

ORIGINAL RESEARCH

# Nomogram for predicting survival after first-line anti-PD-1-based immunotherapy in unresectable stage IV melanoma: a multicenter international study

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**Background:** The introduction of anti-programmed cell death protein 1 (PD-1) immunotherapy has revolutionized the treatment landscape for melanoma, enhancing both response rates and survival outcomes in patients with advanced stages of the disease. Despite these remarkable advances, a noteworthy subset of patients (40%-60%) does not derive advantage from this therapeutic approach. This study aims to identify key predictive factors and create a user-friendly predictive nomogram for stage IV melanoma patients receiving first-line anti-PD-1-based immunotherapy, improving treatment decisions.

**Materials and methods:** In this retrospective study, we included patients with unresectable stage IV melanoma who received first-line treatment with either anti-PD-1 monotherapy or anti-PD-1 plus anti-cytotoxic T-lymphocyte associated protein 4 between 2014 and 2018. We documented clinicopathological features and blood markers upon therapy initiation. By employing the random survival forest model and backward variable selection of the Cox model, we identified variables associated with progression-free survival (PFS) after the first-line anti-PD-1-based treatment. We developed and validated a predictive nomogram for PFS utilizing the identified variables. We assessed calibration and discrimination performance metrics as part of the evaluation process.

**Results:** The study involved 719 patients, divided into a training cohort of 405 (56%) patients and a validation cohort of 314 (44%) patients. We combined findings from the random survival forest and the Cox model to create a nomogram that incorporates the following factors: lactate dehydrogenase (LDH), S100, melanoma subtype, neutrophil-to-lymphocyte ratio (NLR), body mass index, type of immune checkpoint inhibitor, and presence of liver or brain metastasis. The resultant model had a C-index of 0.67 in the training cohort and 0.66 in the validation cohort. Performance remained in different patient subgroups. Calibration analysis revealed a favorable correlation between predicted and actual PFS rates.

**Conclusions:** We developed and validated a predictive nomogram for long-term PFS in patients with unresectable stage IV melanoma undergoing first-line anti-PD-1-based immunotherapy.

**Key words:** nomogram, stage IV melanoma, anti-PD-1-based immunotherapy, progression-free survival, biomarkers, immune checkpoint inhibition

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## INTRODUCTION

The established treatment for unresectable melanoma includes anti-PD-1-based immunotherapy with pembrolizumab or nivolumab as monotherapy or combined with anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) or anti-lymphocyte-activation gene 3.<sup>1,2</sup> For melanomas harboring *BRAF* oncogenic variant, *BRAF* and *MEK* inhibition may also be

considered.<sup>3</sup> Recent clinical trials advocate prioritizing anti-PD-1-based therapy as the first-line option also in this subgroup.<sup>4,5</sup> However, a significant proportion of patients, ranging from 40% to 60%, do not benefit from this treatment.<sup>6,7</sup> Furthermore, immune checkpoint inhibitors (ICIs) may induce severe and irreversible immune-related toxicities.<sup>8</sup> Hence, predictive biomarkers upon therapy start hold significant relevance in daily clinical application and research areas. This is important as novel therapeutic approaches are emerging, such as tumor-infiltrating lymphocytes therapy and bispecific drugs.<sup>9</sup>

The progression-free survival (PFS) and overall survival probabilities after initiating anti-PD-1 therapy for melanoma are mostly based on the RECIST criteria.<sup>7,10-13</sup> Response evaluation is carried out during therapy, underscoring the gap for upfront biomarkers potentially guiding treatment decisions.

Certain biomarkers have been evaluated for their predictive potential. These include tumor-infiltrating cells, the programmed death-ligand 1 status, and gene copy number alterations.<sup>14</sup> Nonetheless, literature reports inconsistent findings, impeding their validation as a reliable biomarker.

The American Joint Committee on Cancer (AJCC) classification eighth edition lacks substages for stage IV melanoma in contrast to the substages for stages I, II, and III, which stratify patients into groups with different survival outcomes. Within stage IV, M category is reported according to metastatic sites and lactate dehydrogenase (LDH) level.<sup>15</sup> Still, there is considerable diversity in survival outcomes among patients with stage IV melanoma, highlighting the need for a more detailed stratification system.

We identified key factors associated with progression-free survival in stage IV melanoma patients upon starting first-line ICI and integrated into an online nomogram.

## MATERIALS AND METHODS

### Study population

This international multicenter study included all inoperable stage IV melanoma patients receiving first-line ICI therapy, either anti-PD-1 monotherapy or in combination with anti-CTLA-4, and met the inclusion criteria: age >18 years, informed consent, and response to be assessed based on RECIST version 1.1.<sup>16</sup> Patients undergoing adjuvant therapy or anti-CTLA-4 monotherapy as first-line treatment were excluded.

The study period ranged from 2014 to 2018. Patients were divided into two cohorts: the training cohort, treated at the skin centers of Tuebingen (Germany), Belgrade (Serbia), and at the Clinic for Medical Oncology in Nis (Serbia); and the validation cohort, treated at the skin centers of Berlin and Dresden (Germany), St Gallen (Switzerland), Madrid (Spain), and Faro (Portugal) (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2024.103661>).

