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Prognostic models based on lymph node density for primary gastrointestinal melanoma: a SEER population-based analysis

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ABSTRACT

Objective This study aimed to construct prognostic models to predict the overall survival (OS) and cancer-specific survival (CSS) of patients with primary gastrointestinal melanoma (PGIM).

Design An observational and retrospective study.

Setting Data were obtained from the Surveillance, Epidemiology and End Results (SEER) programme database, encompassing a broad geographical and demographic spectrum of patients across the USA.

Participants A total of 991 patients diagnosed with PGIM were included in this study.

Methods A total of 991 patients with PGIM were selected from the SEER database. They were further divided into a training cohort and a validation cohort. Independent prognostic factors were identified by Cox regression analysis. Two prognostic models were constructed based on the results of multivariable Cox regression analysis. The concordance index (C-index) and area under the time-dependent receiver operating characteristic curve (time-dependent AUC) were used to evaluate the discriminative ability. Calibration curves were plotted to evaluate the agreement between the probability as predicted by the models and the actual probability. Risk stratification was developed given the model.

Results By the multivariable Cox regression analysis, we identified four independent risk factors (age, stage, lymph node density and surgery) for OS, and three independent risk factors (stage, lymph node density and surgery) for CSS, which were used to construct prognostic models. C-index, time-dependent AUC, calibration curves and Kaplan-Meier curves of risk stratification indicated that these two models had good discriminative ability, predictive ability as well as clinical value.

Conclusions The prognostic models of OS and CSS had satisfactory accuracy and were of clinical value in evaluating the prognosis of patients with PGIM.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The lymph node density as a dichotomous variable with a threshold value of 20% was first introduced in the nomograms.
⇒ Risk stratification was performed and had a satisfactory discriminative ability.
⇒ This study included patients for a long period of 19 years, which might influence the results of the analysis.
⇒ Primary gastrointestinal melanoma is a rare disease and the cases in our hospital are too limited to perform an external validation.

INTRODUCTION

Mucosal melanoma (MM) is a rare disease, accounting for 1.3% of all melanomas in the USA.[1] The risk factors for cutaneous melanoma (CM) include increased ultraviolet exposure and a positive family history of CM, while the risk factors and aetiology of MM remain unclear.[2 3]

Primary gastrointestinal melanoma (PGIM) is thought to originate from melanocytes in the gastrointestinal tract or enteric neuroendocrine tissue of amine precursor uptake decarboxylation cells. Most PGIMs are located in the anorectal region.[4 5] Compared with CM, PGIM is more prone to metastasis due to the indirectly observable anatomical site and the dense lymphatic vasculature network of the gastrointestinal tract. Therefore, at diagnosis, regional and/or distant metastases in MM are usually three to five times more common than in CM and have a worse prognosis.[6]

Current studies have found that factors related to the prognosis of PGIM included age, lymph node involvement, tumour stage, presence of non-pigmented melanoma and different treatment modalities.[7 8] In a study on bladder cancer, the authors put forward the concept of lymph node (LN) density, which provided a rational basis for treatment and the estimation of the prognosis of cancer. They found that LN density with a threshold value of 20% was an independent prognostic factor.[9] LN density is obtained by dividing the number of positive LNs by the total number of removed LNs. To date, studies on PGIM have not included LN density, that is, converted to dichotomous variables as a prognostic factor.

This study aimed to construct and validate a new survival and prognostic model with the inclusion of LN density and other independent prognostic factors.

METHODS

Data source

Data for this study were retrieved from the Surveillance, Epidemiology and End Results (SEER, www.seer.cancer.gov) database. SEER programme collects diagnosis, treatment and survival data of cancer for approximately 30% of the US population.[10]

Patient selection

We used the SEER*Stat software (V.8.4.0.1; Surveillance Research Program, NCI, Bethesda, Maryland, USA) to get access to the database of Incidence—SEER Research Plus Data, 17 Registries, November 2021 Sub (2000–2019).

Included in this study were patients diagnosed with PGIM between the years 2000 and 2019. Patients with missing survival data were excluded from the analysis. Patients diagnosed with PGIM were selected by the following items: (1) histology recode for melanomas (International Classification of Diseases (ICD)-O-3 8720–8799); (2) primary site codes for the oesophagus (C15.0–C15.9), stomach (C16.0–C16.9), small intestine (C17.0–C17.9), colon (C18.0–C18.9 and C26.0), rectum (C19.9, C20.9) and anus (C21.0, C21.1, C21.2 and C21.8).

