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Transformer-based AI approach to unravel long-term, time-dependent prognostic complexity in patients with advanced NSCLC and PD-L1 ≥50%: insights from the pembrolizumab 5-year global registry

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ABSTRACT

Background With nearly one-third of patients with advanced non-small cell lung cancer (NSCLC) and PD-L1 Tumor Proportion Score≥50% surviving beyond 5 years following first-line pembrolizumab, long-term outcomes challenge traditional paradigms of cancer prognostication. The emergence of non-cancer-related factors and time-dependent trends underscores the need for advanced analytical frameworks to unravel their complex interplay.

Methods We analyzed the Pembro-real 5Y registry, a global real-world dataset of 1050 patients treated across 61 institutions in 14 countries with a long-term follow-up and a large panel of baseline variables. Two complementary approaches were employed: ridge

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune checkpoint inhibitors have redefined the prognosis of patients with advanced non-small cell lung cancer (NSCLC), particularly those with PD-L1 expression ≥50%, with nearly one-third surviving beyond 5 years when treated with pembrolizumab. However, conventional models struggle to capture the long-term, time-dependent influence of host and non-cancer-related factors, and there is a need for innovative analytical frameworks that address data complexity and missingness in real-world settings.

WHAT THIS STUDY ADDS

⇒ This study applies a novel integrative framework combining ridge regression and a transformer-based artificial intelligence (AI) model (not another imputation method) to analyze a large, global, real-world cohort of patients with advanced NSCLC treated with first-line pembrolizumab. It reveals that the prognostic relevance of clinical features evolves over time: while Eastern Cooperative Oncology Group Performance Status, steroid use, and metastatic burden dominate early mortality, long-term outcomes are more strongly influenced by systemic health indicators such as dyslipidemia, body mass index, and absence of cardiovascular disease. The AI model successfully handles missing data without imputation and uncovers dynamic, non-linear patterns not detected by traditional methods.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports a shift toward holistic, time-aware patient management strategies in immunotherapy-treated NSCLC. It emphasizes the need to integrate dynamic risk assessment tools into clinical practice and highlights the growing importance of systemic health and comorbidities in survivorship care. The findings also encourage future research to validate AI-based models and adopt explainable, real-world compatible methodologies in prognostication.

regression, chosen for its ability to address multicollinearity while retaining interpretability, and not another imputation method (NAIM), a transformer-based artificial intelligence model designed to handle missing data without imputation. Endpoints included risk of death at 6, 12, 24, 60 months and 5-year survival.

Results The ridge regression model achieved a c-statistic of 0.66 (95% CI: 0.59 to 0.72) for the risk of death and an area under the curve (AUC) of 0.72 (95% CI: 0.65 to 0.78) for 5-year survival, identifying Eastern Cooperative Oncology Group Performance Status (ECOG-PS)≥2, increasing age, and metastatic burden as primary risk factors. However, wide CIs for some predictors highlighted statistical instability. NAIM demonstrated robust handling of missing data, with a c-index of 62.98±2.11 for risk of death and an AUC of 60.52±3.71 for 5-year survival. The comprehensive SHapley Additive exPlanations analysis revealed dynamic, time-dependent patterns, with early mortality dominated by acute factors (eg, ECOG-PS, steroids) and long-term outcomes increasingly influenced by systemic health markers (eg, absence of hypertension, increasing body mass index). Unexpected insights included the protective role of dyslipidemia (but not statins) and the nuanced impact of smoking status, reflecting evolving disease dynamics and host-tumor interplay.

Conclusions Our integrative framework illuminates the complexity of long-term outcomes in patients with NSCLC treated with pembrolizumab, uncovering dynamic, non-linear prognostication trends. This analysis provides insights into patient trajectories, emphasizing the need for holistic, long-term management strategies.

INTRODUCTION

The treatment landscape of non-small cell lung cancer (NSCLC) has undergone a profound transformation with the advent of immune checkpoint inhibitors (ICIs) and targeted therapies. These advances have established unprecedented long-term survival outcomes, particularly in patients with oncogene-addicted tumors and those with high PD-L1 expression treated with ICIs.[1 2] In the context of ICIs and chemo-immunotherapy, survival rates of ≈20% at 5 years have become a consistent reality in advanced NSCLC populations,[3–5] with single-agent PD-1 inhibition achieving 5-year survival rates of 30% in patients with PD-L1 expression ≥50%.[6 7]

This shift is leading the oncology community to a re-evaluation of traditional paradigms in the prognostication and management of patients with NSCLC. Historically, the expected survival of advanced-stage patients was limited to less than 1 year,[8] with baseline prognostic factors such as performance status (PS) and metastatic burden exerting a proportional and consistent impact on outcomes throughout the disease trajectory.[9] However, as survival horizons expand, non-cancer-related, host-specific factors are emerging as critical determinants of long-term outcomes.

