Journal of Surgical Oncology

WILEY

Journal of SURGICAL ONCOLOGY

RESEARCH ARTICLE OPEN ACCESS

Are Nomograms Useful for Predicting Sentinel Lymph Node Status in Melanoma Patients?

Kristel Lourdault[1] | Arthur W. Cowman[1] | Douglas Hanes[2] | Anthony J. Scholer[1] | Tyler Aguilar[1] | Richard Essner[1]

[1]Saint John's Cancer Institute at Providence St. John's Health Center, Santa Monica, California, USA | [2]Providence Research Network, Portland, Oregon, USA

Correspondence: Richard Essner (Richard.essner@providence.org)

Received: 1 July 2024 | **Revised:** 30 September 2024 | **Accepted:** 18 October 2024

Funding: This study was supported by the Borstein Family Melanoma Program, the Melamed Family Foundation, the John Wayne Cancer Foundation, and the Donald L Morton Melanoma Research Fund.

Keywords: melanoma | MSLT-I | NCDB | nomogram | risk assessment | sentinel lymph node biopsy | surgery

ABSTRACT

Background and Objectives: Clinical nomograms have been developed to predict sentinel lymph node (SLN) status in early-stage melanoma patients, but the clinical utility of these tools remains debatable. We created and validated a nomogram using data from a randomized clinical trial and assessed its accuracy against the well-validated Melanoma Institute Australia (MIA) nomogram.

Methods: We developed our model to predict SLN status using logistic regression on clinicopathological patient data from the Multicenter Selective Lymphadenectomy Trial-I. The model was externally validated using the National Cancer Database (NCDB) data set, and its performance was compared to that of the MIA nomogram.

Results: Our model had good discrimination between positive and negative SLNs, with a training set area under the curve (AUC) of 0.706 (0.661–0.751). Our model achieved an AUC of 0.715 (0.706–0.724) compared to 0.723 (0.715–0.731) with the MIA model, using the NCDB set.

Conclusion: Our model performed similarly to the MIA model, confirming that despite using different clinical features and data sets, no clinical nomogram is currently accurate enough for clinical use.

1 | Introduction

With the expected increase in cutaneous melanoma cases and the importance of accurate staging for guiding treatment [1], sentinel lymph node biopsy (SLNB) remains an important feature of melanoma care.

Numerous studies have identified the tumor status of sentinel lymph nodes (SLNs) as the most significant prognostic tool for cutaneous melanoma [2–5]. While there are some risks associated with performing SLNBs, they affect only a small percentage (6%–14%) of patients and tend to be minor and short term, including wound infection, seroma, cutaneous nerve injury, and lymphedema [4, 6, 7]. In contrast, the staging benefits of SLNB play a crucial role in guiding care by facilitating early identification of metastases and the use of adjuvant systemic therapies [7–9].

The National Comprehensive Cancer Network recommends that patients undergo SLNB based on the likelihood of a tumor-positive SLN (+SLN), which is estimated using clinicopathological features of patients and their tumors. If the probability of nodal positivity is greater than 10%, SLNB is recommended. For patients with less than a 5% likelihood of a +SLN, SLNB is not recommended. Between 5% and 10% likelihood, surgeons are advised to discuss SLNB risks and benefits with patients and individualized decision-making [10].

Summary

- We created and then validated a clinical nomogram to predict sentinel lymph node status in melanoma patients.
- Similarly to existing nomograms our model shows good performance but fails to accurately identify all patients with nodal metastases.

To improve on the clinical models, other noninvasive tests, including gene expression profiles such as the Castle Biosciences 31-GEP score and the SkylineDx Merlin Assay, have been developed to help predict SLN status [4, 6, 11–15]. However, performance of these models, including specificity and sensitivity of prediction of +SLNs, remains far from clinically valuable. Most concerning, these models fail to identify some patients at high risk, resulting in missed +SLNs [16, 17]. All these predictive tools appear to offer limited clinical benefit when compared with the standard of care SLNB.

