therapies [2–4]. Several inflammation-based biomarkers, including cytokines, leukocyte-derived indices, and acute-phase proteins, have demonstrated prognostic relevance across various tumor entities [12–16]. Tumor-associated inflammation, both at the local and systemic level, has been shown to correlate with aggressive tumor behavior and adverse oncological outcomes [17–19]. In this context, chronic inflammation may impair antitumor immune responses and reduce the efficacy of immune checkpoint inhibition.

Inflammation and nutritional status are closely interconnected, particularly in advanced cancer. Cancer-associated cachexia is characterized by systemic inflammation, loss of lean body mass, increased resting energy expenditure, and functional decline, all of which negatively affect treatment tolerance and survival [6,7]. Elevated C-reactive protein levels reflect ongoing inflammatory activity, while hypoalbuminemia represents a combined marker of inflammatory burden and nutritional impairment. Both parameters have been independently associated with increased morbidity and reduced overall survival in patients with malignant disease [7–9]. By integrating CRP and albumin levels into a single score, the mGPS provides a biologically plausible and clinically meaningful assessment of patient condition.

Originally developed to assess prognosis in patients with advanced cancer, the mGPS has since been validated as an independent prognostic factor across multiple tumor entities, disease stages, and treatment modalities [14–

16,22–25]. Its prognostic value has been demonstrated in gastrointestinal, lung, breast, and genitourinary malignancies. Our findings are consistent with previous reports showing that elevated mGPS values are associated with inferior survival and reduced treatment efficacy [14,23,24,26]. Importantly, the present study extends these observations to patients with metastatic urothelial carcinoma treated with immunotherapy, a population for which data on inflammation-based prognostic scores remain limited.

Beyond survival prediction, our results indicate that higher mGPS values are associated with increased treatment-related and disease-related morbidity. Patients with elevated systemic inflammation may be more susceptible to immune-related adverse events or less able to tolerate therapy due to compromised physiological reserves. Although immunotherapy was generally well tolerated in our cohort and no treatment-related deaths occurred, the observed association between mGPS and morbidity highlights the potential value of this score in identifying patients who may benefit from closer monitoring or supportive interventions.

In addition to these findings, the interpretation of inflammation-based prognostic markers must also be considered in the context of rapidly evolving systemic treatment strategies. Recent advances in the systemic treatment of metastatic urothelial carcinoma are likely to further reshape therapeutic strategies. In particular, the combination of enfortumab vedotin and pembrolizumab has demonstrated significant improvements in survival outcomes compared with standard chemotherapy and immune checkpoint inhibitor monotherapy and is expected to become an important component of first-line treatment in eligible patients. In this evolving therapeutic landscape, robust and easily accessible prognostic biomarkers remain highly relevant. Inflammation-based scores such as the mGPS may continue to provide clinically meaningful information for baseline risk stratification, patient counseling, and identification of individuals who may benefit from closer monitoring or supportive interventions, even in the context of novel combination regimens.

With regard to the individual components of the mGPS, it is important to note that hypoalbuminemia and C-reactive protein reflect overlapping yet distinct biological processes. While CRP is a dynamic marker of acute systemic inflammation, serum albumin additionally captures nutritional status, metabolic reserve, and the chronic inflammatory burden. In our cohort, hypoalbuminemia showed a significant association with overall survival, whereas CRP alone did not reach statistical significance, likely reflecting biological variability and the limited sample size. The mGPS integrates both parameters and was originally designed to weight hypoalbuminemia only in the presence of elevated CRP, thereby identifying patients with a sustained and clinically relevant systemic inflammatory response. This composite approach may explain the superior prognostic performance of the mGPS compared with its individual components and supports its use as a pragmatic prognostic tool in patients with metastatic urothelial carcinoma undergoing immunotherapy.

The present study has several limitations that should be acknowledged. Its retrospective design introduces potential sources of bias, including unmeasured confounding factors and incomplete data capture. In addition, the relatively small sample size limited statistical power and precluded multivariate analyses, necessitating cautious interpretation of hazard ratio estimates. Furthermore, as a single-center study, the generalizability of our findings may be limited. Prospective multicenter studies with larger patient cohorts are warranted to validate the prognostic role of the mGPS in metastatic urothelial carcinoma treated with immune checkpoint inhibitors.

Despite these limitations, our data suggest that baseline mGPS provides clinically relevant prognostic information in patients with metastatic urothelial carcinoma undergoing immunotherapy. Given its simplicity, low cost, and widespread availability, the mGPS may serve as a valuable tool for risk stratification and individualized treatment planning in routine clinical practice. Moreover, identifying patients with impaired nutritional status and heightened inflammatory burden may offer opportunities for early supportive and nutritional interventions aimed at optimizing treatment outcomes.

The role of systemic inflammation in cancer progression and treatment resistance is complex and remains incompletely understood. While direct modulation of inflammatory pathways is currently limited, optimization of nutritional status represents a feasible and actionable strategy in daily clinical practice. Future studies should investigate whether interventions targeting inflammation and nutrition can improve outcomes in patients with metastatic urothelial carcinoma receiving immunotherapy.

CONCLUSION

Baseline assessment of the modified Glasgow Prognostic Score provides clinically meaningful prognostic information in patients with metastatic urothelial carcinoma of the bladder undergoing immunotherapy. Elevated mGPS values are associated with inferior survival outcomes, reduced treatment response, and increased morbidity.