The interaction between host factors and tumor biology is particularly pronounced in the context of ICIs, which modulate the immune-tumor interplay. Factors linked to the metabolic status,[10–13] body composition,[14–17] and systemic inflammation[18 19] are not only relevant to immune function but also influence treatment efficacy and patient trajectories. As such, the evolving complexity of patient outcomes demands novel analytical methodologies capable of capturing dynamic, non-linear, and time-sensitive trends.

The Pembro-real 5Y is a comprehensive real-world, global, dataset derived from 61 institutions including patients with stage IV NSCLC with PD-L1 Tumor Proportion Score (TPS) of ≥50% treated with first-line pembrolizumab monotherapy outside of clinical trials.[20] It captures detailed clinical, demographic, and treatment-related data, with a particular emphasis on long-term outcomes, including overall survival (OS) at 5 years.

In this study, we propose an integrative approach to the Pembro 5Y dataset that combines conventional statistical models with advanced artificial intelligence (AI)-based methodologies.

This dual framework aims to address the growing granularity of available clinical data by combining the traditional need for interpretable metrics with the modern imperative for dynamic risk stratification, leveraging conventional and AI-driven methodologies to uncover non-linear prognostic patterns that extend beyond traditional oncologic determinants.

METHODS

Study design

The objective of this study is to uncover novel insights into the risk of death and the determinants of 5-year survival

in patients with advanced stage NSCLC with PD-L1 TPS ≥50% treated with first-line pembrolizumab, leveraging conventional and AI-driven methodologies. With this approach, we aim to delineate both expected and unexpected prognostic factors, offering a comprehensive understanding of patient trajectories and informing personalized strategies in this rapidly evolving field.

The Pembro-real 5Y is a large real-world global dataset that includes 1050 patients with stage IV NSCLC and PD-L1 TPS ≥50%, treated with first-line pembrolizumab at 61 institutions across 14 countries and has already been reported in detail.[20] The primary eligibility criteria included receiving first-line pembrolizumab monotherapy outside of clinical trials, having a PD-L1 TPS of ≥50%, and starting treatment by May 31, 2018. To ensure at least 5 years of follow-up for long-term responders, the minimum data cut-off for patients still alive was set at May 1, 2023.

The 5-year survival rate, defined as the crude rate of patients alive at the 5-year mark from the treatment initiation date, and OS, defined as the time from treatment initiation to death or loss to follow-up, were selected as the clinical endpoints of interest.

To address the complexity of the dataset, characterized by long-term follow-up, extensive baseline information with inherent collinearity, and significant missing data, we adopted a dual analytical approach: conventional statistical modeling using ridge regression and a transformer-based AI model. These methods were applied to the same panel of baseline variables (provided in the online supplemental methods) including clinicpathologic oncological characteristics, demographics, concomitant medications, and comorbidities. Ridge regression was chosen because it allows us to address the challenges of multicollinearity and high-dimensional datasets without eliminating potentially important variables and maintaining interpretability. To complement the conventional analysis, we employed NAIM (not another imputation method), a transformer-based AI model specifically designed for resilience to missing data. This model was originally developed and tested in the context of OS prediction in NSCLC patients and has demonstrated superior performance over conventional imputation-based approaches in prior studies.[21–23] While external validation in independent cohorts is still lacking, its architecture offers promising features for real-world application, particularly in datasets characterized by missingness and high-dimensional clinical information. Unlike traditional methods requiring complete datasets or imputations, NAIM uses a masked self-attention mechanism to make predictions solely from available data without imputing missing values. Additionally, explainable AI techniques, specifically the SHAP (SHapley Additive exPlanations) method,[24] were applied to quantify each feature's contribution to model predictions. SHAP values, rooted in game theory and economics, provide an interpretable measure of each variable's effect on survival or death. This nuanced approach captures time-dependent and non-linear interactions, offering insights unavailable through conventional regression models. By combining these methodologies, we balanced the interpretability and clinical applicability of conventional statistics with the flexibility and depth of AI, aiming to extract meaningful patterns and provide actionable insights into the predictors of long-term outcomes in NSCLC patients.

