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Modified Glasgow prognostic score predicts the prognosis of patients with advanced esophageal squamous cell carcinoma: A propensity score-matched analysis

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Abstract

Objective: The aim of this study is to evaluate the prognostic value of the modified Glasgow prognostic score (mGPS) in advanced esophageal squamous cell carcinoma (SCC) patients.

Methods: The study enrolled 311 patients with advanced esophageal SCC from January 2012 to December 2018. Univariate and multivariate analyses were calculated by the Cox proportional hazards regression model in advanced esophageal SCC patients. The Kaplan–Meier method was used to evaluate the ability of the mGPS for survival rates. Propensity score-matched (PSM) analysis was carried out to balance imbalanced variables.

Results: The Cox proportional hazards analysis showed that factors including M stage, ECOG, mGPS group, and sex were identified as independent predictors. The mGPS presented a good level of overall survival (OS) prediction with a risk-adopted classification for advanced esophageal SCC patients. The survival rates in advanced esophageal SCC patients with mGPS 0, 1, and 2 were 18.8%, 8.4%, and 4.2%, respectively ($p < 0.001$). Moreover, before and after PSM, the mGPS was associated with 3-year survival rates of advanced esophageal SCC patients in the Kaplan–Meier survival analysis. In addition, the mGPS for OS prediction demonstrated better performance than sex and ECOG score. The area under curve (AUC) of the mGPS combined with M stage for the prognosis of advanced esophageal SCC was 0.677 (0.592–0.763).

Conclusion: The mGPS is a cost-effective, accessible tool capable of prognosticating in this cohort. It could be a useful surveillance system of prognosis in advanced esophageal SCC patients.

KEYWORDS
esophageal squamous cell carcinoma, modified Glasgow prognostic score, prognosis, propensity score-matched

INTRODUCTION

Esophageal cancer is the sixth most diagnosed cancer worldwide, with about 509 000 deaths per year.[1] Esophageal squamous cell carcinoma (SCC) is the most common histology in East Asian, such as China.[2] In China, esophageal SCC accounts for about 90% of cases.[3] Although detection methods have been greatly improved, nearly 50% of esophageal cancer patients present with locally advanced disease at the time of initial diagnosis.[4] Radiation therapy and

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chemotherapy have been recommended as the optimal treatment strategies for advanced esophageal cancer patients,[2] but the 5-year overall survival (OS) rate is still poor, from 5% to 20%,[5–7] and the 5-year OS rate of metastatic esophageal cancers is only 5%.[4,8] Recently, some new treatment modalities, such as adjuvant or neoadjuvant chemoradiation therapy, immunotherapy, and targeted therapy, have been applied to improve the prognosis of esophageal cancers,[2,9] therefore the choice of treatment modality is mainly based on the assessment of the prognosis.

Recent studies have revealed that the Glasgow prognostic score (GPS) is a useful predictive scoring system in various cancers, such as renal cell carcinoma, gastric cancer, and lung cancer.[10–12] Serum C-reactive protein (CRP) and serum albumin levels are included in the GPS. However, systemic inflammation has been known to have negative prognostic value across cancers.[13] CRP is a sensitive inflammatory marker that increases in response to proinflammatory cytokines such as interleukin (IL)-1β and IL-6.[14] A growing number of studies has shown that the heavier weighting of the inflammatory factor of the GPS was found to better correlate with survival outcomes in cancers. In the study of Woosung Son, the modified GPS (mGPS) paid more attention to the role of inflammation.[15] This mGPS scoring system was assigned as follows: mGPS 0 for CRP ≤ 10 mg/L, mGPS 1 for CRP > 10 mg/L and albumin ≥3.5 g/dL, and mGPS 2 for CRP > 10 mg/L and albumin <3.5 g/dL.

Over recent decades, a number of prognostic factors for esophageal cancers have been suggested, such as the pathological tumor-node-metastasis (TNM) stage, treatment strategies, and other miscellaneous factors,[16,17] but few studies regarding the mGPS in the esophageal cancer, especially SCC, are available. Esophageal SCC is more likely to localize near the tracheal bifurcation and has a proclivity for earlier lymphatic spread,[18] therefore compared with advanced esophageal adenocarcinoma, esophageal SCC is associated with a poorer prognosis.[18] The aim of this study was to evaluate the prognostic value of the mGPS in advanced esophageal SCC patients.