Given its simplicity, low cost, and widespread availability, the mGPS represents a practical tool for risk stratification and may support individualized treatment decision-making in routine clinical practice. Incorporating the mGPS into pretreatment evaluation may help identify patients who could benefit from intensified monitoring, early supportive care, or nutritional interventions.

IMPLICATIONS FOR CLINICAL PRACTICE

The modified Glasgow Prognostic Score is a simple, inexpensive, and readily available biomarker that can be easily integrated into routine clinical practice. It provides valuable prognostic information in patients with metastatic urothelial carcinoma of the bladder receiving immunotherapy.

Assessment of the mGPS prior to treatment initiation may support clinical risk stratification, facilitate individualized treatment planning, and help identify patients who may benefit from closer monitoring, supportive care, or early nutritional interventions. Incorporation of the mGPS alongside established clinical and pathological parameters may improve informed decision-making in daily oncological practice.

Statement of Ethics

Study approval statement:

This study protocol was reviewed and approved by the Institutional Review Board of the Rostock University Medical Centre, approval number A 2021-0259.

Consent to participate statement:

Written informed consent to participate in this study was obtained from all participants prior to inclusion in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare

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Author Contributions

DLD, JH, FO and BB collected clinical data and analyzed the data. DLD and AB wrote the manuscript. All authors provided critical feedback and helped shape the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical and data protection requirements but can requested from corresponding author upon reasonable request and subject to review.

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TABLES

Tab. 1 Baseline characteristics of the included patients

Characteristics	Included patients (n = 48)
Age (median in years)	64.9 (14.1) years; Range (54-88)
Gender	
Male	36 (75%)
Female	12 (25%)
Smoker	28 (60%)
ECOG-Performance-Status	
0-1	41 (86%)
2-3	7 (14%)
mGPS	
mGPS 0	16 (33%)
mGPS 1	22 (46%)
mGPS 2	10 (21%)
T-state	
pT2	40 (85%)
pT3	5 (10%)
pT4	3 (5%)
N-state	
pN1	43 (90%)
pN2	5 (10%)
M-state	
cM0	24 (50%)
cM+	24 (50%)
Localisation of distant metastases	
Lymph nodes	48 (100%)
Lung	17 (35%)
Liver	10 (21%)
Bones	2 (4%)
Number of prior therapies	
0	13 (27%)
1-2	35 (73%)
Prior therapy with Gemcitabin/Cisplatin	35 von 35 (100%)
Immunotherapy-Substance	
Atezolizumab	3 (6%)
Pembrolizumb	44 (92%)
Nivolumab	1 (2%)
BMI (median)	23,8
Follow-up	
Overall survival (OS)	11.8 months (6.5-21.9)
Diseasefree survival (DFS)	9.1 months (3–19.5)

Tab 2 Multivariate Cox Regression Analysis to estimate the impact of mGPS and clinicopathological parameters on OS and DFS

preT	p-value	HR	95%-CI
Overall survival (OS)			
- preT-Albumin (≥35.0 g/l vs. <35.0 g/l)	0.05	0.53	0.29–0.87
- mGPS (1+2 vs. 0)	0.015	1.86	1.11–2.97
Disease free survival (DFS)			
- preT-Albumin (≥35.0 g/l vs. <35.0 g/l)	0.03	0.53	0.31–0.85
- T-stages (pT2 vs. pT3)	0.05	0.59	0.33–0.89
- mGPS (0 vs. 1+2)	0.019	1.68	1.11–2.55

Tab 3 Serum Albumin, CRP, and mGPS before Immunotherapy (preT = Pre-Immunotherapy)

Characteristic	**Included patients (n = 48)**
preT-Albumin	Mean 37.8 (+/- SD 8.6)
- < 35.0 g/l	20 (42 %)
- ≥ 35.0 g/l	28 (58 %)
preT-CRP	Mean 6,7 (+/- SD 3.9)
- < 10 mg/l	25 (53 %)
- ≥ 10 mg/l	23 (47 %)
preT-mGPS	
- 0	16 (33 %)
- 1 + 2	32 (67 %)

Tab 4 Correlation between mGPS and response rate (CR = complete response; PR = partial response; SD = stable disease)

mGPS	**Patients** (n = 48)	**Reponse** (CR+PR)	**p-value**	**clinical benefit** (CR+PR+SD)	**p-value**
mGPS 0	16	11 (71%)	0.05	12 (76%)	0.03
mGPS 1	22	7 (34%)	0.25	11 (50%)	0.37
mGPS 2	10	3 (26%)		3 (34%)	

Tab 5 Relationship between mGPS and treatment/tumor-reladed toxicities

Toxicity (CTC) ≥ Grad 2	**mGPS 0 (n = 16)**	**mGPS 1 (n = 22)**	**mGPS 2 (n = 10)**	**p-value**
Anemia	1 (9 %)	7 (34 %)	6 (60 %)	< 0.01**
Nausea/Vomiting	3 (16 %)	8 (36 %)	7 (74 %)	< 0.01**
Anorexia	3 (16 %)	8 (37 %)	6 (60 %)	< 0.01**
Mucositis	1 (6 %)	2 (10 %)	3 (34 %)	< 0.05
Fatigue	3 (18 %)	6 (30%)	5 (49 %)	< 0.01**
Immune-mediated adverse events	2 (13%)	5 (25%)	6 (61%)	<0.01**