Collected variables included age, sex, primary site, tumour size, summary stage, surgery, radiotherapy, systemic therapy, regional LNs removed, regional LNs positive, survival time and cause of death. The median age of patients at diagnosis is approximately 70 years old.[11] Therefore, we converted age to a dichotomous variable with a cut-off value of 70 years old. Summary stage is defined as stage I (local disease), stage II (regional metastasis) or stage III (distant metastasis).[12] The number of positive LNs times 100% divided by the total number of removed LNs was LN density, and the continuous variable was converted to a dichotomous variable with a threshold value of 20%. Overall survival (OS) and cancer-specific survival (CSS) were derived from the cause of death.

Patients were randomly assigned to the training cohort and validation cohort by a ratio of 7:3.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analysis

R software (V.4.2.0) was used for all statistical analyses. The R package 'cmprsk'[13] was used for competing risk analysis to estimate cancer-specific death. A Cox proportional-hazards model was used to investigate the association between the survival time of patients and prognostic variables via R package 'survival'.[14] In the univariable Cox regression analyses, variables with p value<0.1 were included in the multivariable Cox regression analyses. Wald tests for the multiclass categorical variables were performed. A multicollinearity assessment was conducted among the covariates included in the nomogram, using the variance inflation factor (VIF) as the criterion. In line with established guidelines, variables exhibiting a VIF greater than 4.0 were considered indicative of multicollinearity. Consequently, those variables exceeding the VIF threshold were excluded from the final model analysis. Prognostic models were constructed (with missing values removed) using the R package 'rms'[15] based on the results of multivariable Cox regression analysis, and the maximum score for each factor was defined as 100. The score of the prediction of nomograms for each patient was calculated via the R package 'nomogramFormula'.[16] The concordance index (C-index) and area under the time-dependent receiver operating characteristic curve (time-dependent AUC) were used for the evaluation of discriminative ability. The R package 'Hmisc' was used to determine C-index[17] and the R package 'timeROC'[18] was used to perform the time-dependent ROC analysis. Calibration curves were plotted using the R package 'rms' to evaluate the agreement between the probability as predicted by the model and the actual probability. The X-TILE software was used to determine the optimal cut-off value for risk stratification.[19] The X-TILE software uses a method known as the 'minimum P-value approach' to determine the optimal cut-off points. It systematically tests different potential cut-off points in the data to identify the points that maximise the statistical significance or discrimination ability of the predictor variable. A two-sided p value<0.05 was considered statistically significant.

RESULTS

Demographic and clinicopathological characteristics

The flowchart of patient selection was shown in online supplemental figure S1. A total of 991 patients were included in the study. The training and validation cohorts were comparable in terms of demographic and clinical characteristics. The demographic and clinicopathological characteristics of patients were summarised in online supplemental table S1. In the training cohort, 54.3% of patients were over 70 years of age at diagnosis. Female patients accounted for 57.1% of all, whereas male patients accounted for 42.9%. The most common site involved was the anorectum (AM) (84.1%).38% of patients had PGIM larger than 4 cm. At diagnosis, 35.4% of patients had stage I PGIM, 36.1% stage III and 28.4% stage II. 72.6% of patients underwent surgery, of whom, 66.4% did not undergo lymphadenectomy, 20.2% undergoing lymphadenectomy had an LN density of less than 20% and 13.4% undergoing lymphadenectomy had an LN density greater than 20%. 26.2% of patients received radiotherapy, whereas 45.6% of patients received systemic therapy.

Survival and prognostic analysis

In the training cohort, the predicted 1-year, 3-year and 5-year OS probabilities were 55.7%, 24.0% and 12.9%, respectively, while the 1-year, 3-year and 5-year CSS probabilities were 61.3%, 35.7% and 18.5%, respectively. The estimated median OS time was 14.0 months, and the median CSS time was 18.0 months.

According to the results of the univariable Cox regression analyses, eight variables including age, primary site, tumour size, stage, surgery, radiotherapy, systemic therapy and LN density were significantly associated with OS and CSS (online supplemental table S2). Subsequently, these variables were included in the multivariable Cox regression analyses. Results showed that four variables including age, stage, surgery and LN density were independent prognostic factors for OS of PGIM, whereas three variables including stage, surgery and LN density were independent prognostic factors for CSS of PGIM. The results were summarised in table 1.

