


Glasgow Prognostic Score Serves as a Prognostic Factor of Clinical Outcome in Patients with Newly Diagnosed Multiple Myeloma

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Purpose: The Glasgow Prognostic Score (GPS), a systemic inflammation-based prognostic model incorporating C-reactive protein (CRP) and serum albumin levels, has been widely validated in solid tumors and several hematologic malignancies. However, its prognostic value in newly diagnosed multiple myeloma (NDMM) remains unclear. This study aimed to evaluate the association between GPS and survival outcomes in NDMM patients.

Patients and Methods: We retrospectively analyzed a real-world cohort of 865 NDMM patients. Patients were stratified based on GPS, and overall survival (OS) and progression-free survival (PFS) were assessed by using Kaplan-Meier analysis. Cox proportional hazards models were used to determine the independent prognostic significance of GPS, adjusting for confounding factors. To compare the prognostic stratification capacity of GPS to its two modified variants, the same Kaplan-Meier analysis was applied to evaluate both the modified Glasgow Prognostic Score (mGPS) and the hypersensitivity-modified Glasgow Prognostic Score (Hs-mGPS). Quantitative comparisons utilized area under the curve (AUC) values derived from time-dependent Receiver Operating Characteristic (ROC) analysis.

Results: A higher GPS was significantly associated with inferior OS and PFS in NDMM patients. Multivariate analysis confirmed that GPS was an independent prognostic factor after adjusting for disease stage and other clinical variables. Additionally, patients with elevated GPS scores presented with more advanced disease stages, as reflected by higher Durie-Salmon and International Staging System (ISS) classifications. And GPS exerts better prognostic stratification capacity than mGPS and Hs-mGPS.

Conclusion: The baseline GPS at the time of diagnosis is an independent prognostic factor that negatively relates to the MM patient survival, for which GPS may serve as a supplement tool in risk stratification upon the primary medical assessment.

Keywords: multiple myeloma, survival, inflammation model, prognosis

Introduction

Multiple myeloma (MM) is a heterogeneous, hematological malignancy, which is characterized by monoclonal proliferation of malignant plasma cells accumulated in the bone marrow and production of abnormal monoclonal immunoglobulin.¹ Multiple myeloma, the second most prevalent blood cancer in high-income countries, has an increasing global incidence rate, which is approximately 6–7 per 100,000 people per year.^{2,3}

Although, with the application of novel agents, including proteasome inhibitors,⁴ immunomodulatory drugs,⁵ CD38 targeting antibodies,⁶ as well as CAR-T cell therapy,⁷ bispecific antibodies,⁸ and immune checkpoint inhibitors,⁹ the life

expectancy of MM has achieved encouraging improvement, but the majority of MM patients will experience the relapses or progression of the disease, for which MM is still considered to be incurable. For that reason, it is important to perform risk stratification within the MM population for their individualized precision therapy. Nowadays, several staging systems, including Durie-Salmon (DS) stage,¹⁰ International Staging System (ISS),¹¹ the Revised ISS (R-ISS),¹² and Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART)¹³ have been used to guide clinical work. However, even for R-ISS, the most widely applied staging system, its capability of predicting survival or performing stratification of patients is still limited.¹⁴ Therefore, a new staging system with convenient indicators that improve the accuracy and sensitivity of prognosis is highly required for precision treatment in MM.

The Glasgow prognostic score (GPS)¹⁵ is a simple index that expresses the degree of inflammation within the body. In this score, there are two biomarkers, C-reactive protein (CRP) and serum albumin. CRP is an acute-phase protein that reflects the systemic inflammation levels. Furthermore, the serum concentration of CRP is negatively correlated with prognosis within a variety of cancers, probably because it is modulated by several proinflammatory cytokines like IL-1, IL-6, and TNF- α .¹⁶ And for serum albumin, research has indicated that hypoalbuminemia is associated with poor survival chances.¹⁷ GPS ranges from 0 to 2 points, with 1 point assigned for each of the following: increasing CRP level ($>10\text{mg/L}$) and hypoalbuminemia ($<35\text{g/L}$). The modified GPS (mGPS) and the high-sensitivity modified GPS (Hs-mGPS) are two modified versions of the original GPS. mGPS highlights the significance of CRP, where cases with hypoalbuminemia but without elevated CRP levels remain scored as 0 points.¹⁵ Hs-mGPS, which has a more sensitive cut-off value for CRP (3mg/L), has been proven to enhance the prognostic value of the mGPS.¹⁸

Several previous studies have proven that GPS has the capabilities of predicting patients' survival in various types of cancers, including non-small cell lung cancer,¹⁹ colorectal cancer,²⁰ prostate cancer²¹ and so on. However, in MM, the prognostic value of GPS has not been verified yet. Considering that immunity and inflammatory response contribute to the progression of MM,²² we assume that GPS may also be applicable for prognostic prediction in MM. Therefore, the current study aimed to validate the prognostic value of GPS in a large population of newly diagnosed multiple myeloma (NDMM).

Patients and Methods

Patient Selection

In this retrospective study, the clinical and laboratory data of a total of 865 patients with NDMM between July 2001 and August 2021 were collected and analyzed. The specific inclusion criteria for our study were as follows: 1) age ≥ 18 years; 2) newly diagnosed multiple myeloma based on the International Myeloma Working Group (IMWG) diagnostic criteria; 3) all patients should receive antineoplastic therapy; 4) complete baseline clinical and laboratory data were available before treatment. Specific data were shown in the Results section. All these data were collected from the electronic medical record. Patients with any exclusion criteria as follows were excluded from this study: 1) diagnosed with MM and comorbid with other neoplastic disease; 2) had received antineoplastic therapy before being diagnosed in our center. 3) did not receive any antineoplastic therapy after being diagnosed; 4) diagnosed with other plasma cell dyscrasias such as Waldenström macroglobulinemia, primary AL amyloidosis, systemic light chain deposition disease; 5) lacked sufficient baseline data for analysis. All the patients were divided into three subgroups based on their GPS at diagnosis, and these groups were designated as GPS-0, GPS-1, and GPS-2 in the subsequent text.