METHODS

Study design

We performed a retrospective study of 311 advanced esophageal cancer patients who were treated at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between January 2012 and December 2018. The inclusion criteria were: (1) aged ≥18 years and (2) patients who were pathologically diagnosed with advanced esophageal squamous cell carcinoma. The exclusion criteria were: (1) unable to obtain complete basic
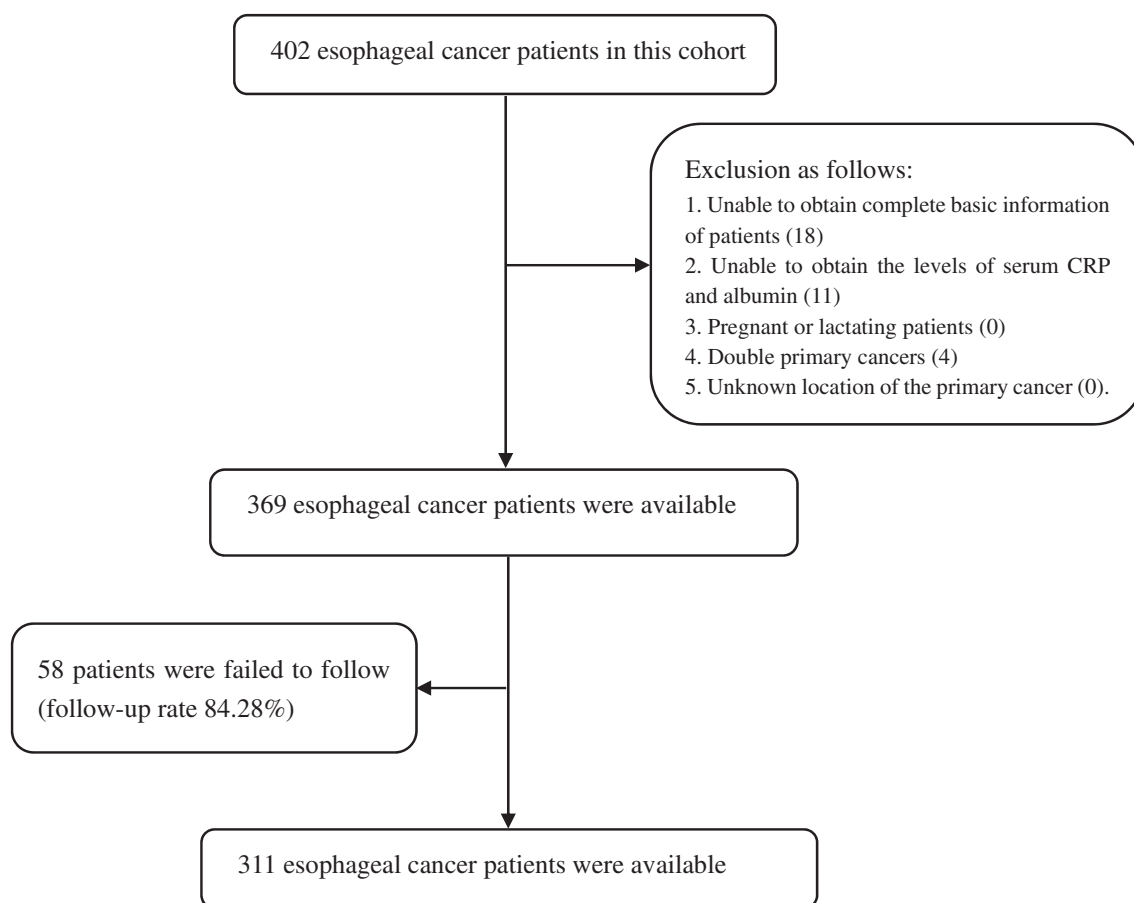
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┌─────────────────────────────────────────────┐
│ 402 esophageal cancer patients in this cohort │
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                      │
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                      │        │ Exclusion as follows:                │
                      │        │ 1. Unable to obtain complete basic   │
                      ├───────▶│    information of patients (18)      │
                      │        │ 2. Unable to obtain the levels of    │
                      │        │    serum CRP and albumin (11)        │
                      │        │ 3. Pregnant or lactating patients (0)│
                      │        │ 4. Double primary cancers (4)        │
                      │        │ 5. Unknown location of the primary   │
                      │        │    cancer (0).                       │
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│ 369 esophageal cancer patients were available │
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  ┌───────────────────────────────┐   │
  │ 58 patients were failed to     │◀──┤
  │ follow (follow-up rate 84.28%) │   │
  └───────────────────────────────┘   │
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┌─────────────────────────────────────────────┐
│ 311 esophageal cancer patients were available │
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FIGURE 1 Selection of participants in this cohort for analysis

information for patient; (2) unable to obtain levels of serum CRP and albumin; (3) pregnant or lactating; (4) double primary cancers; and (5) unknown location of the primary cancer.