To further analyze the importance of the included variables in determining the risk of death over time, we used a graphical representation of the cumulative sum of the absolute contributions of the features across four pre-established time points: 6 months, 12 months, 24 months and 60 months. This approach aggregates the absolute SHAP values, allowing for the identification of feature importance independent of specific time points. Visualizing these cumulative sums allows us to assess which features consistently play a dominant role in influencing predictions throughout the observed period. This representation provides a comprehensive view of feature relevance, aiding in the interpretation of the model's behavior and offering insights into the underlying clinical factors that drive survival outcomes.

Statistical analysis

We used descriptive statistics to report baseline clinicopathologic features of interest, assessing differential distribution through the χ^2 test. The 5-year survival rate was reported as a crude rate with 95% CIs. Median follow-up was estimated using the reverse Kaplan-Meier method, while the median OS was computed using the Kaplan-Meier method and compared with the log-rank test.

In the ridge regression analysis, given the substantial heterogeneity in missingness across the baseline variables (ranging from 1.4% to 89.6%), we opted for a pragmatic and reproducible strategy in the modeling phase. Specifically, categorical variables with residual missingness were retained with "unknown/not-tested" encoded as an explicit factor level. This allowed us to preserve the full analytic sample and avoid the introduction of uncertain or artificial imputations, particularly in variables where the proportion of missing data exceeded commonly accepted thresholds for reliable multiple imputation. This approach aligns with the real-world nature of the dataset, where data incompleteness may reflect systemic differences in clinical documentation, patient complexity, or diagnostic work-up and may carry independent prognostic information. Consequently, HRs reported for the "unknown/not-tested" levels in the regression models represent the impact of such data absence, rather than true biological strata. The extent of missingness for each baseline variable is detailed in table 1.

For the risk of death, a Cox proportional hazards model with ridge regularization was applied to manage multicollinearity and penalize large coefficients. Cross-validation was used to determine the optimal penalty parameter (λ), minimizing the partial likelihood deviance. Variables with non-zero coefficients were subsequently refitted into a standard Cox model to estimate HRs and 95% CIs. Model performance was evaluated using the concordance

Table 1 Patients' characteristics of the overall cohort

	Overall study population		Overall study population
	No 1050 (%)		No 1050 (%)
Age, (years)		Baseline corticosteroids	
Median (range)	69 (31–92)	None	845 (80.5)
		<10 mg pred	114 (10.8)
		≥10 mg pred	91 (8.7)
Sex		Baseline proton pump inhibitors	
Female	422 (40.2)	No	598 (57.0)
Male	628 (59.8)	Yes	400 (38.1)
		Unknown	52 (5.0)
Ethnicity		Baseline antibiotics	
White	870 (82.9)	No	943 (89.8)
Black/African-American	31 (3.0)	Yes	107 (10.2)
Asian	29 (2.7)		
Hispanic	9 (0.8)		
Others	26 (2.5)		
Unknown	85 (8.1)		
WHO BMI category		Baseline statins	
Obese	162 (15.4)	No	681 (64.9)
Overweight	286 (27.2)	Yes	313 (29.8)
Normal-weight	418 (39.8)	Unknown	56 (5.3)
Under-weight	41 (3.9)		
Unknown	143 (13.7)		
ECOG-PS		Baseline metformin	
0–1	859 (81.8)	No	887 (84.5)
≥2	161 (15.3)	Yes	124 (11.8)
Unknown	30 (2.9)	Unknown	39 (3.7)
Histology		Other glucose-lowering medications	
Squamous	238 (22.8)	No	787 (75.0)
Adenocarcinoma	768 (73.5)	Yes	64 (6.1)
Others/NOS	39 (3.7)	Unknown	199 (19.0)
Smoking status		Hypertension	
Current smokers	280 (26.7)	No	469 (44.7)
Former smokers	660 (62.9)	Yes	523 (49.8)
Never smokers	95 (9.0)	Unknown	58 (5.5)
Unknown	15 (1.4)		
PD-L1 TPS		Myocardial infarction	
≥90%	559 (53.2)	No	858 (81.7)
50%–89%	281 (26.8)	Yes	128 (12.2)
Not specified	210 (20.0)	Unknown	64 (6.1)
CNS metastases		Other cardiovascular conditions	
No	841 (80.1)	No	715 (68.1)
Yes	209 (19.9)	Yes	271 (25.8)
		Unknown	64 (6.1)
Bone metastases		Type 2 diabetes	
No	686 (65.3)	No	809 (77.0)