The sample size calculation was based on an exponential maximum likelihood test of equality of survival curves test.<sup>17</sup>

This study was approved by the ethics committees of the institutions involved and was conducted in accordance with

consensus ethical principles derived from international ethical guidelines, including the Declaration of Helsinki. This study was approved by the Ethics Commission of the Eberhard Karls University Tuebingen with the number 774/2022BO2. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

### Statistical analysis

Descriptive statistics included counts (*n*) and percentages (%) for categorical variables and mean and standard deviation or medians and interquartile range (IQR) for continuous variables. Input variables comprised sex, age, melanoma subtype (acral cutaneous, non-acral cutaneous, occult, mucosal, uveal), tumor thickness, ulceration, *BRAF* and *NRAS* mutational status, LDH level, protein S100 level, neutrophil-to-lymphocyte ratio (NLR), brain or liver metastasis at therapy initiation, body mass index (BMI), and ICI therapy type. To mitigate extreme value influence and ensure interpretability, values below the fifth percentile were set to the fifth percentile. LDH and S100 were capped at 1000 and 1, respectively.

Primary endpoint was PFS, defined as the time between therapy start and disease progression. For patients not experiencing progressive disease (PD), the last follow-up date was considered the censoring point.

Kaplan–Meier curves were employed for survival analysis. Candidate factors were selected by using the random survival forest (RSF) analysis,<sup>18-20</sup> operating as a decision trees ensemble for right censored survival data. We employed 500 trees and log-rank splitting criteria. The backward approach of the Cox proportional hazards model with the Breslow method, select criterion of significant level, and entry significance level of 0.15 was used to select the final model.<sup>21</sup>

The linear relationship between continuous predictors and the logarithm of hazard was evaluated by plotting martingale residual plots, while the Schoenfeld test confirmed the proportionality assumption requisite. The bootstrapping sampling method (1000 resamples) was used for internal validation.

A nomogram was developed based on selected features. Based on the calculated score, the patients were divided into quartiles and log-rank tests were used for comparisons between groups. Discrimination was evaluated using Harrell's concordance index (C-index) and the area under the receiver operating characteristic curve (AU-ROC). Calibration was evaluated using the Brier score and calibration plots. Decision curve analysis (DCA) was carried out to evaluate the clinical benefit. External validation was assessed using a validation cohort.

Missing data were imputed via multiple imputation by chained equation. All statistical analyses and data visualization were executed using R. Reported *P* values were two-sided, with significance set at *P* < 0.05.

## RESULTS

### Patients' characteristics

We enrolled 719 patients in our study—405 patients (56%) in the training and 314 patients (44%) in the validation

cohort. Demographic and clinical characteristics are shown in [Supplementary Table S1](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>.

In the training cohort, the median age was 68 years (IQR 57-77 years), and most (61%) were male. More than half (67%) of the patients presented non-acral cutaneous melanoma. Twenty-eight percent exhibited *BRAF* mutation, whereas 26% had *NRAS* mutation. Upon therapy initiation, 21% and 38% had brain and liver metastasis, respectively. Thirty-six percent of patients received anti-PD-1 and CTLA-4 inhibitors, while 64% received anti-PD-1 monotherapy.

Within the validation cohort comprising 314 patients, the median age was 69 years (range 57-76 years), 64% of patients had non-acral cutaneous melanomas and 47% received combined anti-PD-1 and CTLA-4 inhibitors.

The median follow-up in the training cohort was 54 months (range 47-56 months). The median PFS after therapy initiation was 25 months [95% confidence interval (CI) 21-36 months] ([Supplementary Figure S2](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>).

The validation cohort had a median follow-up of 50 months (95% CI 45-58 months). The median PFS following therapy initiation was 5 months (95% CI 4-8 months) ([Supplementary Figure S2](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>).

### Random forest model and Cox model

The RSF analysis showed that the most important factors influencing PFS after starting ICI were LDH, followed by the melanoma type and NLR. Factors including S100 level, BMI, liver metastasis, age at therapy start, ulceration in primary tumor, brain metastasis, and the specific type of ICI therapy also played a role with decreasing importance. On the other hand, *BRAF* and *NRAS* mutational status, tumor thickness, and sex did not improve the model ([Figure 1 & Supplementary Figure S3](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>).

The 10 variables selected by RSF were included in the Cox model. Based on backward selection process, a model was constructed including the following variables: LDH, NLR, melanoma subtype, S100 levels, BMI < 18.5, presence of brain metastasis, presence of liver metastasis, and ICI therapy type ([Supplementary Table S2](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661> and [Supplementary Figure S4](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>).