The primary endpoint we measured was overall survival (OS), which was defined as the time from the date of diagnosis to the date of death for any reason or the time of last follow-up, and the progression-free survival (PFS) was defined as the time interval between the date of diagnosis to the date of progression based on the IMWG criteria, death from any cause, or the last follow-up.

GPS/mGPS/Hs-mGPS Calculation

Table 1 presents the specific calculation rules for the scores of GPS, mGPS, and Hs-mGPS.

Table 1 The Scoring Criteria for GPS, mGPS, and Hs-mGPS

The Glasgow Prognostic Score (GPS)	Score
C-reactive protein \leq 10mg/L and albumin \geq 35g/L	0
C-reactive protein > 10mg/L or albumin < 35g/L	1
C-reactive protein > 10mg/L and albumin < 35g/L	2
The modified Glasgow prognostic score (mGPS)	
C-reactive protein \leq 10mg/L (regardless of albumin level)	0
C-reactive protein > 10mg/L and albumin \geq 35g/L	1
C-reactive protein > 10mg/L and albumin < 35g/L	2
The high-sensitivity modified Glasgow prognostic score (Hs-mGPS)	
C-reactive protein \leq 3mg/L (regardless of albumin level)	0
C-reactive protein > 3mg/L and albumin \geq 35g/L	1
C-reactive protein > 3mg/L and albumin < 35g/L	2

Statistical Analysis

All clinical and laboratory data were presented as categorical variables and were analyzed by the chi-square test. To assess the relationship between baseline GPS/mGPS/Hs-mGPS and the survival outcome (OS and PFS), Kaplan-Meier curves were drawn and compared by the Log rank test. The median follow-up, median OS, median PFS, five-year OS rate, and five-year PFS rate were obtained through Kaplan-Meier analysis. Univariate (UVA) and multivariate (MVA) analyses were carried out using the Cox proportional hazard model for OS and PFS. The performance of each GPS variant was assessed by area under the curve (AUC) values at 1, 3, and 5 years, based on time-dependent receiver operating characteristic (ROC) analysis. A two-sided p-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using R 4.3.1.

Results

Patient Characteristics

A total of 865 eligible patients were included in this study. Patients' characteristics are provided in [Table 2](#). The median age was 60 years, and 83.5% of patients were over 50 years old when diagnosed. Of the included patients, 60.2% were male. 89.2% of patients showed a good performance status (ECOG PS 0–1).

The median GPS at diagnosis was 1, and at baseline, the number of patients with GPS of 0, 1, and 2 were 402, 343, and 120, respectively. Patients with high GPS were more likely to have a worse performance status (ECOG PS \geq 2 (GPS ranges from 0 to 2): 6.2% vs 12.8% vs 20.0%, $p < 0.001$), higher DS stage (percentage of DS III (GPS ranges from 0 to 2): 65.2% vs 79.6% vs 85.0%, $p < 0.001$), and higher ISS stage (percentage of ISS III (GPS ranges from 0 to 2): 29.6% vs 46.6% vs 60.0%, $p < 0.001$). Among all the patients, the patients with high GPS at baseline had lower β 2-MG level (β 2-MG \leq 3.5g/L (GPS ranges from 0 to 2): 38.1% vs 66.5% vs 80.0%, $p < 0.001$) and higher LDH level (LDH > 265U/L (GPS ranges from 0 to 2): 7.5% vs 12.5% vs 23.3%, $p < 0.001$). Compared with the lower GPS group, the group with high GPS tended to have impaired renal function, manifesting as elevated creatinine level (CRE > upper limit of normal (GPS ranges from 0 to 2): 20.1% vs 29.7% vs 43.3%, $p < 0.001$). However, we found that patients with high GPS were less frequently comorbid with extramedullary disease (percentage of EMD (GPS ranges from 0 to 2): 26.6% vs 20.7% vs 15.8%, $p = 0.024$). In the following treatment, 12.5% of patients received a transplant, and the chemotherapy regimens patients received were proteasome-based regimens in 29.4%, immunomodulatory-based regimens in 23.3%, regimens combining proteasome and immunomodulatory agents in 23.7%, and other types of chemotherapy in 23.6%.

Baseline GPS Correlated with Survival Outcomes in Kaplan-Meier Analysis

Firstly, we evaluated the association between patients' survival outcomes and baseline GPS in three subgroups. The median follow-up of the study was 47 months. For all 865 patients, the median OS was 58 months (95% CI, 53–66), and the median PFS was 35 months (95% CI, 30–39), as shown in [Figure 1](#). The 5-year OS of patients with baseline GPS of

Table 2 Clinical and Laboratory Characteristics for All Patients Based on GPS Level