Our goal was to develop an alternative risk model to predict SLN status, using variables similar to those used by the Melanoma Institute Australia (MIA) model [4] with highly reliable data extracted from the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) [2]. Subsequently, we compared the performance of both models on the MSLT data set and on a carefully selected subset of the National Cancer Database (NCDB) used as an external validation.

2 | Methods

2.1 | Patients and Data Collection

2.1.1 | MSLT-I Data Set: Training Set

We used the randomized MSLT-I database as the training set for our +SLN predictive model. The MSLT-I study design, patient eligibility, definition of a +SLN, and results have been published previously [2]. Briefly, MSLT-I was designed to study the management and outcomes of the SLNB compared to no surgical evaluation of the nodal basin. All MSLT-I patients underwent a wide local excision of their primary melanoma, combined with an SLNB or nodal basin observation. Patients were excluded from this analysis if they did not have an SLNB, lacked complete information for all pathologic factors, or did not have complete follow-up. A total of 990 patients from the MSLT-I were included in our training data set.

The tumor status of the SLN was determined in a standardized method, and a +SLN was defined by the presence of melanoma cells detected by hematoxylin and eosin and/or immunohistochemical staining (S-100, Mart-1, and HMB-45). Specimens were reviewed by the study pathologists for accuracy of diagnosis. Patients' age at diagnosis, gender, and tumor characteristics (primary site, ulceration status, Breslow thickness, histology subtype, lympho-vascular invasion [LVI], and mitotic rate) were assessed using consistent pathologic definitions.

2.1.2 | NCDB Data Set: Validation Set

We used the NCDB database as the external validation set for our predictive model and to test the MIA model. The NCDB was queried between 2018 and 2020 for data of patients ages 18–75 with a first diagnosis of primary cutaneous melanoma with Breslow thickness ≥ 0.75 mm who had wide excision of their primary tumor, at least one SLN examined, known SLN tumor status, clinically node-negative (cN0), nonmetastatic disease (cM0) at diagnosis, and complete data on ulceration status, mitotic rate, LVI, site of primary tumor, and histologic subtype. We included patients diagnosed after January 1, 2018 when the NCDB implemented the code SLN_EXAM, which specifies the number of SLNs examined during the SLNB, and the code SLN_POS, which specifies the number of +SLNs detected. We excluded patients who had neoadjuvant treatment. Use of NCDB codes for patient selection is described in Table S1. A total of 21 245 patients from NCDB were included in our external validation data set.

We matched the histologic subtypes from the NCDB to those from our model and the MIA model as described in Table S2.

2.2 | SJCI Model Development

Using the MSLT-I data set, we used logistic regression to create a model predicting SLN positivity from the variables: age at diagnosis, site and ulceration status of the primary tumor, Breslow thickness, histological subtype, mitotic rate, and LVI. Breslow thickness was used as a categorical variable (≤ 2, 2.0–4.0, or ≥ 4 mm). The fit model predicts the probability of +SLN in any patient from the same population, given the values of the included risk factors. Given the small number of candidate variables, we did not perform any variable selection in the construction of the model.

2.3 | SJCI Model Validation

External validation was performed using the NCDB data set. The model's ability to discriminate between +SLNs and −SLNs was determined by constructing receiver operating characteristic (ROC) curves and determining a concordance index (c-index; area under the curve [AUC]).

Calibration curves were created to evaluate the agreement between predicted and observed probabilities of +SLN according to each model. We divided predicted probabilities of +SLN into deciles, then plotted the predicted prevalence of +SLN in the decile against the observed prevalence of +SLN in the decile. Curve points above (underpredication) or below (overprediction) the line of perfect agreement suggest a deviation of predictions from actual estimates.

2.4 | Comparison With the MIA Model

The MIA model was described by Lo et al. [4], which provides logistic regression coefficients from which ROC curves on new

data can be obtained. Regression fits (coefficients) of both models are provided in Figure S1.

As described above, the performance of our SJCI and MIA models was assessed using AUC and calibration curves on the NCDB validation set.