### Nomogram

We constructed a nomogram based on the eight identified variables ([Figure 2](https://doi.org/10.1016/j.esmoop.2024.103661)), also found online [Dynamic Nomogram Predicting Progression-Free Survival in Stage IV Melanoma Patients after First-Line Anti-PD-1-Based Immunotherapy (<https://science1.shinyapps.io/Melanoma/>)]. The relationship between the total points of the nomogram (score) of the patients in the training cohort and the PFS as continuous is depicted in [Figure 2](https://doi.org/10.1016/j.esmoop.2024.103661). Patients were split into three

groups based on the quartiles of the score ([Figure 3A](https://doi.org/10.1016/j.esmoop.2024.103661) and B). The first group had individuals with total points ranging from 0 to 74.88 (below the lower quartile), the second group spanned from 74.88 to 153.28 points (inter-quartile), and the final group exceeded 153.28 points (above upper quartile). We decided to divide into three groups as no significant differences were observed between patients having a score between the lower quartile and median and median and the upper quartile ([Supplementary Figure S5](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>).

Among the three groups in the training cohort, differences in median PFS (mPFS) were observed, and the Kaplan–Meier curves showed that PFS between the three groups was statistically significantly different (log-rank test,  $P < 0.001$ ) ([Figure 3C](https://doi.org/10.1016/j.esmoop.2024.103661)). Pairwise comparisons, conducted using the log-rank test and adjusted with Benjamini Hochberg correction, revealed significant differences in survival outcomes among the three groups. The mPFS was not reached (95% CI 58 months-not applicable) for the first group. In the second group, the mPFS was 27.1 months (95% CI 19-36 months), with a hazard ratio (HR) of 2.50 (ref: first group: 95% CI 1.7-3.6,  $P < 0.001$ ). The third group displayed an mPFS of 9 months (95% CI 6-14 months) and HR of 6.19 (ref: first group: 95% CI 4.1-9.3,  $P < 0.001$ ) ([Figure 3C](https://doi.org/10.1016/j.esmoop.2024.103661)).

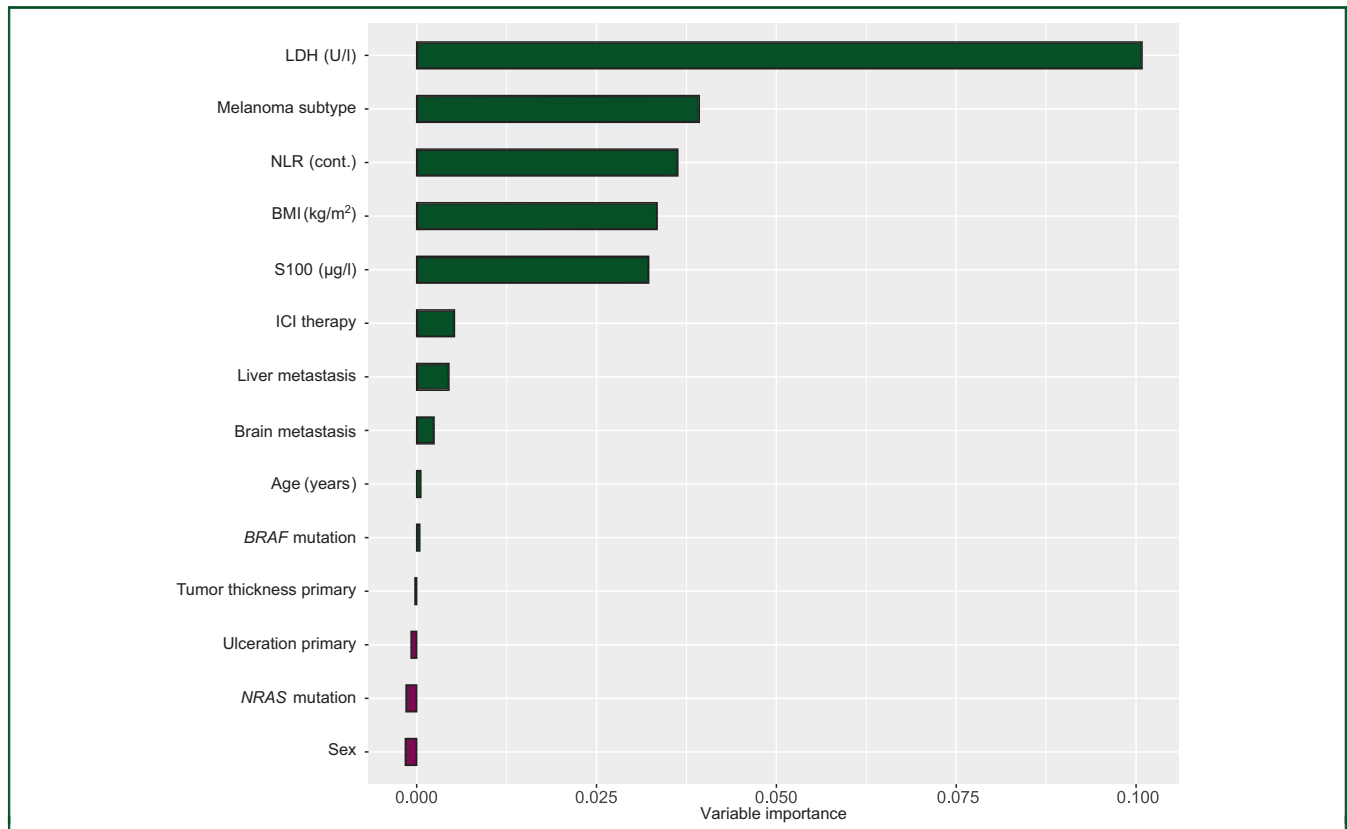
In the training cohort, the same score stratified patients based on melanoma-specific survival (MSS) ([Figure 3D](https://doi.org/10.1016/j.esmoop.2024.103661)).