Continued

Table 1 Continued

	Overall study population		Overall study population
	No 1050 (%)		No 1050 (%)
Yes	364 (34.7)	Yes	177 (16.9)
		Unknown	64 (6.1)
Liver metastases		Pulmonary disease	
No	885 (84.3)	No	711 (67.7)
Yes	165 (15.7)	Yes	275 (26.2)
		Unknown	64 (6.1)
Lung metastases		Dyslipidemia	
No	396 (37.7)	No	666 (63.4)
Yes	654 (62.3)	Yes	314 (29.9)
		Unknown	70 (6.7)
Pleural metastases		Autoimmune diseases	
No	787 (75.0)	No	933 (88.9)
Yes	263 (25.0)	Yes	53 (5.0)
		Unknown	64 (6.1)
Adrenal glands metastases		Other comorbidities	
No	839 (79.9)	No	563 (53.6)
Yes	211 (20.1)	Yes	374 (35.6)
		Unknown	113 (10.8)
Other metastatic sites		–	–
No	900 (85.7)	–	–
Yes	150 (14.3)		
Number of metastatic sites		–	–
≤3	946 (90.1)	–	–
>3	104 (9.9)		
EGFR mutation status		–	–
No	890 (84.8)	–	–
Yes	19 (1.8)		
Not-tested	141 (13.4)		
ALK translocation status		–	–
No	883 (84.1)	–	–
Yes	6 (0.6)		
Not-tested	161 (15.3)		
ROS-1 translocation status		–	–
No	710 (67.6)	–	–
Yes	9 (0.9)		
Not-tested	331 (31.5)		
KRAS mutation status		–	–
No	367 (35.0)	–	–
Yes	224 (21.3)		
Not-tested	459 (43.7)		
BRAF mutation status		–	–
No	491 (46.8)	–	–
Yes	26 (2.5)		
Not-tested	533 (50.7)		

Continued

Table 1 Continued

	Overall study population		Overall study population
	No 1050 (%)		No 1050 (%)
Tumor mutational burden		–	–
Non-high	92 (8.8)	–	–
High	17 (1.6)		
Not-tested	941 (89.6)		

Missing values were reported as "unknown", "not-specified" or "not-reported" as appropriate.
ALK, anaplastic lymphoma kinase; BMI, body mass index; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; pred, prednisone; ROS-1, proto-oncogene tyrosine-protein kinase ROS; TPS, Tumor Proportion Score.

index (C-index). For the 5-year survival analysis, logistic ridge regression was employed on the same imputed datasets and covariates, with the binary outcome indicating survival at 5 years. Cross-validation identified the optimal λ, and selected variables were refitted into a logistic regression model to estimate ORs and 95% CIs. Model discrimination was assessed via the area under the receiver operating characteristic curve (AUC) and c-statistics. These analyses were performed using the R-studio software, R Core Team (2021). R: A language and environment for statistical computing implemented with the *glmnet*, *survival* packages, ensuring robust handling of multicollinearity and providing interpretable, clinically relevant metrics like ORs and HRs.

As previously described, the NAIM method is a transformer-based AI model that does not require imputation. Instead, it leverages a masked self-attention mechanism that allows the model to learn directly from partially observed data, using only the available features without artificially reconstructing missing values. Numerical features were normalized to (0,1), and categorical variables were encoded numerically. The first block of the model, called feature embedding, encoded these inputs as embeddings, which involves assigning trainable vectors to each possible clinical characteristic. At this stage, missing data were already addressed by assigning it a specific, non-trainable vector. Following this, the core of the model used masked self-attention to make predictions based exclusively on the available patient data.