2.5 | Statistical Analysis

Descriptive data, including patient demographics and tumor characteristics, were summarized by mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables and frequency with percentage for categorical data.

For each data set, patient and tumor characteristics were compared between the +SLN and −SLN groups using ANOVA, Wilcoxon rank-sum, or chi-squared tests, as appropriate to the type of variable. The SJCI prediction model was fitted to MSLT-I data by logistic regression. This model's coefficients were then used to build ROC curves on each data set. We used the R package pROC to generate curves and to calculate AUC with 95% confidence intervals. We checked model calibration by plotting observed prevalence against mean predicted prevalence in prediction deciles. Predicted probabilities, according to each model, were compared in a two-dimensional scatterplot.

Model sensitivity, specificity, and net benefit were calculated across a plausible range of risk thresholds. The net benefit is calculated as the mean patient benefit of conducting SLNB according to model predictions, relative to no SLNB, at any prespecified threshold for risk required to initiate SLNB [18]. The benefit of the model can also be compared to the net benefit of conducting SLNB in all patients.

All tests were two-sided, and statistical significance was set at $p < 0.05$. Statistical analyses were performed using the R software, version 4.1.2 (R Core Team 2022).

This study was approved through Providence Health and Services and IRB protocol studies.

3 | Results

3.1 | Patients' Characteristics

Among patients in the MSLT-I database, we identified 990 who underwent an SLNB and had complete data for all clinical and pathological variables. 809 (81.7%) of these patients had a −SLN, and 181 (18.3%) had one or more +SLN. In this cohort, the average age of patients was 51.5 ± 13.8 years, most were male ($n = 577$, 58.3%) and the median Breslow thickness was 1.9 mm (IQR 1.4–3.0). The majority of patients had a primary tumor of an extremity ($n = 474$, 47.9%), followed by the trunk ($n = 362$, 36.6%) and head and neck region ($n = 154$, 15.6%). Most primary tumors were not ulcerated ($n = 674$, 68.1%), did not have LVI ($n = 925$, 93.4%), and of malignant NOS subtype ($n = 568$, 57.4%) or superficial spreading subtype ($n = 343$, 34.6%).

Of the 21 245 patients in the NCDB data set, 17 223 (81.1%) had a −SLN and 4022 (18.9%) had a +SLN. In this data set, patients were on average age of 56.5 ± 12.9 years, most were male ($n = 11\ 794$, 55.5%) and the median Breslow thickness was 1.5 mm (IQR 1.0–2.7). The majority of patients had tumors of an extremity ($n = 10\ 341$, 48.7%), followed by the trunk ($n = 7174$, 33.8%) and head and neck region ($n = 4514$, 21.2%). Most primary tumors were not ulcerated ($n = 15\ 755$, 74.2%), did not have LVI ($n = 20\ 037$, 94.3%), and were of malignant subtype ($n = 10\ 632$, 50.0%) or superficial spreading ($n = 9177$, 43.2%).

The patients in the NCDB cohort were slightly older (56.5 ± 12.9 vs. 51.5 ± 13.8 years old; $p < 0.001$), with had thinner primary tumors (median Breslow 1.5 vs. 1.9 mm, $p < 0.001$), and lower percent of ulcerated primaries (25.8% vs. 31.9%, $p < 0.001$) than MSLT-I patients. More patients in the NCDB cohort had superficial spreading subtype than in MSLT-I (43.2% vs. 34.6%) and fewer had malignant melanoma NOS subtype (50% vs. 57.4%, $p < 0.001$).

Clinical and pathological features are summarized in Table 1.

3.2 | SJCI Model

The SJCI model includes seven clinicopathological patient features: Breslow thickness, age at diagnosis, ulceration status, site of primary tumor, histological subtype, LVI, and mitotic rate. The formula to calculate the predicted probabilities of +SLN is described in Table 2 (and Figure S1). The model had good internal discrimination between +SLN and −SLN, with an AUC of 0.706 (0.661–0.751) (Figure 1A, blue curve). Validation AUC of our model was 0.715 (0.706–0.724) (Figure 1B, blue curve) using the NCDB set.