Nomogram construction and validation

The independent prognostic factors were used to construct the prognostic models for OS (figure 1A) and CSS (figure 1B), which were visualised using the nomograms. Online supplemental figure S2 provided an example of how to use the nomograms for predicting the survival probability of a specific patient. The total score

Table 1 Multivariable Cox regression analyses on variables for OS and CSS in patients with PGIM (Wald test: p<0.001)

	Multivariate-Cox OS			Multivariate-Cox CSS		
Variable	HR (95% CI)	Number of deaths	P value	HR (95% CI)	P value	Number of deaths
Age						
<70	1.00	336		1.00		303
≥70	1.49 (1.11 to 2.02)	431	**0.009**	1.33 (0.97 to 1.82)	0.078	358
Primary site						
Oesophagus	1.00	36		1.00		30
Stomach	0.00 (0.00 to Inf)	28	0.993	0.00 (0.00 to Inf)	0.994	25
Small intestine	1.14 (0.43 to 3.02)	36	0.789	1.02 (0.38 to 2.75)	0.962	30
Colon	0.85 (0.26 to 2.84)	21	0.796	0.73 (0.20 to 2.62)	0.627	15
Anorectum	0.80 (0.35 to 1.80)	645	0.590	0.71 (0.31 to 1.61)	0.414	560
Tumour size						
≤4 cm	1.00	290		1.00		251
>4 cm	1.07 (0.77 to 1.48)	211	0.683	1.09 (0.78 to 1.54)	0.604	188
Stage						
Localised	1.00	214		1.00		167
Regional	1.34 (0.92 to 1.94)	184	0.128	1.36 (0.91 to 2.03)	0.130	165
Distant	2.01 (1.29 to 3.11)	250	**0.002**	1.96 (1.23 to 3.12)	**0.004**	230
Surgery						
Not performed	1.00	217		1.00		192
Performed	0.30 (0.13 to 0.70)	539	**0.006**	0.32 (0.13 to 0.74)	**0.008**	458
Lymph node density						
≤20%	1.00	127		1.00		108
>20%	2.66 (1.70 to 4.18)	105	**0.000**	2.86 (1.80 to 4.54)	**0.000**	100
No removal	1.58 (1.07 to 2.33)	499	**0.023**	1.52 (1.00 to 2.30)	**0.048**	419
Radiotherapy						
Not performed	1.00	450		1.00		376
Performed	0.96 (0.68 to 1.37)	168	0.835	1.04 (0.72 to 1.5)	0.835	151
Systemic therapy						
Not performed	1.00	231		1.00		192
Performed	0.97 (0.70 to 1.35)	201	0.863	0.99 (0.70 to 1.40)	0.957	181

Bold values signifies that P value < 0.05 is commonly used in statistics to indicate a significant result.
CSS, cancer-specific survival ; OS, Overall survival ; PGIM, primary gastrointestinal melanoma .