### Performance metrics of model

The C-index was 0.674 (se = 0.018) in the training cohort, indicating moderate discriminative capacity. We generated calibration plots, revealing good correlations across various timeframes encompassing 1-, 2-, 3-, and 5-year PFS ([Figure 4A](https://doi.org/10.1016/j.esmoop.2024.103661)). The Brier score consistently remained below 0.25, thus showing the higher precision of our nomogram's predictions compared to null model ([Figure 4B](https://doi.org/10.1016/j.esmoop.2024.103661)). The DCA yielded an area under net benefit (AU-NBC) of 0.077 ([Figure 4C](https://doi.org/10.1016/j.esmoop.2024.103661)). The AU-ROC consistently approximated 0.7 across different time intervals ([Figure 5](https://doi.org/10.1016/j.esmoop.2024.103661)). [Supplementary Table S3](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>, shows additional performance metrics. The C-index for different subgroups were as follows: 0.68 (se = 0.029) for females, 0.68 (se = 0.023) for males, 0.70 (se = 0.033) for *BRAF* mutated melanoma, 0.67 (se = 0.021) for *BRAF* wild-type, 0.71 (se = 0.026) for *NRAS* mutated melanoma, 0.69 (se = 0.022) for *NRAS* wild-type melanomas, 0.69 (se = 0.027) for patients <65 years of age, and 0.68 (se = 0.023) for patients aged >65 years.

### Internal validation

The shrinkage coefficient was 1.0003, indicating a 0.03% lack of fit in the model. The optimism-corrected C-index was 0.68, indicating moderated correlation between the log hazard and the observed survival time ([Supplementary Table S4](https://doi.org/10.1016/j.esmoop.2024.103661), available at <https://doi.org/10.1016/j.esmoop.2024.103661>).



**Figure 1.** Plot showing the results of the random survival forest. The x-axis shows the variable importance of each variable. The variables with positive variable importance are depicted in green, while the ones with negative variable importance (vimp) are depicted in burgundy. BMI, body mass index; ICI, immune checkpoint inhibitors; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

### External validation

The performance of nomogram was evaluated using a cohort of 314 patients. Patients were divided into four groups according to their risk score based on the quartiles of the score in the training cohort.

Kaplan–Meier curves showed that the PFS between the four groups were statistically significantly different (log-rank test  $P < 0.001$ ). In the validation cohort, the first group showed an mPFS of 35 months (95% CI 12 months-not applicable), the second group had an mPFS of 5 months (95% CI 4-8 months) and a HR of 2.07 (ref: first group: 95% CI 1.4-2.99), and the third had the shortest mPFS of 2 months (95% CI 1-3 months) and HR of 3.89 (ref: first group: 95% CI: 2.58-5.86) (Figure 3C).

The same score also stratified patients according to MSS in the validation cohort (Figure 3D).

The C-index of the validation cohort was 0.664 (se = 0.021) and the calibration plots showed good correlation (Figure 4A). The AU-NBC value was 0.079 (Figure 4C) and the AU-ROC approximated 0.7 across different time intervals (Figure 5).