Demographic and clinical data included sex, age, TNM stage, tumor location, smoking status, drinking status, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance score, radiotherapy (RT), chemotherapy (CT), diabetes mellitus, chronic obstructive pulmonary disease (COPD), etc. Pertinent laboratory values collected included serum CRP and albumin before therapy.

Procedures

Among these initial 402 subjects, we excluded participants with double primary cancers ($n = 4$), and those who did not provide the complete basic information ($n = 18$) and the levels of serum CRP and albumin ($n = 11$). Thus, a total of 369 participants were included in the study. Forty-two patients gave up treatment for financial reasons and 16 patients went to other hospitals for medical treatment. A total of 58 subjects failed to follow up (follow-up rate 84.28%). After exclusion, 311 subjects remained for further analysis. The flowchart for the selection of participants is shown in Figure 1.

mGPS and mGPS group

The serum CRP and albumin of patients obtained 30 days before therapy were assessed in this study. The mGPS was determined as follows: mGPS 0 = CRP ≤ 10 mg/L, mGPS 1 = CRP > 10 mg/L and albumin ≥3.5 g/dL, and mGPS 2 = CRP > 10 mg/L and albumin <3.5 g/dL. In this study, there were only 24 cases in mGPS 2, therefore mGPS 1 and mGPS 2 were combined. The mGPS group was determined as follows: mGPS group 0 = mGPS 0; mGPS group 1 was defined by the combination of mGPS 1 and mGPS 2.

Follow-up

During follow-up, inpatient and outpatient examinations and regular telephone follow-ups were conducted until the patient's death or December 31, 2021. All patients were followed up by telephone once a year, and their condition was also obtained during outpatient and inpatient visits. The OS was defined as the time from the date of diagnosis to the date of death caused by any reason. Patients who were alive at the last follow-up were censored. Patients lost to follow-up were defined as surviving patients with <3 years of follow-up and those with no record of follow-up within the last year. The median OS of mGPS group 0 was 28.5 months and that of mGPS group 1 was 17 months.

TABLE 1 Patient characteristics

Characteristic	Patient number (n = 311) (%)
Sex	
Female	53 (17.00%)
Male	258 (83.00%)
Age (years)	
<60	154 (49.52%)
≥60	157 (50.48%)
T stage	
T1–2	42 (13.50%)
T3–4	269 (86.50%)
N stage	
N0	24 (7.72%)
N1–3	287 (92.28%)
Distant metastasis	
No	170 (54.66%)
Yes	141 (45.34%)
BMI	
<25	238 (76.53%)
≥25	73 (23.47%)
ECOG	
0–1	243 (78.14%)
2–3	68 (21.86%)
Smoking	
No	83 (26.7%)
Yes	228 (73.3%)
Drinking	
No	83 (26.69%)
Yes	228 (73.31%)
Location	
Upper	90 (28.94%)
Middle	144 (46.30%)
Lower	77 (24.76%)
Diabetes mellitus	
No	279 (89.71%)
Yes	32 (10.29%)
COPD	
No	296 (95.18%)
Yes	15 (4.82%)
Treatment modality	
RT or CT	153 (49.20%)
RT and CT	158 (50.80%)
mGPS	
0	192 (61.74%)
1	95 (30.55%)
2	24 (7.71%)
mGPS group	
0	192 (61.74%)
1	119 (38.26%)

TABLE 2 Univariate and multivariate Cox proportional hazard analysis of factors associated with survival rates