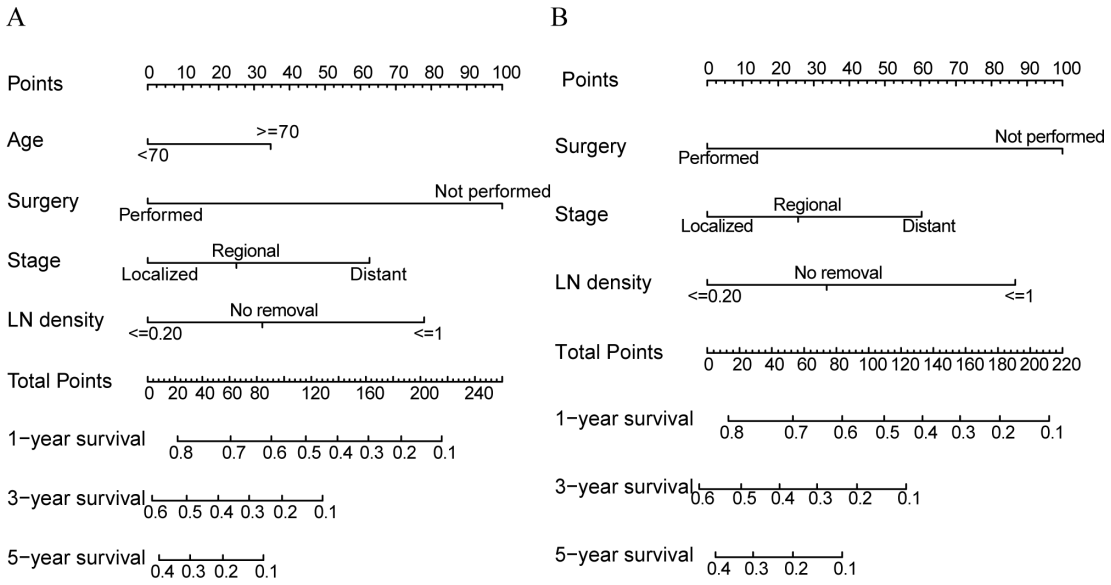

Figure 1 The constructed nomogram for prognostic prediction. (A) A nomogram for overall survival prediction. (B) A nomogram for cancer-specific survival prediction. LN, lymph node.

was derived by summing the individual scores obtained from the nomogram calculations.

For OS and CSS, the C-index value was 0.668 (95% CI=0.648 to 0.688) and 0.654 (95% CI=0.632 to 0.676), respectively, in the training cohort, and 0.691 (95% CI=0.657 to 0.725) and 0.683 (95% CI=0.641 to 0.725), respectively, in the validation cohort, indicating acceptable discrimination by the nomogram. Likewise, the time-dependent AUC was satisfactory in both the training cohort (figure 2A,B) and the validation cohort (figure 2C,D). The calibration curves of the models suggested consistencies between the predicted and observed survival probability in both the training cohort (figure 3A,B) and the validation cohort (figure 3C,D). In summary, these results showed that the models for PGIM had good discriminative and calibrating abilities.

The evaluation of the prognostic models were summarised in online supplemental table S3.

Risk stratification based on the nomogram

Based on the total points calculated from the prognostic models, patients were divided into three groups in the training cohort: low-risk (OS: total points≤93; CSS: total points≤70), intermediate-risk (OS: 93<total points≤140; CSS: 70<total points≤120) and high-risk groups (OS: 140<total points≤230; CSS: 120<total points≤220); in the validation cohort: low-risk (OS: total points≤60; CSS: total points≤70), intermediate-risk (OS: 60<total points≤140; CSS: 70<total points≤120) and high-risk groups (OS: 140<total points≤200; CSS: 120<total points≤220).

The estimated median OS time was 41, 14 and 5 months in the low-risk, intermediate-risk and high-risk groups, respectively, whereas the estimated median CSS time was 37, 11 and 5 months in the low-risk, middle-risk and high-risk groups, respectively. The Kaplan-Meier (KM) curves of OS and CSS for high-risk, intermediate-risk and low-risk groups are shown in figure 4 (A, B: the training cohort; C, D: the validation cohort), demonstrating a significant difference between groups.

We further analysed the impact of different treatment modalities on survival outcomes within each risk stratification group by applying the KM method for survival analysis and assessing survival differences using the log-rank test. The survival outcomes of high-risk patients were not related to whether they received radiotherapy, systemic therapy or surgery (p>0.05). The survival outcomes of low-risk and intermediate-risk patients were also not related to whether they received radiotherapy or systemic therapy (p>0.05). Since all low-risk and intermediate-risk patients underwent surgery, we could not evaluate the impact of surgery on survival outcomes, but the multivariable Cox regression analysis showed that surgery was an independent prognostic factor.

DISCUSSION

In this study, we constructed two prognostic models for OS and CSS of PGIM, respectively. C-index, time-dependent AUC, calibration curves and KM curves of risk stratification indicated that the models had a satisfactory discriminative ability, predictive ability as well as clinical value.