### DISCUSSION

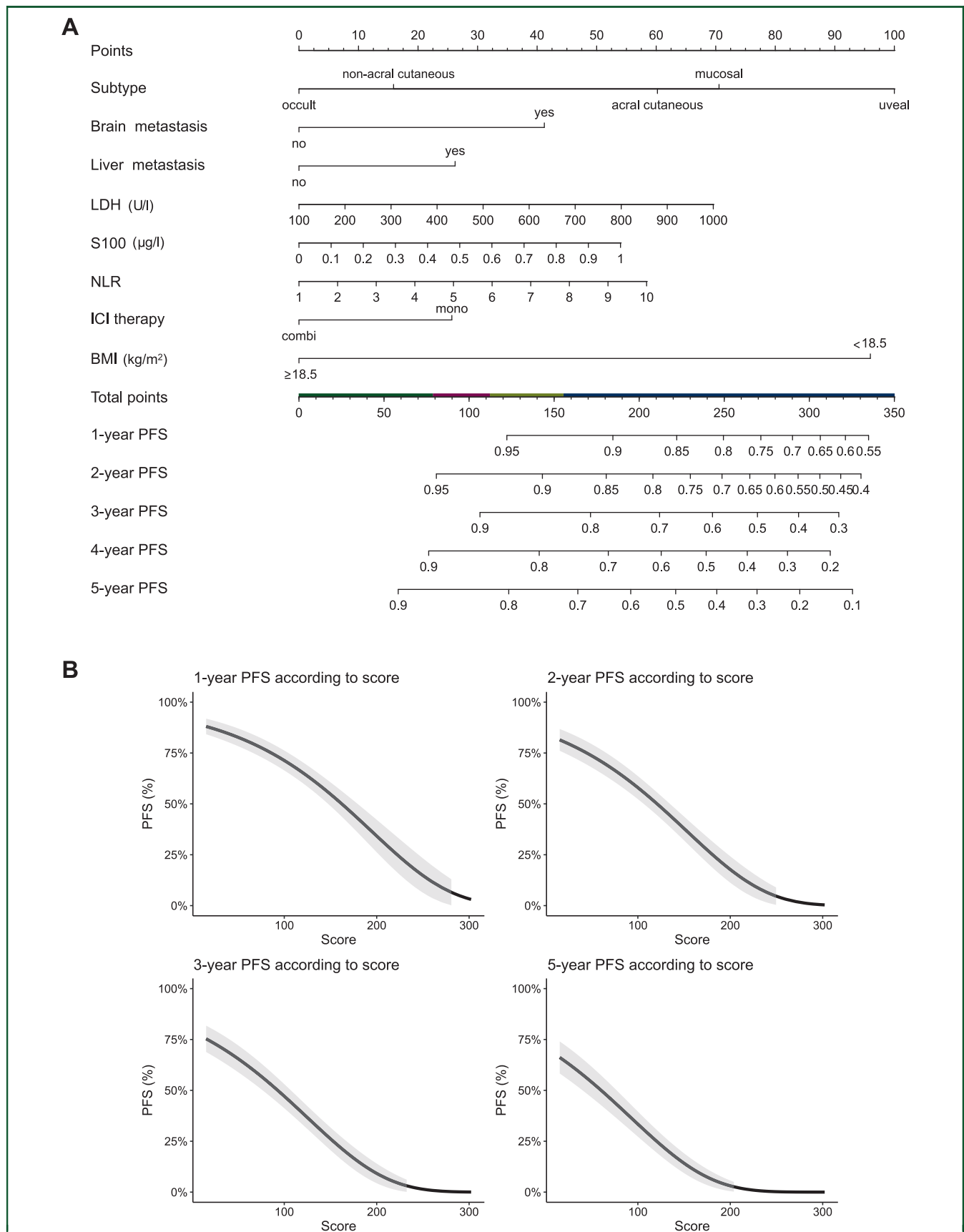
We developed and validated a novel nomogram designed for predicting PFS in stage IV melanoma patients after first-line anti-PD-1-based therapy. This tool can tailor

personalized therapeutic decisions and individualized patient follow-up strategies, and facilitate risk stratification.<sup>22</sup> This model is in the form of a dynamic, web-based nomogram to ensure accessibility and user-friendliness. The clinical utility has been assessed using DCA alongside other established performance metrics.<sup>22</sup>

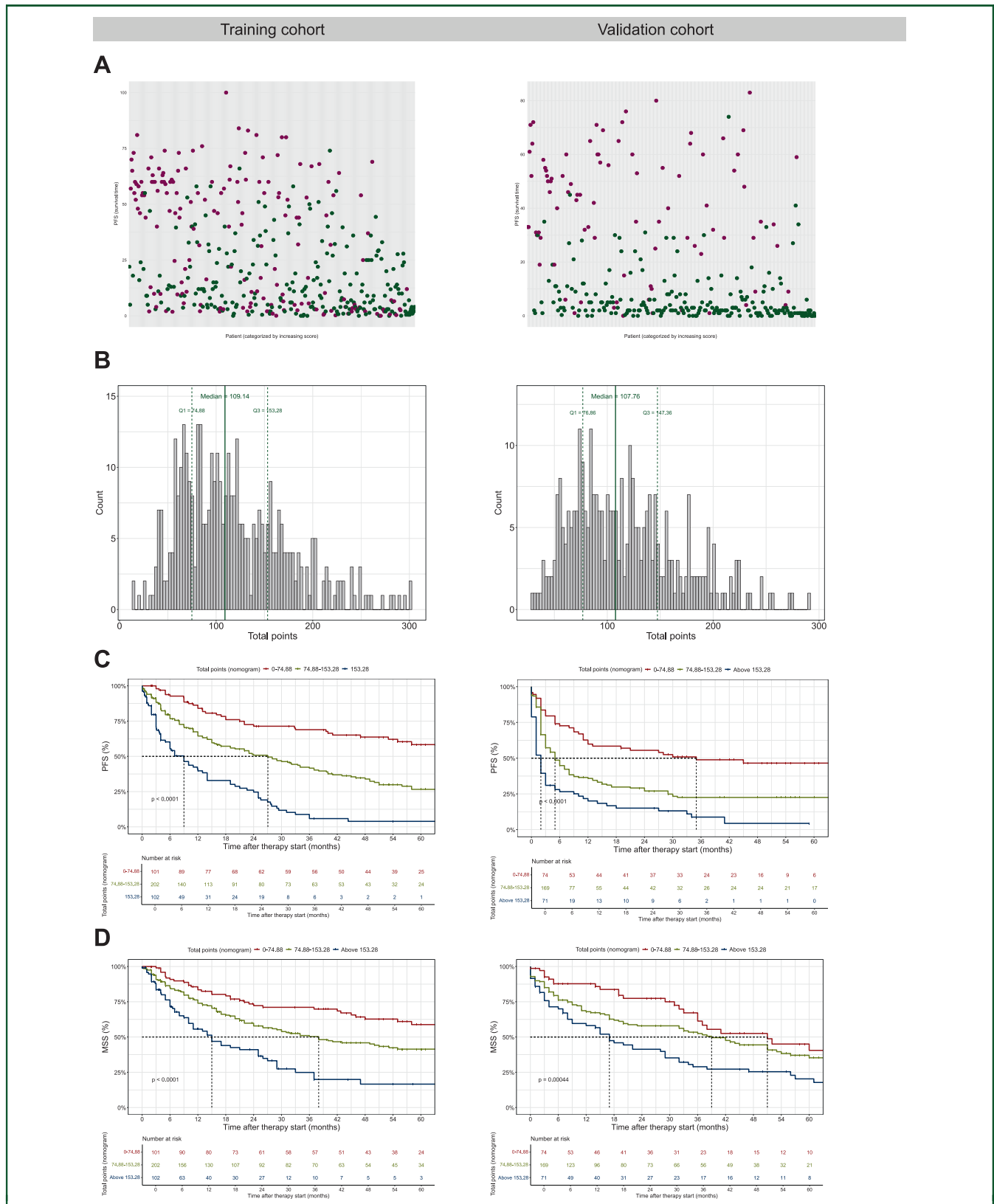
Within AJCC v8 stage IV melanoma, no substages have been identified. The M category is subdivided based on the localization of metastases and LDH levels. Given the significant variability in survival outcomes among stage IV melanoma patients, there is a need to introduce a more nuanced stratification system.