Characteristics	All patients n=865	GPS-0 n=402	GPS-1 n=343	GPS-2 n=120	P value
Age(years)					0.003
≤50	143(16.5)	84(20.9)	48(14.0)	11(9.2)	
>50	722(83.5)	318(79.1)	295(86.0)	109(90.8)	
Sex					0.007
Male	521(60.2)	222(55.2)	215(62.7)	84(70.0)	
Female	344(39.8)	180(44.8)	128(37.3)	36(30.0)	
ECOG					<0.001
0-1	772(89.2)	377(93.8)	299(87.2)	96(80.0)	
≥2	93(10.8)	25(6.2)	44(12.8)	24(20.0)	
Transplant					0.346
Yes	108(12.5)	57(14.2)	39(11.4)	12(10.0)	
No	757(87.5)	345(85.8)	304(88.6)	108(90.0)	
DS					<0.001
I	70(8.1)	45(11.2)	21(6.1)	4(3.3)	
II	158(18.3)	95(23.6)	49(14.3)	14(11.7)	
III	637(73.6)	262(65.2)	273(79.6)	102(85.0)	
ISS					<0.001
I	248(28.7)	212(52.7)	36(10.5)	0(0.0)	
II	266(30.7)	71(17.7)	147(42.9)	48(40.0)	
III	351(40.6)	119(29.6)	160(46.6)	72(60.0)	
β2-MG(g/L)					<0.001
>3.5	388(44.9)	249(61.9)	115(33.5)	24(20.0)	
≤3.5	477(55.1)	153(38.1)	228(66.5)	96(80.0)	
LDH(U/L)					<0.001
>265	101(11.7)	30(7.5)	43(12.5)	28(23.3)	
≤265	764(88.3)	372(92.5)	300(87.5)	92(76.7)	
CRE					0.001
>ULN	235(27.2)	81(20.1)	102(29.7)	52(43.3)	
≤ULN	630(72.8)	321(79.9)	241(70.3)	68(56.7)	
EMD					0.024
Yes	197(22.8)	107(26.6)	71(20.7)	19(15.8)	
No	668(77.2)	295(73.4)	272(79.3)	101(84.2)	
Treatment					0.148
PIs	254(29.4)	117(29.1)	101(29.4)	36(30.0)	
IMids	202(23.3)	90(22.4)	85(24.8)	27(22.5)	
PI+IMids	205(23.7)	110(27.4)	75(21.9)	20(16.7)	
Other	204(23.6)	85(21.1)	82(23.9)	37(30.8)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; DS, Durie-Salmon staging system; ISS, international staging system; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; CRE, creatinine, ULN, upper limit of normal; EMD, extramedullary disease.

0, 1, and 2 were 56.6%, 42.2%, and 37.9%, respectively. The 5-year PFS of patients in three subgroups were 39.8%, 32.7%, and 24.3%, respectively.

Considering that GPS is a categorical variable, Kaplan-Meier survival curves were constructed for each subgroup. And we applied the Log rank test to compare the OS and PFS between the three GPS subgroups, for which we confirmed that the higher the GPS at baseline was, the worse the survival outcomes would be. (median OS (GPS ranges from 0 to 2): 77 months (95% CI, 63–138) vs 48 months (95% CI, 42–60) vs 44 months (95% CI, 31–62), $p<0.001$; median PFS (GPS ranges from 0 to 2): 42 months (95% CI, 36–55) vs 27 months (95% CI, 23–38) vs 24 months (95% CI, 17–36), $p<0.001$; Figure 2).

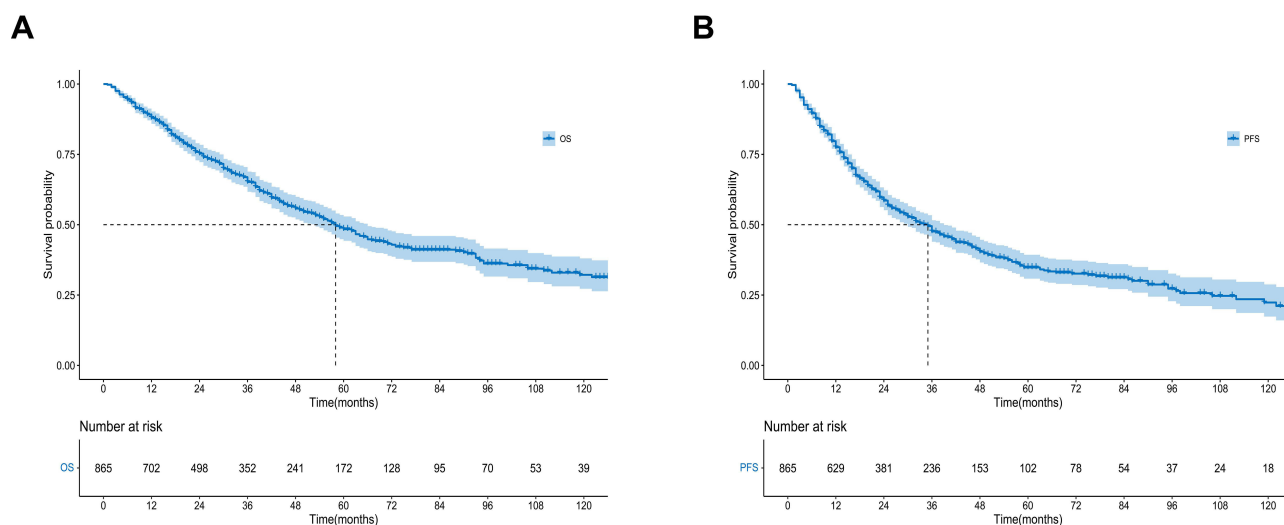


Figure 1 Survival curves for all patients (n=865) obtained with Kaplan-Meier analysis. (A) Survival curves for OS. (B) Survival curves for PFS.