There is currently no standardised staging system for PGIM. The eighth edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma is only used for CM and MM of the head and neck.[20] Due to the different features between CM and MM, the AJCC staging system cannot be fully applied to MM. Though the Ballantyne staging system (summary stage) was initially developed for MM of the head and neck,[12] it is recommended for all MM subsites. Due to the lack of a specific association between nodal involvement and prognosis in MM, the prognostic value of this system is limited; nevertheless, because of its ease of use, and a wide range of applications, it remains a commonly used

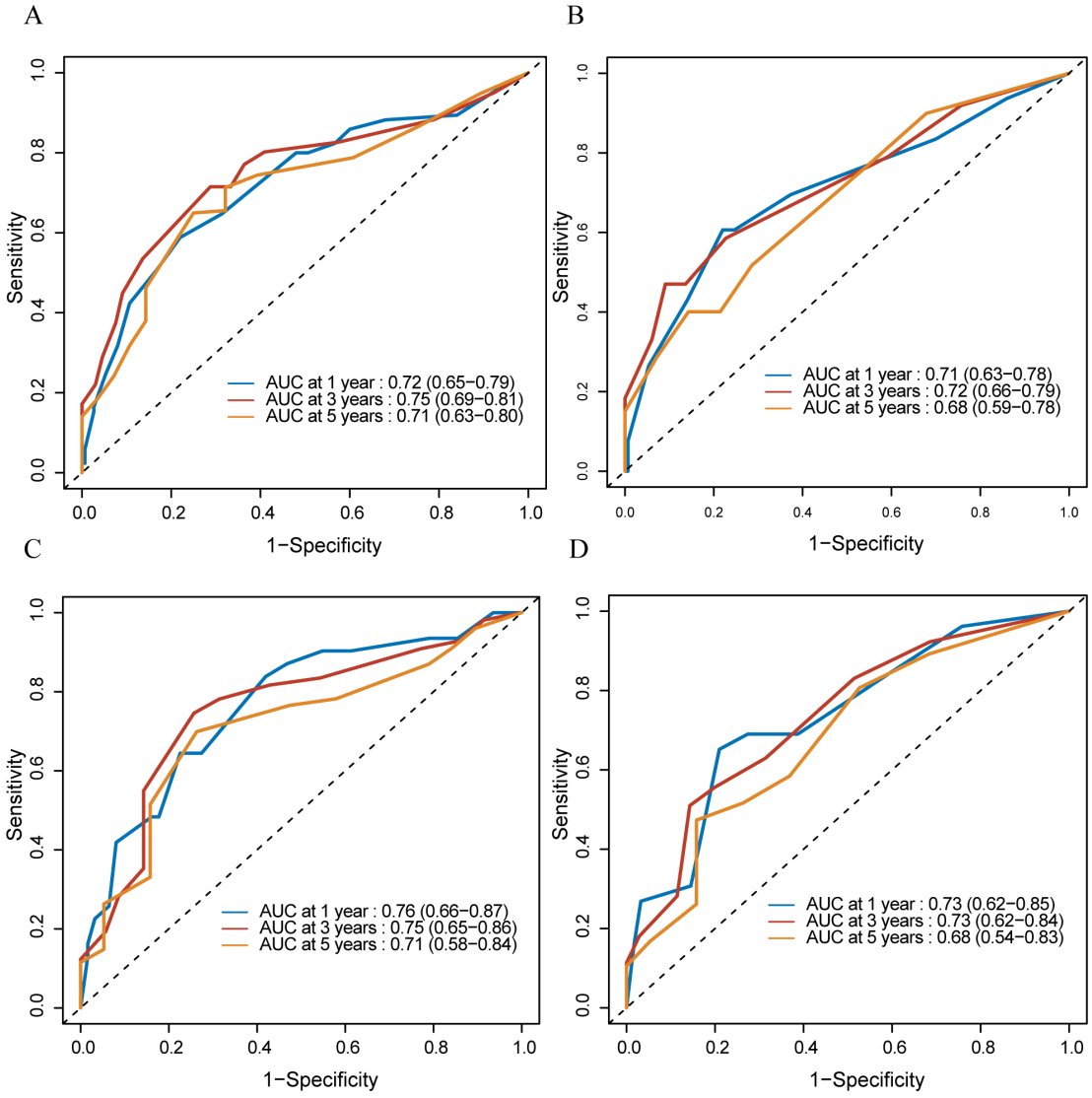

Figure 2 Time-dependent AUC curves of the prognostic models. (A) Time-dependent AUC curves of 1-year, 3-year and 5-year OS in the training cohort. (B) Time-dependent AUC curves of 1-year, 3-year and 5-year CSS in the training cohort. (C) Time-dependent AUC curves of 1-year, 3-year and 5-year OS in the validation cohort. (D) Time-dependent AUC curves of 1-year, 3-year and 5-year CSS in the validation cohort. AUC, area under the curve; CSS, cancer-specific survival; OS, overall survival.