We initiated our investigation by identifying predictors of PFS in patients undergoing ICI therapy. The variables finally included in our nomogram have exhibited predictive abilities in prior studies.<sup>23,24</sup>

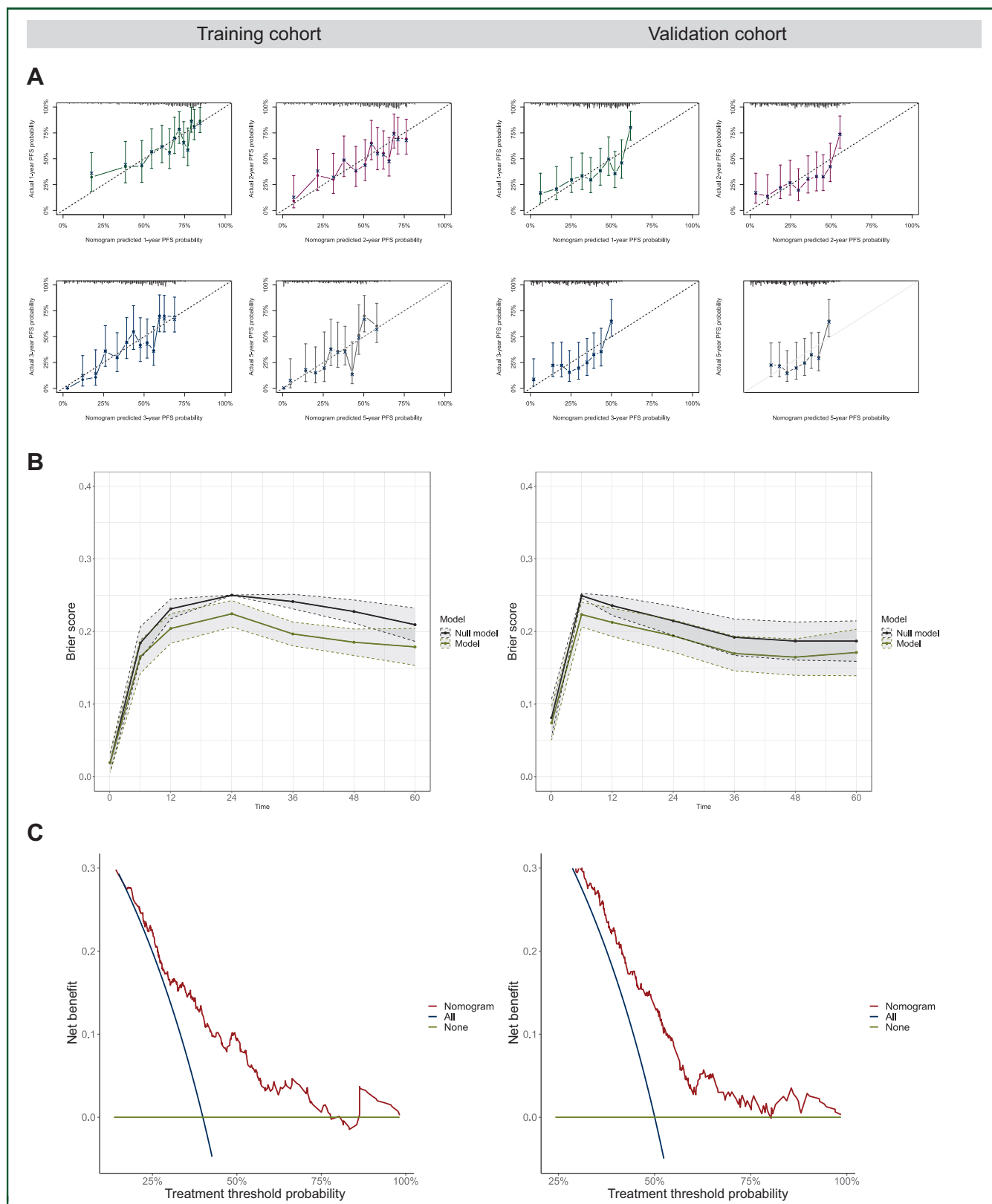
Among the variables, LDH, markers of tumor burden, NLR, and melanoma subtype were significant PFS predictors. These findings align with earlier research, emphasizing the role of pretherapy LDH along with the melanoma subtype, underlining its distinct genomic profiles.<sup>23,25-30</sup> Claps et al. reviewed the role of LDH in cancer showing its role in immunosuppression, metabolism, and glycolysis.<sup>31</sup> Despite the counterintuitive role of neutrophils in tumors, elevated NLR has been correlated with unfavorable outcomes across various cancers. This may be attributed to the effect of lowered lymphocyte levels.<sup>32-36</sup> S100, although