Calibration plots indicated that our model is well calibrated in MSLT-I and NCDB data sets, showing a good correlation between predicted and observed probabilities of +SLN (Figure 2A,B, blue curves).

3.3 | Comparison With the MIA Model

SJCI and MIA models have six features in common. The main differences are the inclusion of the location of the primary tumor in our model, the use of Breslow thickness as a continuous variable in the MIA model compared to as a categorical variable in our model (≤ 2, 2.1–4, and > 4 mm) and the use of mitotic rate as categorical in the MIA model (1, 2–3, or ≥ 4) compared to present or absent in our model.

The AUC of the MIA model was 0.688 (0.644–0.731) and 0.723 (0.715–0.731) with the MSLT-I and NCDB sets, respectively (Figure 1, red curves). The performance of the two models is equivalent for all data sets tested.

The MIA model is well calibrated in the NCDB data set, showing a good correlation between predicted and observed

TABLE 1 | Clinical and pathological patients' characteristics in the Multicenter Selective Lymphadenectomy Trial I and II and NCDB data sets used in this study.

Total	MSTL-I 990		NCDB 21 245		
	Number	%	Number	%	*p*
Age (years)					< 0.001
Mean (SD)	51.5 (13.8)		56.5 (12.9)		
Gender					0.084
Female	413	41.7%	9451	44.5%	
Male	577	58.3%	11 794	55.5%	
Primary site					0.118
Extremity	474	47.9%	10 341	48.7%	
Head/neck	154	15.6%	3730	17.6%	
Trunk	362	36.6%	7174	33.8%	
Breslow thickness (mm)					< 0.001
≤ 2.0	550	55.6%	13 776	64.8%	
2.1–3.9	326	32.9%	4514	21.2%	
≥ 4.0	114	11.5%	2955	13.9%	
Breslow thickness (mm)					< 0.001
Median (IQR)	1.9 (1.4–3.0)		1.5 (1–2.7)		
Ulceration					< 0.001
Absent	674	68.1%	15 755	74.2%	
Present	316	31.9%	5490	25.8%	
Mitotic rate (mitosis/mm^2)					< 0.001
0	6	0.6%	3909	18.4%	
1	393	39.7%	4833	22.7%	
2–3	280	28.3%	5363	25.2%	
> 4	311	31.4%	7140	33.6%	
Lymphovascular invasion					0.273
No	925	93.4%	20 037	94.3%	
Yes	65	6.6%	1208	5.7%	
Histologic type					< 0.001
Superficial spreading	343	34.6%	9177	43.2%	
Malignant melanoma	568	57.4%	10 632	50.0%	
Desmoplastic	32	3.2%	404	1.9%	
Lentigo melanoma	24	2.4%	578	2.7%	
Acral melanoma	23	2.3%	454	2.1%	
SLN status					0.625
Positive, *n* (%)	181	18.3%	4022	18.9%	
Negative, *n* (%)	809	81.7%	17 223	81.1%	

probabilities of +SLN (Figure 2B, red curve), but is not well calibrated in the MSLT-I, as shown in Figure 2A (red curves). The MIA model predicts much higher risks in the top few deciles, relative to our model. From the NCDB data, for example, the MIA model predicts over 80% risk in the highest tertile of risk, while the SJCI model predicts less than 50% risk, even in the higher tertile.

3.4 | Clinical Decision Analysis Capabilities of the Models

We performed DCA on both MIA and SJCI models to assess their net benefit to the patients (Figure S3). Our results indicate a small net benefit to using the MIA algorithm relative to SLNB for all patients at thresholds less than 10%. At thresholds of

TABLE 2 | Multivariable analysis by +SLN status on MSLT-I data set.