staging system for MM.[21] To fully evaluate the impact of LN involvement on prognosis, we included LN density in the study.[22] In our study, multivariable Cox regression analysis was performed on different levels of LN density, and 20% was found to be a suitable cut-off value whereby LN density was divided into a low-density group of less than 20% and a high-density group of greater than 20%, and a significant difference was observed between the low-density and high-density group in OS and CSS. Compared with a positive LN count alone, this variable took into account the number of LNs removed. Consistently, previous studies found that the involvement of regional LNs was an independent prognostic factor for MM.[23 24]

LN involvement plays a crucial role in the prognosis of various cancers, including PGIM. LN density provides valuable information about the extent of tumour spread within the regional lymphatic system. A higher LN density suggests a more advanced stage of the disease, indicating increased tumour burden and a greater likelihood of distant metastasis. Consequently, patients with higher LN density are more likely to experience poorer outcomes and shorter survival times. Of note, in the models, there was no significant difference in OS and CSS between stage I and stage II, which seemed unreasonable. It was due to the inclusion of LN density, because patients with a low LN density had a better prognosis than patients with a high LN density, which suggested that the current summary staging system should include nodal involvement as a prognostic indicator. Hence, the prognostic models developed in the study can be considered as a supplementary postoperative staging system.

Based on the three-level risk stratification derived from the nomogram, the predicted OS and CSS between the three risk groups were statistically different, which means that the risk stratification is reasonable and has clinical