Variable	Univariate analysis HR (95% CI)	p value	Multivariate analysis HR (95% CI)	p value
Sex				
Female	Ref	NA		
Male	0.695 (0.502–0.960)	0.028	0.663 (0.440–0.999)	0.049
Age (years)				
<60	Ref	NA		
≥60	1.139 (0.894–1.451)	0.293		
T stage				
T1–2	Ref	NA		
T3–4	1.196 (0.841–1.700)	0.320		
N stage				
N0	Ref	NA		
N1–3	1.878 (1.159–3.041)	0.010	1.600 (0.971–2.638)	0.065
Distant metastasis				
No	Ref	NA		
Yes	1.495 (1.174–1.904)	0.001	1.502 (1.159–1.946)	0.002
BMI				
<25	Ref	NA		
≥25	0.936 (0.703–1.246)	0.649		
ECOG				
0–1	Ref	NA		
2–3	1.425 (1.061–1.913)	0.019	1.754 (1.284–2.396)	0.000
Smoking				
No	Ref	NA		
Yes	1.288 (0.979–1.694)	0.071		
Drinking				
No	Ref	NA		
Yes	1.332 (1.010–1.756)	0.042	0.940 (0.660–1.339)	0.733
Location				
Upper	Ref	NA		
Middle	0.945 (0.708–1.261)	0.700		
Lower	1.197 (0.864–1.658)	0.279		
Treatment modality				
CT or RT	Ref	NA		
CT and RT	0.742 (0.582–0.945)	0.016	0.827 (0.646–1.059)	0.133
Chemotherapy				
Paclitaxel + platinum drugs	Ref	NA		
Fluorouracil + platinum drugs	0.924 (0.634–1.348)	0.682		
Nituzumab	1.136 (0.696–1.856)	0.610		
Other chemotherapeutic drugs	1.602 (0.746–3.440)	0.227		
Radiotherapy				
≤55 Gy	Ref	NA		
>55 Gy	0.850 (0.649–1.113)	0.237		
Diabetes mellitus				
No	Ref			
Yes	0.994 (0.672–1.472)	0.978		

(Continues)

TABLE 2 (Continued)

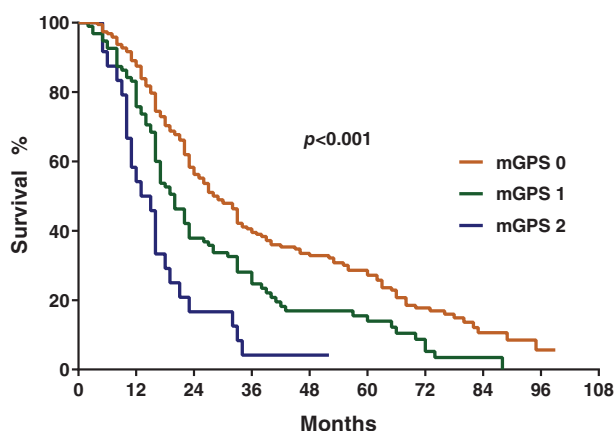| Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
COPD				
No	Ref			
Yes	0.968 (0.541–1.731)	0.911		
mGPS				
0	Ref	NA		
1	1.598 (1.227–2.083)	0.001	1.512 (1.156–1.978)	0.003
2	3.062 (1.957–4.789)	0.000	2.766 (1.751–4.369)	0.000

Abbreviations: NA, not applicable; Ref, reference group.

FIGURE 2 Kaplan–Meier survival curves stratified by the mGPS. The survival rates in advanced esophageal SCC patients with mGPS 0, 1, and 2 were 18.8%, 8.4%, and 4.2%, respectively ($p < 0.001$)

Ethics statement

The study was approved by the local ethics committee from the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 21/110–2781). As a retrospective study in which data analysis was performed anonymously, this study was exempt from obtaining informed consent from patients.

Statistical analysis

The potential risk variables (sex, age, TNM stage, tumor location, smoking status, drinking status, BMI, ECOG performance score, diabetes mellitus, COPD, RT, CT, mGPS group) for the prognosis of advanced esophageal SCC were analyzed by univariate Cox regression analysis. Significant factors ($p < 0.05$) in the univariate Cox regression analysis were entered into multivariate analysis models. The survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Propensity score-matched (PSM) analysis was conducted to diminish the bias between two groups; 1:1 PSM ratio without replacement was used to match patients in mGPS group 0 with patients in mGPS group 1; The propensity score was within the designated caliper size. After PSM, survival rates and baseline covariates were compared between these two groups. The characteristics of mGPS group 0 and mGPS group 1 were assessed by Pearson's χ^2 tests. The ROC and calculated area under curve (AUC) were used to estimate the prognostic capability of the mGPS group. The integrated AUC was used to combine the mGPS group and the distant metastasis. All statistical analyses were performed with SPSS software (Version 23; SPSS Inc., IBM). A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