The analyses were performed using a fivefold cross-validation strategy, stratified on the target variable to maintain the same class proportions in the training and testing sets. The model, which is implemented in Python using the PyTorch library, was evaluated using various metrics, including AUC, accuracy, F1-score, Matthews correlation coefficient (MCC), and G-mean, each of which captures a different aspect of predictive performance. Furthermore, in addition to the results obtained on the test samples, we report the training performance to assess the correlation between the target variable and the various features considered.

SHAP values were then used to provide an interpretable measure of each variable's contribution in defining clinical outcome and were visualized through summary plots. Features were ordered by their absolute contribution, with high values (red) and low values (blue) positioned to indicate their influence on outcomes. For instance, red dots on the right side of the plot imply a positive association with the outcome, while blue dots on the left suggest negative association. Missing values were represented as gray dots. Figure 1 provides a visual overview of the methodological framework and the interpretation of the results.

RESULTS

Cohort characteristics

The Pembro-real 5Y cohort has been extensively described elsewhere[20]; overall 1063 consecutive patients were entered in the registry (online supplemental table 1 reports the number of patients entered by each participating institution) with a final eligible population of 1050 patients after the exclusion of 13 patients lost to follow-up.

Although the overall cohort has been previously described, a comprehensive overview of the clinicopathologic characteristics of the study cohort, including the absolute number and percentage of missing values for each baseline variable, is reported in table 1.

At the median follow-up period of 70.3 months (95% CI: 69.0 to 70.9) and a total of 805 death events, 282 patients were alive at the 5-year landmark, resulting in a 5-year survival rate of 26.9% (95% CI: 23.8% to 30.2%) while the median OS for the study population was 21.8 months (95% CI: 19.1 to 25.7, 805 events).

Ridge regression analysis

The ridge regression analysis for the risk of death was conducted using an optimal penalty parameter (λ) determined via cross-validation, which was 0.631. The multivariate model is reported in table 2 and demonstrated moderate discriminatory ability with a c-statistic of 0.66 (95% CI: 0.59 to 0.72). Significant predictors of