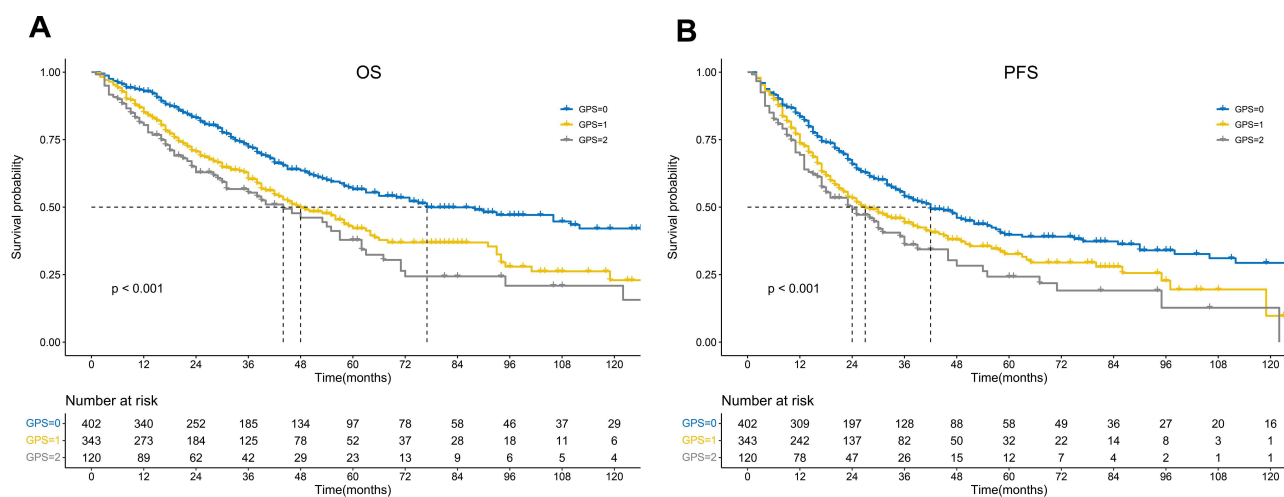


Figure 2 Survival curves obtained with Kaplan-Meier analysis between different GPS groups. (A) Survival curves for OS. (B) Survival curves for PFS.

Baseline GPS Serves as an Independent Prognostic Factor of PFS and OS in Univariate and Multivariate Analyses

Tables 3 and 4 demonstrated the correlation derived from Cox regression analyses between multiple variables, including GPS and survival outcomes (PFS and OS), for both univariable and multivariable assessments. In UVA, GPS was significantly associated with both OS and PFS. (OS: HR 1.721 (95% CI 1.394–2.125), $p < 0.001$, Table 3; PFS: HR 1.487 (95% CI 1.233–1.794), $p < 0.001$, Table 4) The result of following MVA revealed that baseline GPS is an independent prognostic factor for OS and PFS in patients with newly diagnosed multiple myeloma. (OS: HR 1.290 (95% CI 1.025–1.623), $p = 0.030$, Table 3; PFS: HR 1.245 (95% CI 1.017–1.524), $p = 0.034$, Table 4) Besides GPS, poor ECOG PS (OS: HR 1.842 (95% CI 1.399–2.425), $p < 0.001$, Table 3; PFS: HR 1.558 (95% CI 1.197–2.027), $p < 0.001$, Table 4) as well as not receiving transplant (OS: HR 0.578 (95% CI 0.387–0.862), $p = 0.007$, Table 3; PFS: HR 0.693 (95% CI 0.505–0.953), $p = 0.024$, Table 4) and LDH > 265 U/L (OS: HR 1.838 (95% CI 1.402–2.410), $p < 0.001$, Table 3; PFS: HR 1.891 (95% CI 1.471–2.432), $p < 0.001$, Table 4) were found to be independent risk factors for both OS and PFS in MVA. However, we found that the DS stage and ISS, which are widely used in clinical practice, only showed differences among the three groups in UVA, but not in MVA (Table 3 and Table 4).

Table 3 Univariate and Multivariate Analysis of Variables Associated with Overall Survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P value	HR(95% CI)	P value
Age(>50 vs ≤50 years)	1.757(1.289–2.395)	<0.001	1.468(1.070–2.014)	0.017*
Sex(Female vs Male)	0.987(0.802–1.215)	0.902	–	
ECOG(≥2 vs 0–1)	2.245(1.719–2.930)	<0.001	1.842(1.399–2.425)	<0.001*
Transplant(Yes vs No)	0.452(0.306–0.669)	<0.001	0.578(0.387–0.862)	0.007*
DS(III vs I+II)	1.327(1.056–1.669)	0.015	0.983(0.772–1.253)	0.892
ISS(III vs I+II)	1.771(1.431–2.190)	<0.001	1.211(0.935–1.567)	0.147
β2-MG(>3.5 vs ≤3.5g/L)	1.952(1.575–2.418)	<0.001	1.282(0.979–1.678)	0.071
LDH(>265 vs ≤ 265U/L)	2.271(1.747–2.953)	<0.001	1.838(1.402–2.410)	<0.001*
CRE(>ULN vs ≤ULN)	1.558(1.250–1.942)	<0.001	1.148(0.894–1.473)	0.280
EMD(Yes vs No)	0.800(0.608–1.052)	0.111	–	
GPS(≥1 vs 0)	1.721(1.394–2.125)	<0.001	1.290(1.025–1.623)	0.030*

Note: *Indicates P value < 0.05.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; DS, Durie-Salmon staging system; ISS, international staging system; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; CRE, creatinine, ULN, upper limit of normal; EMD, extramedullary disease.

Table 4 Univariate and Multivariate Analysis of Variables Associated with Progression-Free Survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P value	HR(95% CI)	P value
Age(>50 vs ≤50 years)	1.260(0.976–1.625)	0.076	–	
Sex(Female vs Male)	1.008(0.836–1.215)	0.932	–	
ECOG(≥2 vs 0–1)	1.797(1.392–2.319)	<0.001	1.558(1.197–2.027)	<0.001*
Transplant(Yes vs No)	0.632(0.461–0.866)	0.004	0.693(0.505–0.953)	0.024*
DS(III vs I+II)	1.318(1.071–1.621)	0.009	1.096(0.880–1.366)	0.413
ISS(III vs I+II)	1.351(1.116–1.635)	0.002	1.016(0.809–1.276)	0.894
β2-MG(>3.5 vs ≤3.5g/L)	1.557(1.289–1.881)	<0.001	1.168(0.922–1.481)	0.199
LDH(>265 vs ≤ 265U/L)	2.097(1.640–2.681)	<0.001	1.891(1.471–2.432)	<0.001*
CRE(>ULN vs ≤ULN)	1.421(1.163–1.736)	0.001	1.161(0.921–1.464)	0.206
EMD(Yes vs No)	0.893(0.707–1.128)	0.341	–	
GPS(≥1 vs 0)	1.487(1.233–1.794)	<0.001	1.245(1.017–1.524)	0.034*

Note: *Indicates P value < 0.05.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; DS, Durie-Salmon staging system; ISS, international staging system; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; CRE, creatinine, ULN, upper limit of normal; EMD, extramedullary disease.