We identified 311 advanced esophageal SCC patients who met the inclusion criteria (Table 1). Within this study, 83.00% of patients were male and 50.48% of patients were age ≥60 years. The large majority (86.50%) of patients had either T stage 3 or 4. The large majority (92.28%) of patients had N stage 1–3 and 45.34% of patients had distant metastasis. The large majority (76.53%) of patients had BMI <25. The majority (78.14%) of patients had an ECOG score of 0 or 1. Over half of the patients (50.80%) received a combination of RT and CT. At baseline, 61.74%, 30.55%, and 7.71% of the cohort had mGPS 0, 1, and 2, respectively. At baseline, 61.74% and 38.26% of the cohort had mGPS group 0 and 1, respectively.

Univariate and multivariate analyses and identification of prognostic factors

Cox proportional hazards analysis was performed in this study to evaluate each variable in predicting overall survival rates. Univariate analyses indicated that factors such as sex, N stage, distant metastasis, ECOG score, drinking, treatment modality, and mGPS were associated with the prognosis of

T A B L E 3 Clinical characteristics of advanced esophageal SCC patients before and after PSM stratification by the mGPS group

|	Before match			After match		
	mGPS group 0 (n, %)	mGPS group 1 (n, %)	p value	mGPS group 0 (n, %)	mGPS group 1 (n, %)	p value
Total number	192	119		112	112	
Female	35 (66.0%)	18 (34.0%)	0.479	18 (51.4%)	17 (48.6%)	0.854
Age ≥60	91 (58.0%)	66 (42.0%)	0.167	52 (44.8%)	64 (55.2%)	0.109
T stage 3–4	161 (59.9%)	108 (40.1%)	0.083	92 (47.7%)	101 (52.3%)	0.082
N stage 1–3	175 (61.0%)	112 (39.0%)	0.340	104 (49.5%)	106 (50.5%)	0.581
Distant metastasis	84 (59.6%)	57 (40.4%)	0.475	48 (48.5%)	51 (51.5%)	0.686
BMI ≥25	45 (61.6%)	28 (38.4%)	0.985	26 (50.0%)	26 (50.0%)	1.000
ECOG 2–3	36 (52.9%)	32 (47.1%)	0.091	29 (50.0%)	29 (50.0%)	1.000
Smoking	138 (60.5%)	90 (39.5%)	0.467	84 (49.4%)	86 (50.6%)	0.755
Drinking	136 (59.6%)	92 (40.4%)	0.209	89 (49.7%)	90 (50.3%)	0.868
Diabetes Mellitus	20 (62.5%)	12 (37.5%)	0.925	13 (54.2%)	11 (45.8%)	0.666
COPD	9 (60.0%)	6 (40.0%)	0.887	6 (50.0%)	6 (50.0%)	1.000
Location middle	92 (63.9%)	52 (36.1%)	0.768	58 (54.7%)	48 (45.3%)	0.132
Location upper	46 (59.7%)	31 (40.3%)		32 (52.5%)	29 (47.5%)	
RT and CT	107 (67.7%)	51 (32.3%)	0.027	45 (47.9%)	49 (52.1%)	0.588
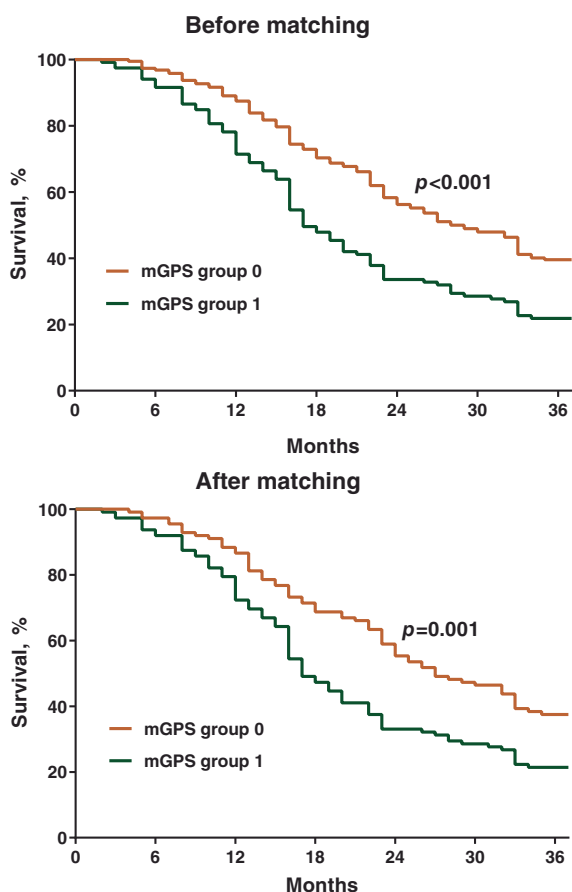
F I G U R E 3 Comparison of the 3-year survival rates between mGPS group 0 and mGPS group 1. In the PSM analysis, 112 patients were selected from mGPS group 1 with matched pairings of 112 patients from mGPS group 0 using a nearest-neighbor algorithm. Before matching, the 3-year survival was 18.8% in mGPS group 0 versus 7.6% in mGPS group 1 ($p < 0.001$). After matching, the 3-year survival was 19.6% in mGPS group 0 versus 7.1% in mGPS group 1 ($p < 0.001$)