	Estimate	OR	Conf. low	Conf. high	*p*
(Intercept)	−1.429	0.239	0.102	0.545	0.001
Age	−0.019	0.981	0.968	0.993	0.003
Primary site					
Head and neck	Ref	1.000			
Extremity	−0.051	0.950	0.560	1.658	0.853
Trunk	0.417	1.517	0.899	2.635	0.127
Ulceration					
No	Ref	1.000			
Yes	0.202	1.223	0.840	1.773	0.289
Breslow thickness (mm)					
0–1.9	Ref	1.000			
2–3.9 mm	0.925	2.521	1.684	3.791	0.0000
> 4 mm	1.495	4.458	2.630	7.568	0.0000
Histology subtype					
Superficial spreading	Ref	1.000			
Malignant melanoma	0.006	1.006	0.685	1.486	0.976
Acral melanoma	−0.277	0.758	0.195	2.355	0.657
Desmolastic melanoma	−1.217	0.296	0.046	1.073	0.111
Lentigo melanoma	−0.718	0.488	0.074	1.836	0.356
Lymphovascular invasion					
No	Ref	1.000			
Yes	1.085	2.960	1.653	5.240	0.0002
Mitotic rate					
0	Ref	1.000			
> 1	0.116	1.123	0.770	1.646	0.549

10%–20%, both models provide a clinical benefit relative to treating all patients.

4 | Discussion

The decision to perform an SLNB for early-stage cutaneous melanoma patients is mainly based on the physician's assessment of the probability of a +SLN. Knowing the pathologic status of the SLN provides accurate staging, is the strongest predictor of survival, and impacts treatment, especially since adjuvant immunotherapy was approved by the US FDA in 2017 for AJCC Stage III melanoma patients [2] and more recently a subgroup of AJCC Stage II patients with −SLN.

In this study, we developed a clinically based nomogram to predict SLN status that performed with an AUC of 0.706 (0.661–0.751) and 0.715 (0.706–0.724) on MSLT-I and NCDB data sets, respectively. Our model demonstrated good calibration on the MSLT-I and NCDB sets. As expected, the performance of our model is similar to that of the MIA model: 0.715 (0.706–0.724) vs. 0.723 (0.715–0.731) with NCDB set. Because different data sets may be imbalanced with respect to particular groups of interest, we tested both models for predictive performance on patients older than 70 years old and on T1b patients. For older patients, the performance of the models remains similar to the performance of the models on the entire NCDB data set and is comparable between the models: AUC of 0.730 (0.708–0.752) and 0.716 (0.691–0.740) for MIA and SCJI models, respectively (data not shown). Additionally, we examined T1b patients from the NCDB cohort. Although we obtained a lower performance on this subgroup compared to the entire NCDB cohort, we still obtained similar performances between the models: AUC of 0.634 (0.604–0.665) and 0.629 (0.597–0.661) for MIA and SJCI, respectively (data not shown).

As can be seen in both the calibration plots (Figure 2) and the scatterplot of predicted probabilities (Figure S2), there is rough agreement between models for most patients; but there is a subset of patients for whom the MIA model predicts much higher risk than our model, leading to an overprediction of rates of positive SLN in the highest deciles. This may be due to the use of continuous Breslow thickness by MIA, even though we trimmed all values to a maximum of 10 mm, as suggested by Lo et al. [4]. Our categorization of Breslow thickness may be more reliable in this respect, particularly for thick melanomas.