GPS Has Better Predictive Value Than mGPS and Hs-mGPS

To compare the predictive capacity of GPS, mGPS, and Hs-mGPS systems, we generated Kaplan-Meier curves stratified by mGPS and Hs-mGPS, respectively, with inter-group differences assessed with the Log rank test. Figure 3A and B showed the survival curves of GPS. Although overall statistically significant differences in OS and PFS were observed across the subgroups classified by both mGPS (OS: $p < 0.001$; PFS: $p = 0.003$; Figure 3C and D) and Hs-mGPS (OS: $p < 0.001$; PFS: $p = 0.002$; Figure 3E and F), the survival curves of mGPS and Hs-mGPS demonstrated closer distance within adjacent curves and more frequent crossings compared to the GPS-based stratified curves. Subsequent pairwise comparisons revealed no significant prognostic distinction between adjacent mGPS categories (0 vs 1, 1 vs 2) in either OS or PFS analyses (Figure 3C and D), indicating that mGPS has suboptimal predictive performance compared to GPS or Hs-mGPS. As shown in Figure 3F, the PFS curves for Hs-mGPS scores 0 and 1 demonstrated significant overlap ($p =$

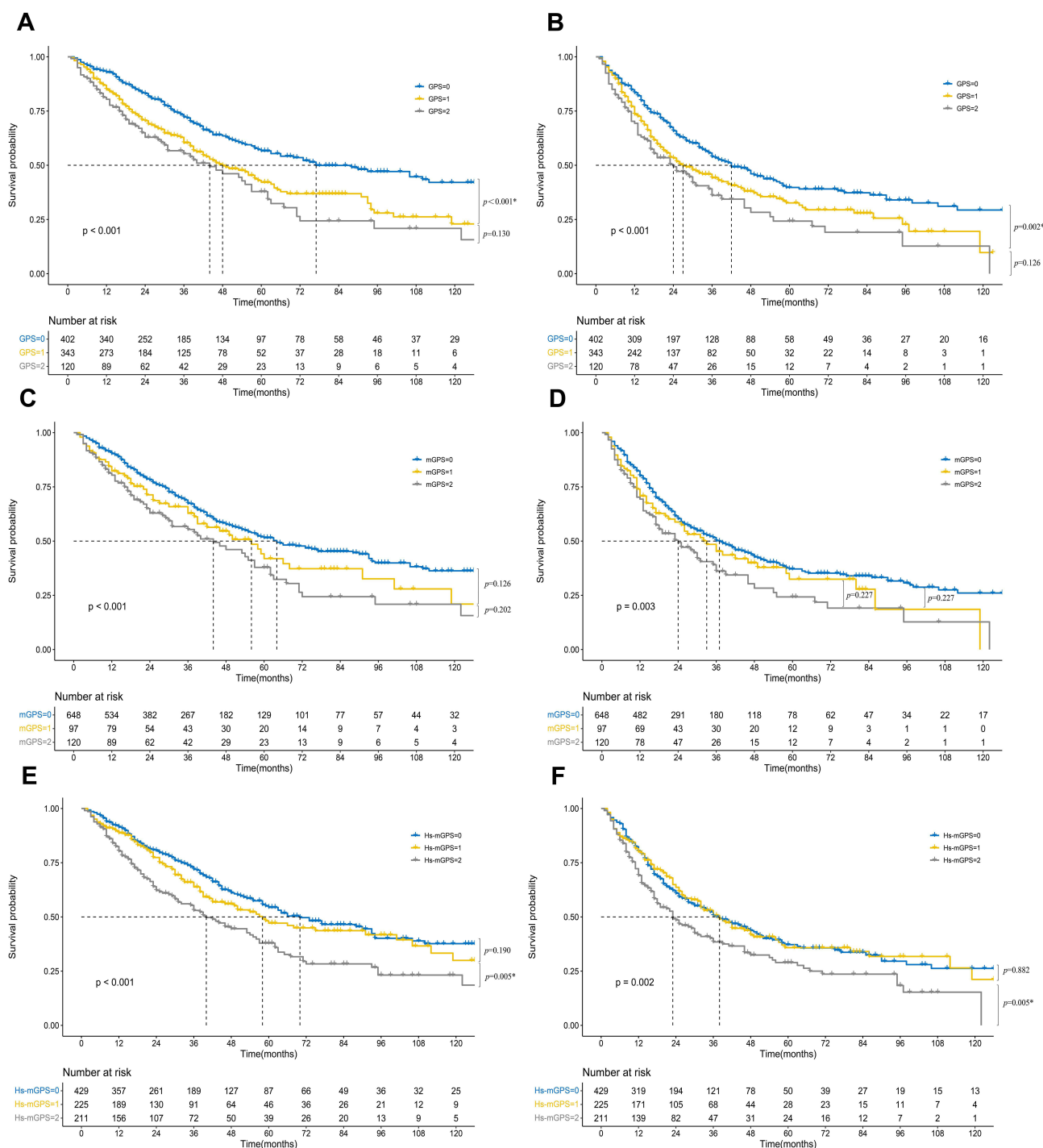


Figure 3 Survival curves and inter-group differences analysis results obtained with Kaplan-Meier analysis between different GPS/mGPS/Hs-mGPS groups. **(A)** Survival curves for OS between different GPS groups. **(B)** Survival curves for PFS between different GPS groups. **(C)** Survival curves for OS between different mGPS groups. **(D)** Survival curves for PFS between different mGPS groups. **(E)** Survival curves for OS between different Hs-mGPS groups. **(F)** Survival curves for PFS between different Hs-mGPS groups.