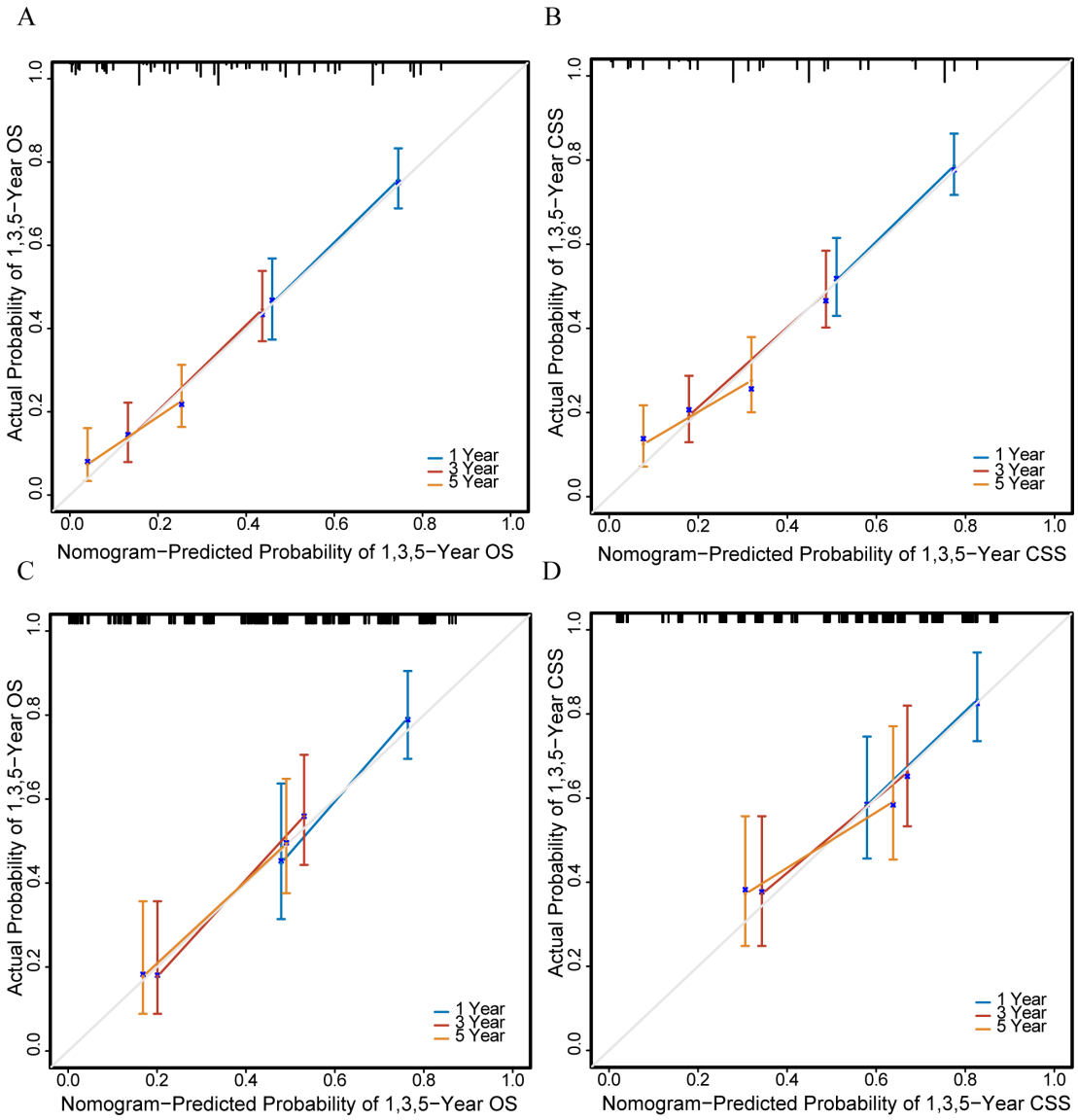

Figure 3 Calibration curves of the prognostic model. (A) Calibration curves comparing actual and predicted OS probabilities at 1-year, 3-year and 5-year follow-up in the training cohort. (B) T Calibration curves comparing actual and predicted CSS probabilities at 1-year, 3-year and 5-year follow-up in the training cohort. (C) Calibration curves comparing actual and predicted OS probabilities at 1-year, 3-year and 5-year follow-up in the validation cohort. (D) Calibration curves comparing actual and predicted CSS probabilities at 1-year, 3-year and 5-year follow-up in the validation cohort. CSS, cancer-specific survival; OS, overall survival.

application value. As of now, no previous studies have developed a risk stratification for PGIM, and we came up with one as a reference for clinical practice. According to our results, the survival outcomes of high-risk patients were not related to whether they received radiotherapy, systemic therapy or surgery, which indicated that these treatment modalities had limited effects on high-risk patients and they might need to look for other treatment strategies or combined treatment plans. The survival outcomes of low-risk and intermediate-risk patients were also not related to whether they received radiotherapy or systemic therapy, which indicated that these treatment modalities had no significant effects on low-risk and intermediate-risk patients. Since all low-risk and intermediate-risk patients underwent surgery, we could not evaluate the impact of surgery on survival outcomes, but the multivariable Cox regression analysis showed that surgery was an independent prognostic factor affecting survival outcomes, so we suggested continuing surgical treatment for low-risk and intermediate-risk patients.

However, it should be noted that this study was a retrospective study, and the number of patients who received treatment in each risk stratification was inconsistent, which might affect the analysis results. Therefore, prospective studies with larger sample sizes and well-controlled treatment allocation are needed to validate and refine the treatment strategies for patients in different risk stratification groups. These future studies should also consider adjusting for potential confounding factors to provide more robust and reliable conclusions