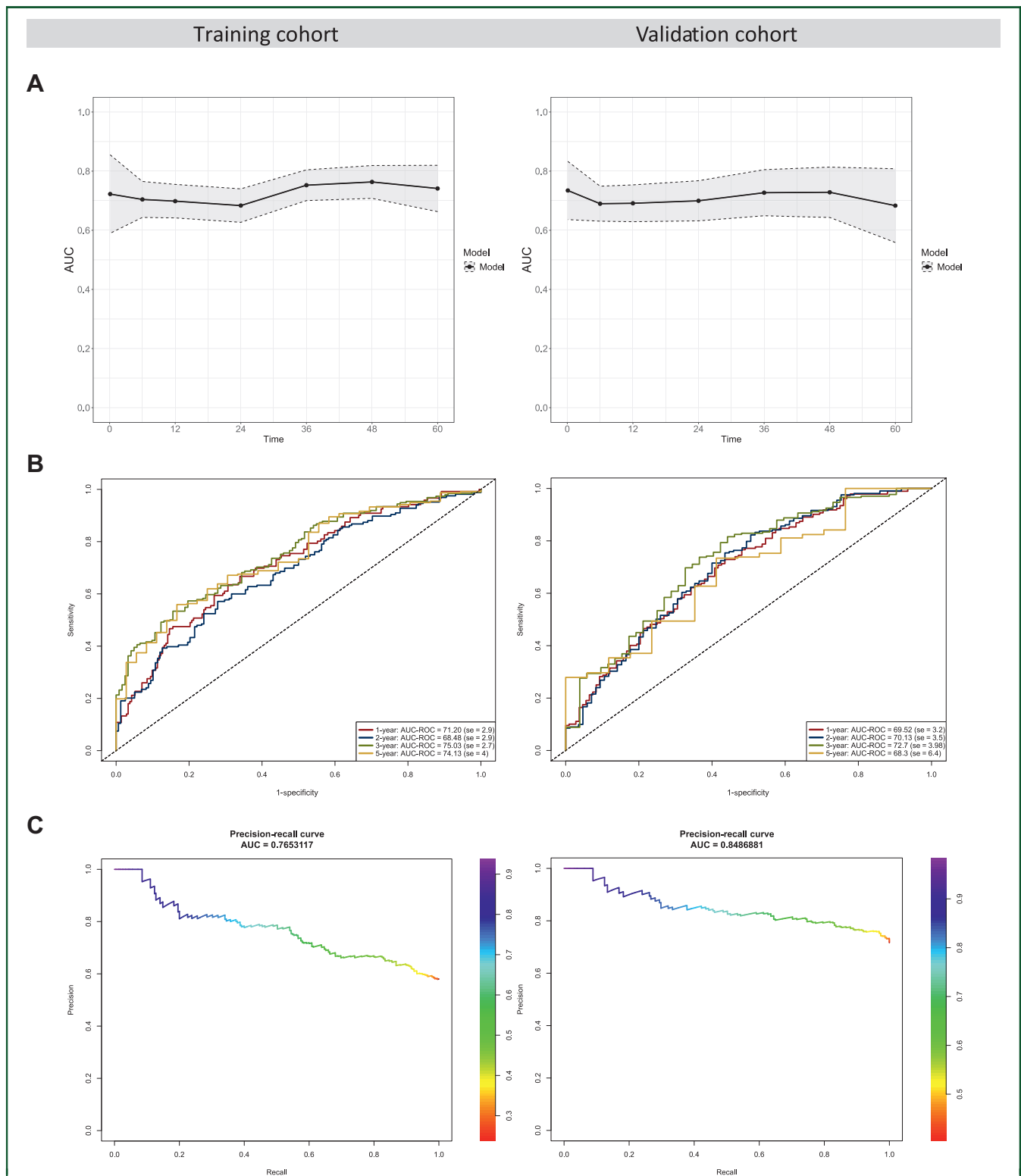
**Figure 2. The nomogram and score creation.** (A) Plot showing the nomogram that was built using the selected eight variables. The nomogram combines these eight clinicopathologic features to predict the PFS of stage IV melanoma patients after first-line anti-PD-1-based therapy. (B) Plots showing the relationship between the total points of the nomogram (score) and the PFS probability at 1, 2, 3, and 5 years after therapy initiation in the training cohort. BMI, body mass index; ICI, immune checkpoint inhibitors; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PD-1, programmed cell death protein 1; PFS, progression-free survival.