patients (Table 2). Factors with $p < 0.05$ in univariate analyses were further analyzed in the multivariate analyses. Finally, the factors of sex, distant metastasis, ECOG score 2–3, and mGPS 1–2 were identified as independent predictors of survival rates (Table 2).

Propensity score-matching analysis

The survival rates in advanced esophageal SCC patients with mGPS 0, 1, and 2 were 18.8%, 8.4%, and 4.2%, respectively ($p < 0.001$) (Figure 2). There were only 24 cases in the mGPS 2 group. Therefore, the mGPS 1 and mGPS 2 groups were combined in this study. mGPS group 0 = mGPS 0; mGPS group 1 was a combination of mGPS 1 and mGPS 2.

As the risk factors were imbalanced between mGPS group 1 and mGPS group 0, we applied a 1:1 PSM ratio to minimize these differences. In the PSM analysis, 112 patients were selected from mGPS group 1 with matched pairings of 112 patients from mGPS group 0 using a nearest-neighbor algorithm. These characteristics were balanced and evenly distributed between the two groups (all $p > 0.05$) (Table 3). The Kaplan–Meier survival curves for the matched groups are shown in Figure 3. Before matching, the 3-year survival was 18.8% in the mGPS group 0 versus 7.6% in the mGPS group 1 ($p < 0.001$). After matching, the 3-year survival was 19.6% in the mGPS group 0 versus 7.1% in the mGPS group 1 ($p < 0.001$).

Comparison of the predictive accuracy for OS between the mGPS group and other risk factors (sex, distant metastasis, ECOG score 2–3)