0.882), indicating compromised discriminative capacity of Hs-mGPS in distinguishing low-risk from intermediate-risk subgroups. In the meanwhile, GPS also showed limited capacity to differentiate between intermediate-risk and high-risk subgroups, but the corresponding survival curves exhibited distinct separation trends with minimal curve crossover (Figure 3A and B).

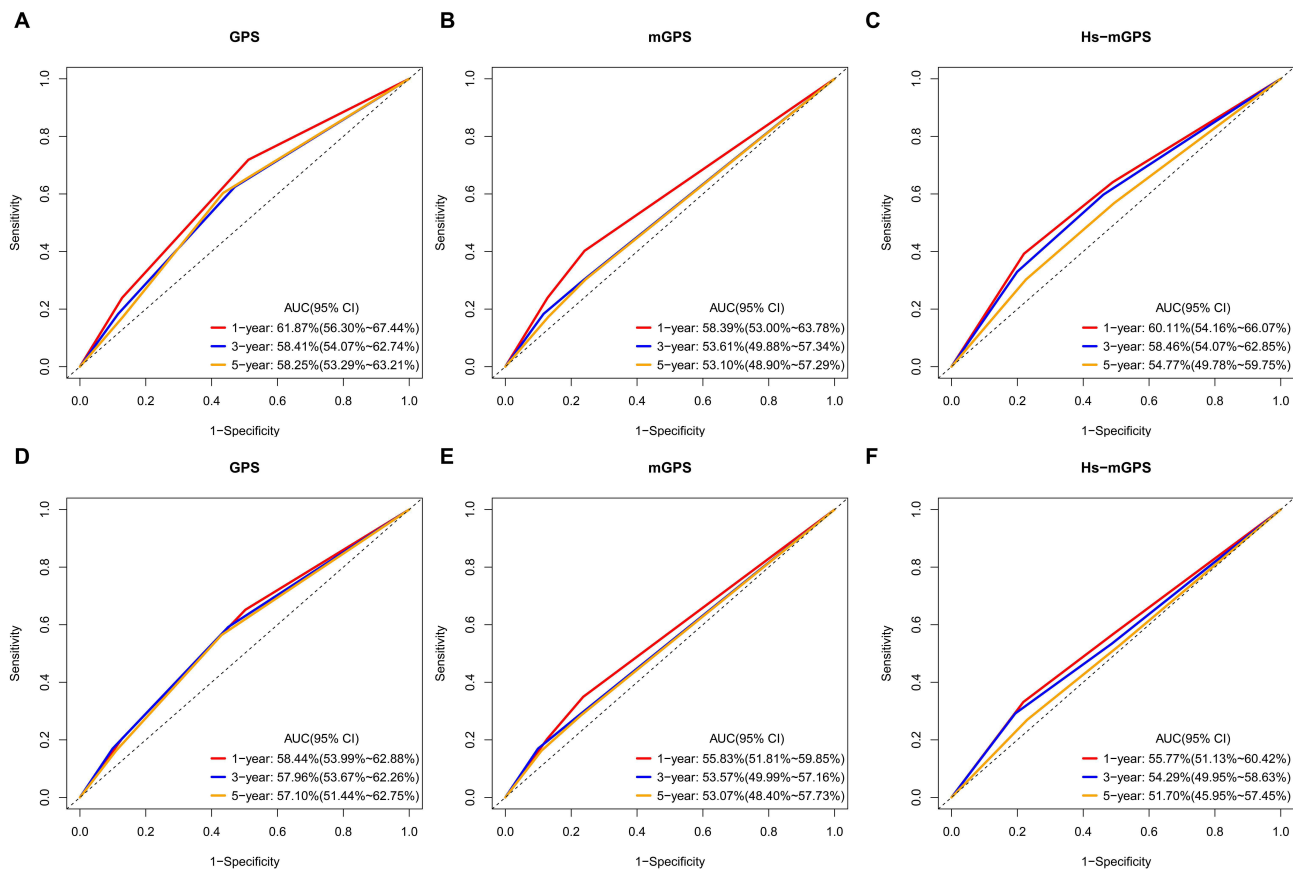


Figure 4 Time-dependent ROC curves and time-dependent AUC values of the GPS/mGPS/Hs-mGPS for predicting OS (A–C) and PFS (D–F). (A and D) ROC curves and AUC values of GPS. (B and E) ROC curves and AUC values of mGPS. (C and F) ROC curves and AUC values of Hs-mGPS.

We subsequently constructed time-dependent ROC curves for GPS, mGPS, and Hs-mGPS, with corresponding AUC values calculated (Figure 4). Except for AUC values from ROC curves for 3-year OS (GPS: 58.41% vs Hs-mGPS: 58.46%), GPS consistently achieved higher AUC values than both mGPS and Hs-mGPS at all other timepoints for both OS and PFS predictions (Figure 4). Additionally, the AUC values of mGPS and Hs-mGPS declined more sharply over time than those of GPS. To compare the prognostic accuracy of GPS, mGPS, and Hs-mGPS for short-term and long-term survival, we selected 1-year and 5-year ROC curves for subsequent comparative analysis (Figure 5). For short-term survival prediction, GPS demonstrated no statistically significant advantage over mGPS or Hs-mGPS (OS: GPS vs mGPS: $p = 0.092$; GPS vs Hs-mGPS: $p = 0.480$; PFS: GPS vs mGPS: $p = 0.105$; GPS vs Hs-mGPS: $p = 0.177$; Figure 5A and B). In contrast, for long-term survival prognosis, GPS exhibited significantly superior discriminatory power, particularly in PFS prediction (OS: GPS vs mGPS: $p = 0.002$; GPS vs Hs-mGPS: $p = 0.094$; PFS: GPS vs mGPS: $p = 0.035$; GPS vs Hs-mGPS: $p = 0.021$; Figure 5C and D).