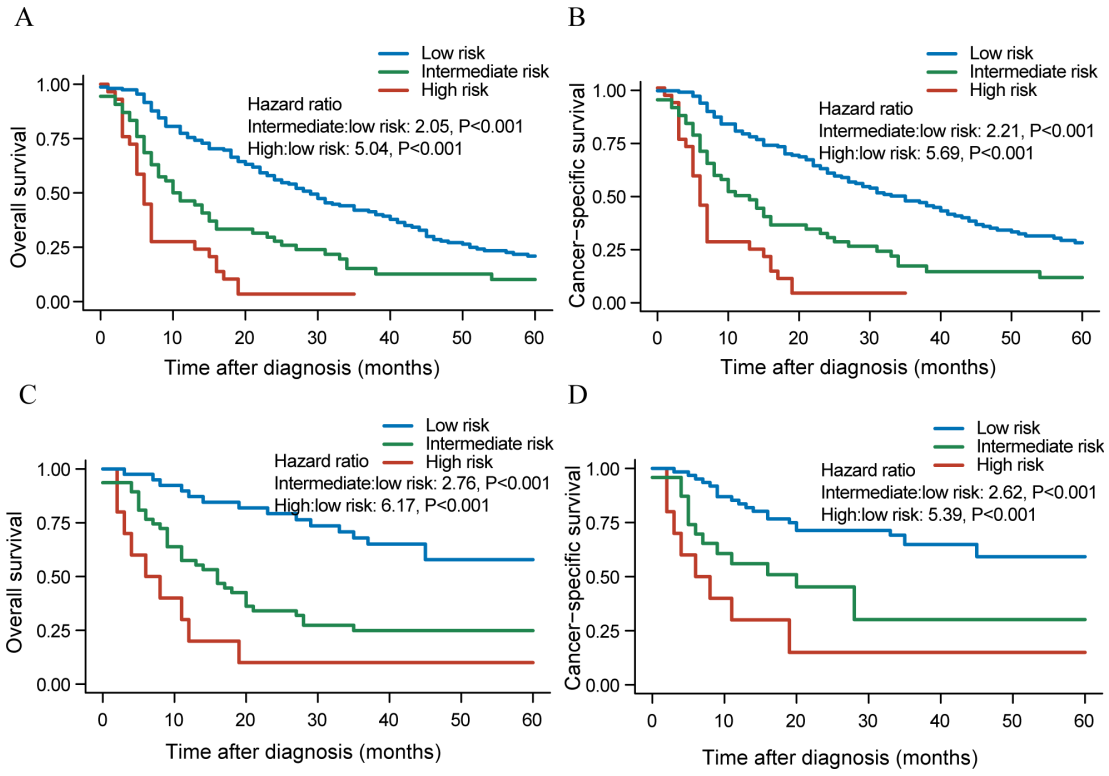

Figure 4 Kaplan-Meier survival curves of patients with primary gastrointestinal melanoma with different risks stratified by the prognostic models. (A) Kaplan-Meier OS curves in the training cohort. (B) Kaplan-Meier CSS curves in the training cohort. (C) Kaplan-Meier OS curves in the validation cohort. (D) Kaplan-Meier CSS curves in the validation cohort. CSS, cancer-specific survival; OS, Overall survival.

regarding the optimal treatment approaches for patients at different risk levels. Our study showed that tumour size was not an independent prognostic factor. The effects of tumour size (tumour thickness) on prognosis are controversial. Some studies showed that this factor was not significantly related to survival,[8 23 24] while others found tumour thickness to be an independent prognostic factor.[6] These conflicting results may be related to different tumour sites and depths of invasion. Depth of invasion is significantly related to survival in cancer, but tumour size is not necessarily associated with depth of invasion.

Surgery is the primary therapeutic intervention and could not only control symptoms but also lead to improvement in prognosis.[4 21] However, the extent of surgery, including limited resection (LR) and extensive resection (ER), is controversial. ER refers to tumour resection and LN removal, and LR refers to tumour resection without LN dissection. Two studies based on the SEER database showed that compared with LR, ER did not increase the survival rate of patients with primary melanoma of the AM,[24 25] even with confounding variables controlled.[25] However, patients having regional metastasis with LN density less than 20% may gain benefits with ER. Unfortunately, in the database, records of the total number of positive regional LNs were mostly acquired after LNs were surgically removed and examined by the pathologist, which meant that cases with recorded LNs mostly underwent ER, so we cannot compare the survival rate of different surgical types based on LN density subgroups.

In this study, adjuvant treatment did not affect the prognosis of PGIM, consistent with other studies.[8 26] However, these findings must be interpreted with caution for the SEER database does not contain information on somatic mutations and specific treatment regimens, hence, it is difficult to perform further subgroup analysis of the data. Radiotherapy has been proposed as a method to achieve local control,[27] but most studies have also failed to identify an improvement in OS by radiotherapy.[28] MMs are molecularly different from CMs, but immunotherapy used for CMs is also recommended for MMs.[29] A 43% response rate was reported when a combination of axitinib and toripalimab was used for locally advanced or unresectable MMs.[30] Relevant research is limited, and large cohort studies on the effects of adjuvant therapy on prognosis are needed.

This study has the following limitations. First, the SEER database lacks information on the depth of invasion, specific treatment regime and resection margin, causing a less comprehensive analysis in this study. Second, this study included patients for a long period of 19 years. There had been changes in the staging system and treatment over time, which might influence the results of the analysis. Third, PGIM is a rare disease and the cases in our hospital are too limited to perform an external validation.

Conclusions

Despite the above limitations, this study included the variable of LN density with a threshold value of 20% and

other variables to construct new prognostic models with satisfactory clinical value, which can be used as a supplementary postoperative staging system. However, studies are still needed to validate this nomogram in the future.

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