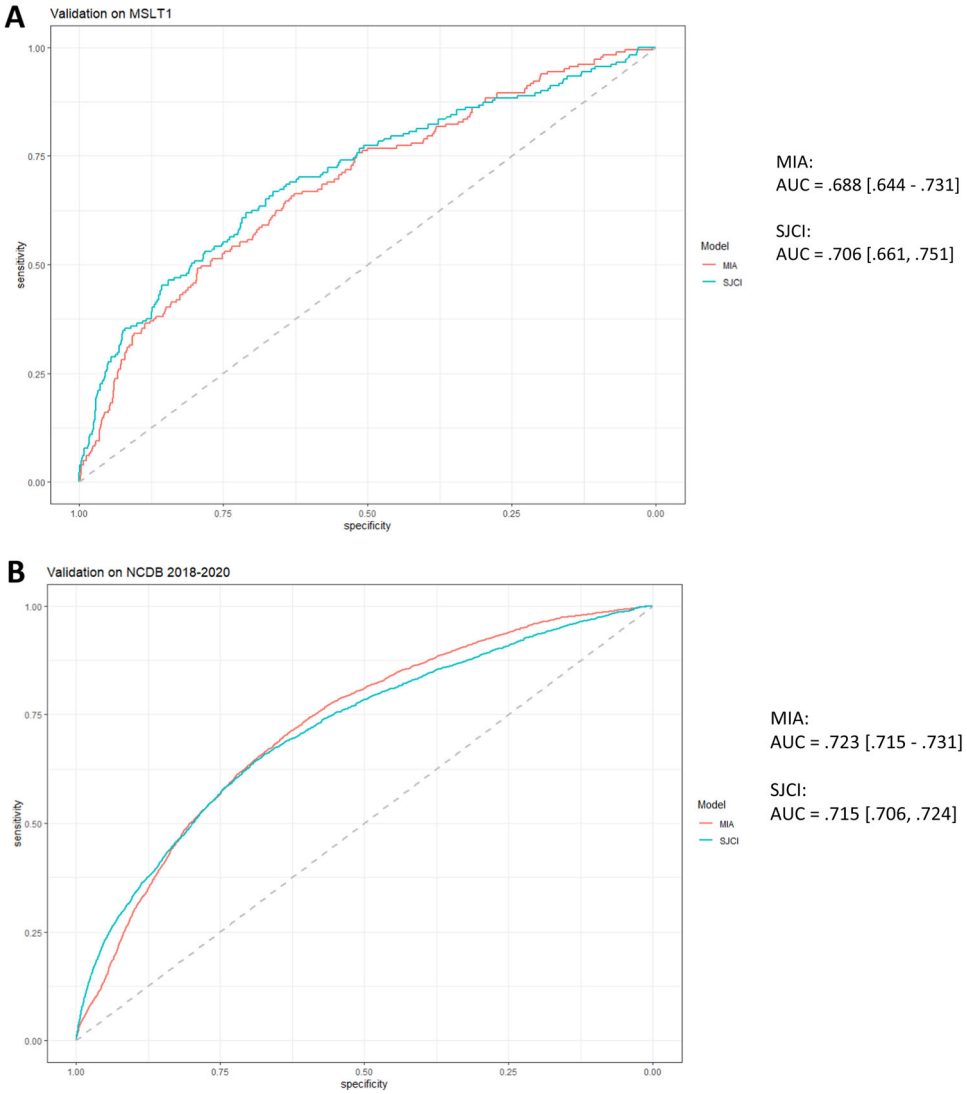

FIGURE 1 | Receiver operating characteristic (ROC) curves showing the performance of the SJCI (in blue) and MIA (in red) models on (A) MSLT-I and (B) NCDB data sets.

A strength of our model is that it was created using data from MSLT-I, where data collection, follow-up schedules, and SLN metastasis detection methods were standardized. This differentiates it from other models, which may have selection biases regarding +SLN prognostic factors or missing data. The MSLT-I trial had 12 consistent primary tumor characteristics with standardized reporting and rigorous pathologic review, primary tumor features that are lacking in most models, and AJCC staging systems [11, 13, 19–21].

One of the first nomograms to predict +SLN was created and validated by Wong et al., using the Memorial Sloan-Kettering Cancer Centre (MSKCC) ($n = 979$) and the Sunbelt ($n = 3108$) data sets. The MSKCC model performed with an AUC of 0.68 [11]. Three small, single-institution retrospective studies investigated the predictive accuracy and application of the model to various melanoma populations, showing satisfactory performance with AUCs ranging from 0.68 to 0.87. However, all these studies included a limited number of patients—less than 550—leaving room for better validation sets and/or model improvement [19–21].