As shown in Figure 4, sex, distant metastasis, and ECOG score 2–3 showed good levels of prognostic stratification between low-risk and high-risk patients (all $p < 0.05$).
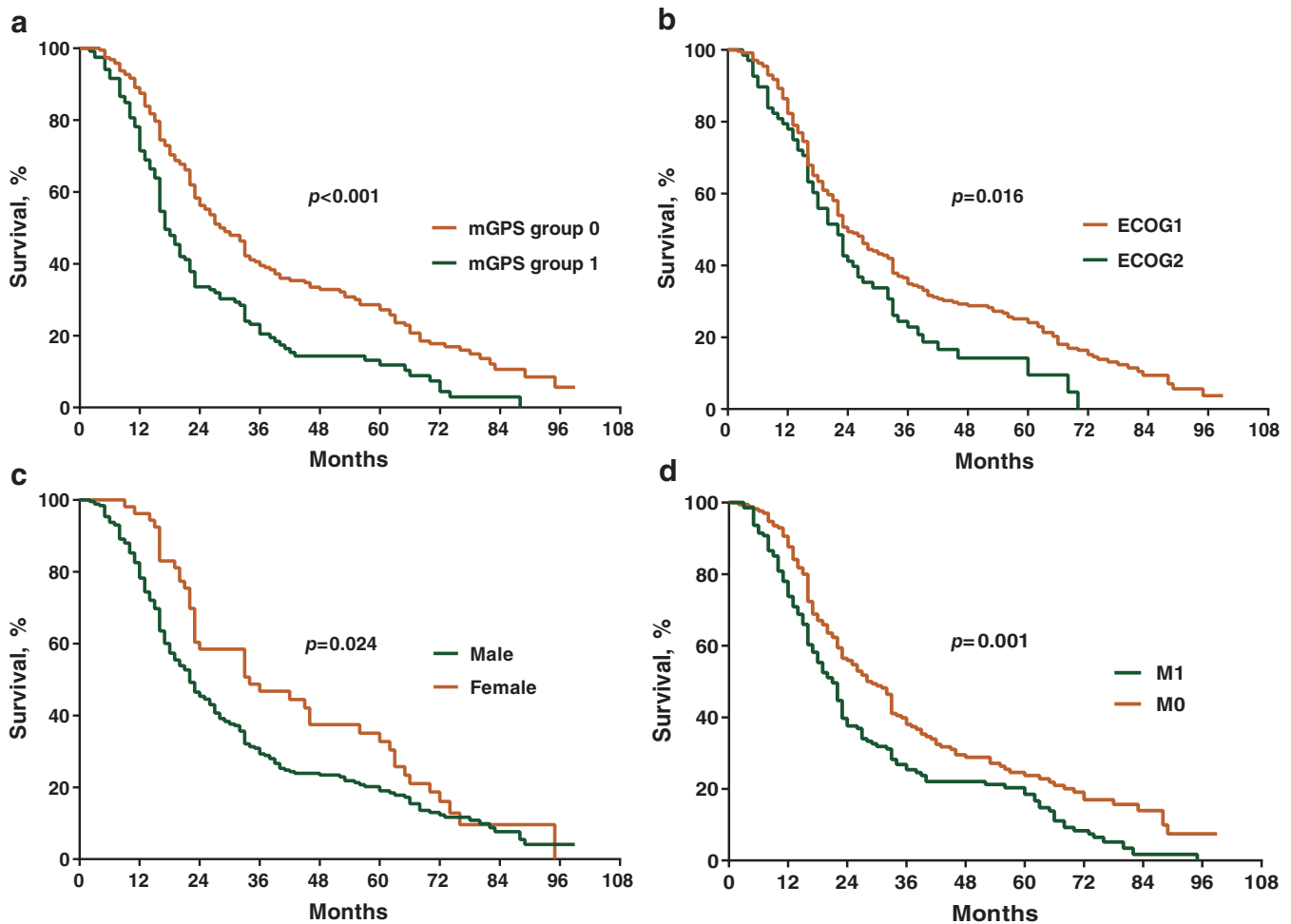
FIGURE 4 Kaplan–Meier survival curves according to mGPS group and other risk factors (sex, distant metastasis, ECOG score 2–3)
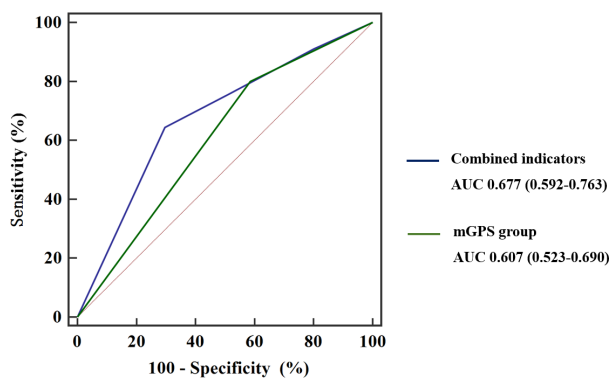

FIGURE 5 Receiver operating characteristic (ROC) among the mGPS and combined indicators for survival rates. The ROC curve of the mGPS showed the AUC value to eb 0.607 (0.523–0.690). The AUC of the mGPS combined with M stage was 0.677 (0.592–0.763)

However, sex was unsatisfactory for the stratification of patients after 72 months (Figure 4c). In addition, the ECOG score was not satisfactory for discriminating between low-risk and high-risk patients within 24 months (Figure 4b). The ROC of the mGPS group revealed an AUC value of 0.607 (0.523–0.690) (Figure 5). The AUC of the mGPS

group combined with M stage was 0.677 (0.592–0.763) (Figure 5).