Comprehensive evaluation of these prognostic models demonstrated that GPS possesses superior predictive validity in clinical outcome stratification.

Discussion

In this study, we evaluated the prognostic value of GPS in a large, real-world cohort of 865 NDMM patients. Our findings indicate that a higher GPS is significantly associated with inferior OS and PFS. Importantly, this association remained robust in multivariate analyses adjusting for confounding factors, indicating that GPS serves as an independent prognostic marker in NDMM.

Our findings extend previous mechanistic studies demonstrating inflammation to adverse prognosis in NDMM. Elevated inflammatory mediators, including CRP, IL-18, and IL-17, promote disease progression through multiple

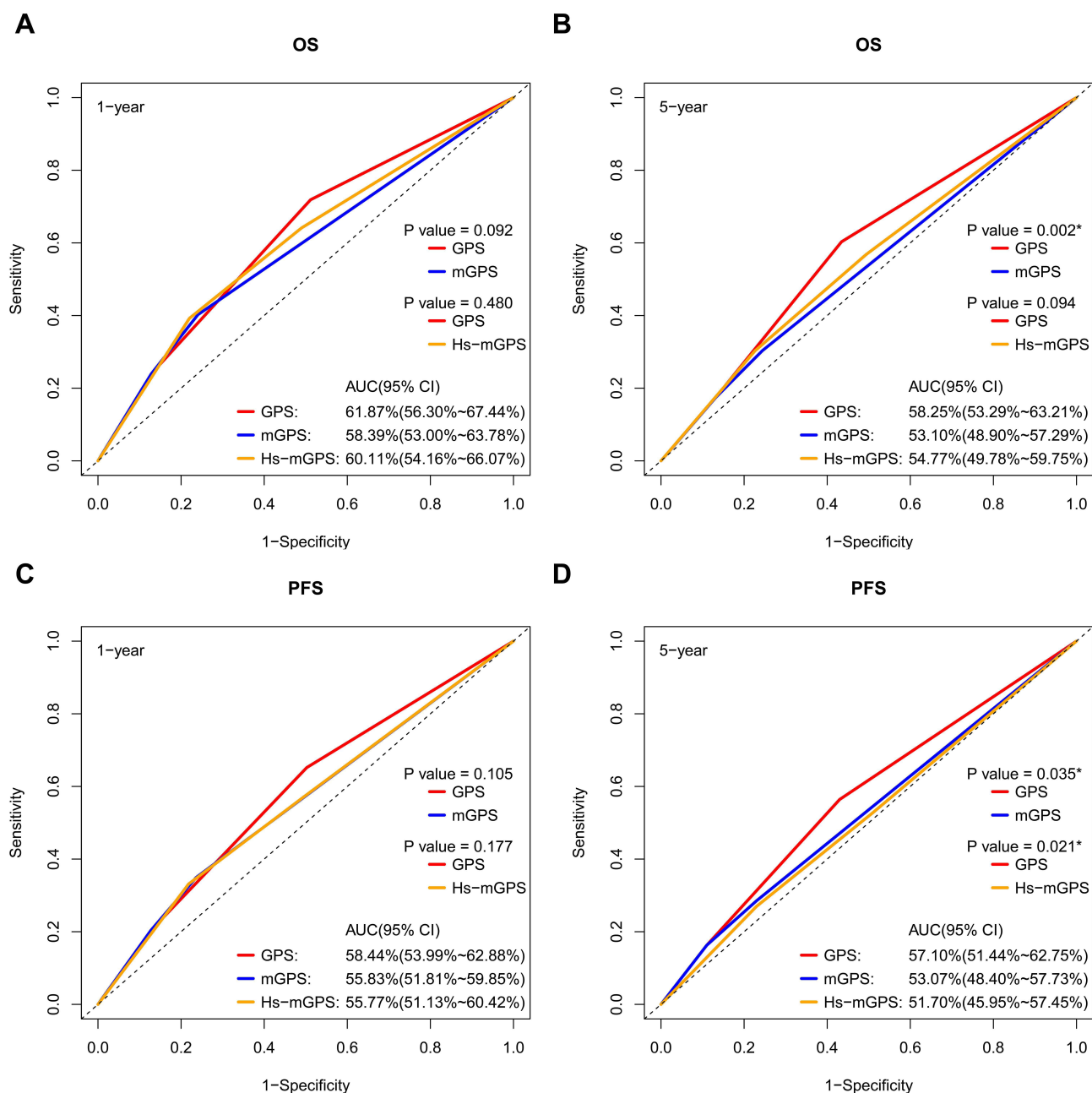


Figure 5 Comparison of prognostic performance for predicting OS (**A** and **B**) and PFS (**C** and **D**) between GPS and mGPS or Hs-mGPS. (**A** and **C**) in terms of short-term survival. (**B** and **D**) in terms of long-term survival.

pathways that include the inhibition of CD8⁺ T-cell function and the induction of myeloid-derived suppressor cells (MDSCs).^{23–26} These findings provide biological plausibility for the adverse impact of a heightened inflammatory state on patient outcomes. Based on these proven mechanisms, many prognostic models based on various inflammatory indicators such as CRP, lactate dehydrogenase (LDH), and immune cell ratio have been developed.^{27–29} These inflammatory prognostic models have shown better risk stratification ability compared to the traditional International Staging System (ISS) and revised ISS (R-ISS).