More recently, Lo et al. developed a predictive model (MIA)—improved from the MSKCC nomogram—that performed with a c-index of 0.739. This model was validated with the MD Anderson data set and reached an AUC of 0.75 [4]. With the Dutch cohort, for which the mitotic rate was missing, the MIA model had an AUC of 0.69 [22]. Freeman et al. reported a c-index of 0.733 when using an NCDB cohort that included data from 60 165 melanoma patients diagnosed between 2010 and 2019. However, since the NCDB did not differentiate SLNs from regional lymph nodes until 2018, the status of most patients' SLNs relies on assumptions that can potentially create bias in the analysis [23]. Additionally, Bagge et al., compared the performances of both MSKCC and MIA models using the Swedish Melanoma Registry ($n = 10\,809$) and showed AUCs of 0.708 and 0.697 for the MSKCC and MIA models, respectively [24].

Molecular profiling has been employed to try to improve SLN status predictions. In 2015, Gerami et al. developed the 31-GEP score, a gene signature that predicts patients' metastasis risk using tissue from their primary tumor [25]. To try to improve the 31-GEP score, Whitman et al. combined it with clinicopathological

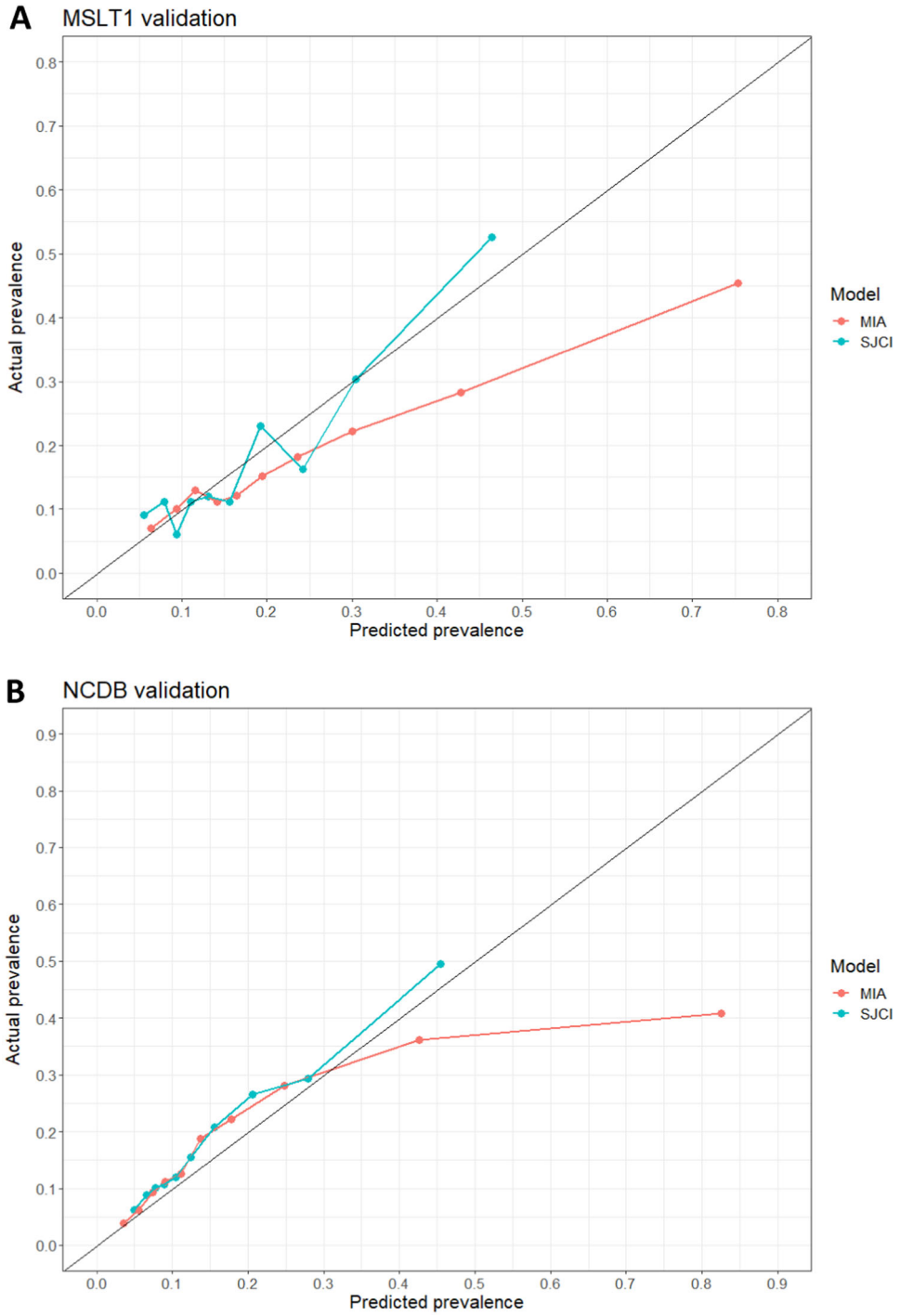

FIGURE 2 | Calibration plots for the SJCI (in blue) and MIA (in red) models, tested on (A) MSLT-I and (B) NCDB data sets. Each point represents one decile of predicted probabilities of +SLN obtained from a single model; the *x*-coordinate of the point is the predicted prevalence of +SLN within the decile; the *y*-coordinate is the actual prevalence of +SLN in the same group. The black line represents perfect agreement between decile predictions and observed decile frequencies.

features (named i31-GEP-SLNB), but this new test remains not completely accurate [15]. Although studies have demonstrated that the i31-GEP-SLNB may outperform the MSKCC and MIA nomograms in identifying T1-T2 patients who can be spared from SLNB [26, 27]. Marchetti et al. demonstrated that the i31-GEP-SLNB only benefitted patients with T1b disease compared to SLNB for all [16]. The i31-GEP-SLNB score requires tissue from primary tumor biopsy which is often small and sometimes not sufficient for molecular testing. The main disadvantage of this test, aside from being expensive ($5800–$6500) and not easily accessible to all patients [6, 25], remains that like other models using clinical features, it is not completely accurate.