DISCUSSION

Esophageal cancers are histologically classified as SCC and adenocarcinoma, which differ in their tumor location, pathology, and prognosis.[18] In contrast to adenocarcinoma, SCC is more likely to localize near the tracheal bifurcation and has a proclivity for earlier lymphatic spread,[18] therefore esophageal SCC have worse survival rates than adenocarcinoma.[18] In China, the large majority of esophageal pathological type is SCC and about 50% of esophageal cancer patients present with locally advanced disease at the time of initial diagnosis.[4] China still has a large disease burden from esophageal cancers. Recently, advances have occurred in the multidisciplinary treatment of advanced esophageal cancers, such as adjuvant or neoadjuvant chemoradiation therapy, immunotherapy, and targeted therapy, but the OS is still poor,[19,20] therefore assessing the prognostic factors of advanced esophageal cancers will become more and more important.

Although the pathological TNM stage is well known as a predictive prognosis factor, the survival outcomes of esophageal cancer patients with the same TNM stage still vary widely.[21] In addition, multiple factors can influence the prognosis of esophageal cancer patients, such as treatment modality, psychological factors, and behavior habits, which will affect the progression of disease.

In our study, Cox proportional hazards analysis showed that factors including M stage, ECOG, mGPS group, and sex were identified as independent predictors. In the study by Cheng and Xin,[4,7] multivariate Cox regression also suggested that TNM stage and sex were independent prognostic factors for advanced esophageal cancer patients.[4,7] ECOG performance status is a widely used method of assessing the functional status of cancer patients in many studies.[22–24] In addition, we found that the mGPS, based on serum CRP and albumin, is a cost-effective, accessible tool capable of prognosticating in this cohort of advanced esophageal SCC patients. Recent studies have revealed that mGPS is inversely related to prognosis in a variety of cancers, such as urothelial carcinoma, colorectal cancer, gastric cancer, and lung cancer,[11,12,15,25] but few studies regarding mGPS in esophageal cancer are available, especially SCC.

In the present study, the Kaplan–Meier survival analysis showed that survival rates in advanced esophageal SCC patients with mGPS 0, mGPS 1, and mGPS 2 were 18.8%, 8.4%, and 4.2%, respectively ($p < 0.001$). This result is similar to that of Dolan and Kikuchi.[26,27] Because the number of mGPS 2 cases was only 24, we combined mGPS 1 and mGPS 2 to form mGPS group 1, and defined mGPS 0 as mGPS group 0. As the risk factors were imbalanced between mGPS group 1 and mGPS group 0, we applied a 1:1 PSM ratio to minimize these differences. The Kaplan–Meier survival curves for the matched groups showed that the mGPS group still remained an independent predictor for survival rates. The potential mechanisms may be used to explain the prognostic values of the mGPS in cancers. Increasing evidence suggests that inflammation and nutritional status are involved in the development of cancers and affect the clinical prognosis.[28–30] These inflammatory mediators promote the proliferation, invasion, and metastasis of cancer cells, and help cancer cells to evade the immune surveillance.[31] Serum CRP is an acute reactive protein synthesized by liver cells or cancer cells that can produce an attractive environment for cancer cell proliferation, promote angiogenesis, induce DNA damage, and favor neoplastic metastasis, revealing the level of inflammation in the body.[26,27] Albumin reflects the malnutrition status of the body, triggers the malignant transformation, and promotes the progression of tumors.[24]

The multivariate analysis suggested that sex, M stage, and ECOG score showed good levels of prognostic stratification between low-risk and high-risk patients (all $p < 0.05$). However, the mGPS for OS prediction demonstrated a better performance than that of sex and ECOG score. Sex was unsatisfactory for the stratification of patients after 72 months and the ECOG score was not satisfactory for discriminating between low-risk and high-risk patients within 24 months. The mGPS scoring system can effectively predict the prognosis of cancers. The ROC of the mGPS group revealed an AUC value of 0.607. When the mGPS group was combined with M stage, the AUC reached 0.677.

There are several limitations in the study. First, this study was retrospective and there may be some selection bias in the data collection. However, we used PSM analysis, which can minimize the baseline differences between two groups. Second, this study was conducted at a single center using a relatively small number of patients. Thus, a multicenter, prospective study is required to further verify this result.

CONCLUSION

The mGPS is a cost-effective, accessible tool capable of prognosticating in this cohort. It could be a useful surveillance system for prognosis in advanced esophageal SCC patients.

CONFLICT OF INTEREST
None declared.

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