The GPS is also a prognostic assessment model based on the systemic inflammatory response, incorporating serum CRP and serum albumin levels. It is one of the most useful prognostic models for various common solid tumors.^{19,20} Recent studies have also shown that GPS is an independent prognostic factor of PFS and OS in patients with hematologic malignancies, including diffuse large B-cell lymphoma,³⁰ NK/T-cell lymphoma,³¹ and Hodgkin lymphoma.³² In the

context of multiple myeloma, our study further extends these observations. We found that patients with elevated GPS scores also presented with more advanced disease stages, as reflected by higher Durie-Salmon and ISS classifications. This suggests that the inflammatory milieu, as captured by the GPS, is intricately linked with disease burden and progression. We demonstrated that GPS is significantly associated with survival outcomes, including OS and PFS. Patients with higher GPS scores exhibited worse survival outcomes, a correlation that remained robust even after adjusting for confounders in MVA.

Furthermore, the original GPS shows better prognostic predictive value than its two modified versions, mGPS and Hs-mGPS. Several studies reported that hypoalbuminemia harms the survival outcome of MM patients.^{33,34} However, under the scoring rules of mGPS and Hs-mGPS, the role of hypoproteinemia is excluded when identifying the low-risk patient groups, which may lead to some intermediate-risk patients who present with hypoalbuminemia but non-elevated CRP being incorrectly classified into the low-risk group. In our cohort, among 343 patients classified as GPS-1, over 70% (246/343) were classified into the low-risk group by mGPS. The exclusion of hypoalbuminemia would contribute to the overlap of the curves between the low-risk and intermediate-risk groups. Furthermore, under the mGPS stratification framework, only 25.1% (217/865) of patients were categorized into intermediate/high-risk groups. Previous studies have indicated that the majority of patients were assigned to the low-risk group by mGPS, thereby compromising the prognostic stratification capability of mGPS.³⁵ And for Hs-mGPS, it adopts a stricter CRP threshold, which to some extent enhances the discrimination capability for identifying the intermediate- and high-risk groups. Hs-mGPS may also demonstrate potential for identifying patients with exceptional prognosis.¹⁸ As shown in Figure 3E and F, employing high-sensitivity CRP indeed enhanced the identification of high-risk patients but still failed to distinguish intermediate-risk patients from low-risk groups. Collectively, we propose that optimizing the thresholds for CRP and albumin may significantly enhance the prognostic performance of these readily available biomarkers. In summary, these findings highlight the potential of GPS as an independent prognostic marker for MM and suggest its value in enhancing the current risk stratification system.

Besides the prognostic impact of GPS, this score has actionable clinical importance and can be assessed quickly. GPS only requires CRP and serum albumin, two easily available clinical biomarkers, to complete the risk assessment of patients. GPS has advantages over R-ISS, which has widely used clinical staging systems. Calculate the R-ISS, requiring a cytogenetic diagnosis, which causes a certain delay, while the components of the GPS are always available within the initial blood sampling range. Furthermore, the collected biomarkers used for calculating R-ISS were less representative in reflecting general inflammatory activity, while GPS can reflect the inflammatory state of the organism. Considering that the systemic inflammation level undergoes dynamic evolution throughout tumorigenesis and tumor progression of MM,³⁶ we wonder whether GPS has the potential to serve as a dynamic prognostic model for MM. Firstly, it is simple and feasible to conduct dynamic monitoring of GPS because of its data accessibility. Secondly, several studies have confirmed that dynamic changes of GPS or its modified variants exhibit predictive capacity for disease progression in some other cancers.^{37–39} However, it is regrettable that our study only collected baseline GPS values from MM patients before treatment initiation. In future work, we intend to gather GPS values at multiple time points, including post-treatment remission and disease progression. Furthermore, following the methodological blueprint of the DIPSS model,⁴⁰ we are going to evaluate the acquisition of risk factors (elevated CRP and hypoalbuminemia) during follow-up. Integrating these serial GPS values with treatment response, survival status, and other clinical variables, we will comprehensively explore the potential of GPS as a dynamic prognostic model.

Our study has several limitations. First, this is a single-center retrospective study; therefore, selection bias was inevitable, and our results must be validated in large-scale, prospective studies conducted across multiple centers. Secondly, this is a retrospective study with a large period. Due to differences in treatment protocols across regions and variations in individual patient treatment regimens, these factors may contribute to differences in survival outcomes. Lastly, this research did not include the cytogenetic data. Since the 2010s, with the role of high-risk cytogenetics being elucidated,^{41,42} FISH has gradually become more widely used in clinical practice.^{43,44} However, the wide period of the initial diagnosis of the enrolled patients in our study means that many patients did not undergo FISH or other cytogenetic tests. Therefore, whether there exists an association between GPS and high-risk cytogenetic results, and whether

combining GPS with cytogenetic data demonstrates better prognostic stratification capability, needs to be further elucidated in future studies.

In summary, our study provides novel evidence that the Glasgow Prognostic Score is an independent prognostic marker in NDMM, highlighting the pivotal role of systemic inflammation in disease progression. Given its simplicity and rapid availability, the GPS has the potential to enhance risk stratification and guide therapeutic strategies in clinical practice.

Conclusion

The baseline GPS at the time of diagnosis is an independent prognostic factor that negatively relates to the MM patient survival, for which GPS may serve as a supplement tool in risk stratification upon the primary medical assessment.

Data Sharing Statement

The data of this study can be obtained from the corresponding author Yang Liang upon reasonable request.

Ethics Approval and Informed Consent

This study got the approval of the Institutional Ethics Committee of Sun Yat-sen University Cancer Center. According to the regulations of the Ethics Committee, the criteria for granting a waiver of informed consent included: 1) all human specimens and data for research are previously collected and properly preserved; 2) all included patients are uncontactable; 3) the research involves no risks to personal privacy or commercial interests; 4) all included patients had previously provided informed consent for authorizing the use of donated materials and associated information for all medical research purposes. The requirement for informed consent was waived because it was a retrospective study and all included patients were no longer contactable. The waiver of informed consent will not adversely affect the rights or health of the participants, and we covered patient data confidentially. This retrospective study was performed in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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