Like other nomograms, the main limitation of our study is the limited accuracy and the questionable clinical utility of predictive models. The sensitivity and specificity vary greatly depending on where the threshold is placed, and the performance of the model may not justify its use at any threshold

relative to universal SLNB. From a clinical perspective, the most important part of an SLNB is to identify all patients who have +SLNs, which would imply having an extremely low cutoff threshold to not miss patients with a +SLN. In such cases, the number of patients spared from surgery will be negligible. For example, with our model, if we use 0.05 as a clinically relevant cutoff, the error rate would be 0.2%, the sensitivity would be close to 94.7%, but the specificity would then be extremely low (3.4%), and the number of patients who would be spared unnecessary surgery would only be 3%. Additionally, our nomogram was developed with a data set that includes around 2% of desmoplastic melanoma, known for low rate of +SLN compared to cutaneous melanoma. However, when we excluded desmoplastic patients from the NCBD cohort, we observed similar performances to those obtained on the whole sample: AUC of 0.723 (0.715–0.713) and 0.715 (0.706–0.729) for MIA and SJCI models, respectively (data not shown).

Due to the minimal risk of the SLNB procedure and the minimal net benefit of using nomograms as decision tools (Figure S3), we concur with other studies suggesting SLNB should be recommended for all patients with invasive melanoma [17, 28]. With the advancement of molecular techniques and artificial intelligence, there are hopes that predicting SLN status will improve, but currently, no predictive tool can be clinically justified.

Acknowledgements

The authors acknowledge the investigators and centers who participated in the MSLT-I study and the data provided in this work. This study was supported by the Borstein Family Melanoma Program, the Melamed Family Foundation, the John Wayne Cancer Foundation, and the Donald L. Morton Melanoma Research Fund.

Ethics Statement

This study was approved through Providence Health and Services and eIRB protocol studies 2020000522 and 2019000139.

Consent

Informed consent was obtained from all individual participants included in the MSLT-I clinical trial.

Conflicts of Interest

Richard Essner serves on the advisory board for Castle Biosciences and IntraMedical Imaging. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.