**Figure 3. The score derived from the nomogram and the survival outcomes.** (A) Plots that show the distribution of the score in the patients in the two cohorts. Green represents the patients who did develop progression after anti-PD-1-based therapy and burgundy dots represent patients who did not progress. (B) Plot showing the distribution, the median, the lower, and the upper quartile of the total points, calculated using the nomogram among patients in the two cohorts. Using the quartiles of the training cohort, three groups were created. (C) Kaplan–Meier curves showing the PFS of the three groups that were created using the quartiles of the total points in the training cohort in the training (left) and validation (right) cohorts. (D) Plot showing the MSS of the three groups defined by the total points of the nomogram in the training cohort for the training (left) and validation (right) cohorts. MSS, melanoma-specific survival; PD-1, programmed cell death protein 1; PFS, progression-free survival.



**Figure 4. Performance metrics plots regarding progression-free survival and its clinical application.** (A) Calibration curves of the model in the training (left) and validation (right) cohort. (B) Brier score in relation to time in months after therapy start for the training (left) and validation (right) cohort. (C) Decision curve analysis depicting the net clinical benefit of the model in the training (left) and validation (right) cohort. PFS, progression-free survival.



**Figure 5. Performance metrics to predict risk of progression.** (A) Area of the receiver operating characteristic curve (AU-ROC) in relation to time in months after therapy start for the training (left) and validation (right) cohorts. (B) ROC curves. (C) Precision and recall curves.

primarily used as a biomarker in daily clinical practice only in some countries, has demonstrated promise in risk prediction and should be integrated into nomograms.<sup>23,27,37</sup> Patients with brain metastasis exhibited worse outcomes compared to those without brain metastases, as reflected

by the AJCC v8 classification, where presence of brain metastases is included in a separated substage M1d. The presence of hepatic metastases and the influence of hepatic microenvironment on immunotherapy resistance has also been demonstrated before.<sup>24,26,38,39</sup> Low BMI was

associated with worse outcomes, with underweight individuals showing poorer outcomes compared to those with normal or elevated BMI, similar to what other groups published before.<sup>40,41</sup>

Our work has significant strengths and one of the most important lies in its simplicity and user-friendly design.<sup>42</sup> The study underwent internal and external validation, yielding a nomogram tailored to the subgroup of stage IV patients undergoing first-line ICI. Handling of missing values through multiple imputations enhances its internal validity.

Given the ICI approval in 2015, our choice of PFS as the primary endpoint aligns with the clinical context. Our cohort of 719 melanoma patients from diverse European centers, and the long median follow-up of >50 months, contribute to the study's robustness. The decision to use upper and lower cut-offs for continuous variables (LDH, NLR, S100) aimed to reduce the impact of extreme values and enhance applicability.

This study does have limitations, including its retrospective nature. While the nomogram can be used as a predictive tool, it should not be misinterpreted that ICI lacks efficacy in patients with higher scores. The nomogram reflects only the features upon therapy initiation and does not consider the dynamics of biomarkers.<sup>40,43,44</sup> We included the LDH, S100, and NLR as continuous variables associated with survival; however, the exact relationship is more complex than linear. Higher pathological (above cut-off) values are correlated with worse outcomes. However, the absolute values of those with normal values (below cut-off) seem to be associated with different outcomes. Despite this, the overall score remains the critical determinant in prognosis. In the training cohort, the number of patients with *BRAF* mutation was lower than expected. Individuals with *BRAF* mutation and unfavorable baseline characteristics were most likely directed toward first-line targeted therapy at this time. Despite this, the nomogram did not identify a predictive role for *BRAF* mutation. Moreover, the training cohort had a significant number of acral melanoma patients. Partly, this relates to the high number of patients treated in Tuebingen. Acral melanomas, requiring specialized surgical treatment, are typically managed in experienced centers, where patients then remain in follow-up. Our model, shown from calibration plots in the validation cohort, predicted more favorable results than observed. The primary recruitment from reference centers across Europe may introduce bias.

### Conclusions

We identified survival predictors in stage IV melanoma patients upon first-line anti-PD-1-based immunotherapy initiation and established a web-based nomogram requiring the input of eight features upon therapy initiation.

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### DISCLOSURE

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### DATA SHARING

Data from this research study will be made available to qualified researchers upon request.

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