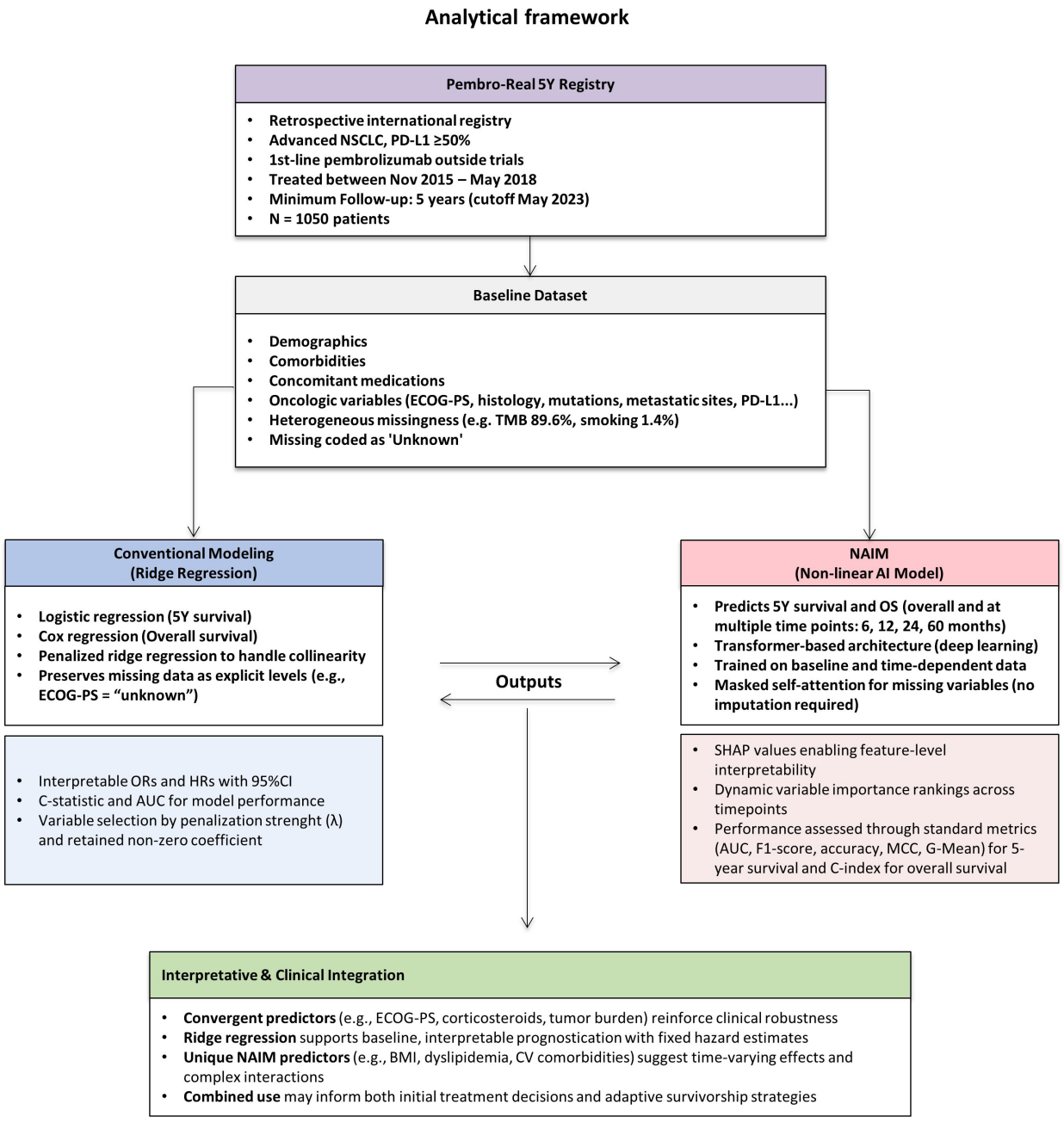

Figure 1 Visual summary of the methodological pipeline used to analyze long-term outcomes of patients with advanced NSCLC (PD-L1 ≥50%) treated with first-line pembrolizumab in the Pembro-Real 5Y Registry. Two parallel approaches were adopted: Conventional modeling using penalized ridge regression for both 5-year survival (logistic) and overall survival (Cox), producing interpretable ORs and HRs with associated CIs, and model performance metrics (eg, C-statistic, AUC). NAIM (AI model) employing a transformer-based deep learning architecture to model time-dependent survival dynamics using SHAP values for feature interpretability and multiple performance metrics (AUC, F1-score, Matthews correlation coefficient [MCC], etc). Outputs were compared side-by-side. Shared predictors (eg, ECOG-PS, corticosteroid use) reinforced robustness, while NAIM identified additional time-sensitive or non-linear predictors (eg, BMI, dyslipidemia). This integrative approach supports both baseline prognostication and longitudinal survivorship strategies. AUC, area under the curve; BMI, body mass index; CV, cardiovascular; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NAIM, Not Another Imputation Method; NSCLC, non-small cell lung cancer; SHAP, SHapley Additive exPlanations; TMB, Tumor Mutational Burden.

increased mortality risk included Eastern Cooperative Oncology Group Performance Status (ECOG-PS)≥2 (HR 2.06, 95% CI: 1.67 to 2.53), the use of both low dose (HR 1.64, 95% CI: 1.29 to 2.08) and high dose steroids (HR 1.37; 95% CI: 1.04 to 1.81), the presence of liver (HR 1.35, 95% CI: 1.07 to 1.69), bone (HR 1.34, 95% CI: 1.13 to 1.58), and pleural metastases (HR 1.21, 95% CI: 1.01 to 1.45), the presence of other cardiovascular comorbidities (HR 1.22, 95% CI: 1.01 to 1.46), being never smoker (HR 1.35, 95% CI: 1.01 to 1.81), the exposure to proton pump inhibitors (PPI) at baseline (HR 1.20, 95% CI: 1.02 to 1.40) and increasing age (HR 1.01 per

Table 2 Ridge regression multivariable analyses for the risk of death (overall survival—using Cox proportional hazard model) and the 5-year survival state (using logistic regression)

Variable (data missingness)	Overall survival (risk of death)	5 year survival (probability of being alive)
	HR (95% CI)	OR (95% CI)
Age (continuous)	1.01 (1.01 to 1.02)	0.97 (0.96 to 0.99)
Sex		
Male vs female	0.97 (0.83 to 1.14)	1.01 (0.73 to 1.39)
Ethnicity (8.1%)		
White	1	1
Black/African American	0.66 (0.41 to 1.06)	1.68 (0.69 to 3.93)
Asian	1.10 (0.72 to 1.67)	0.42 (0.11 to 1.21)
Hispanic	0.29 (0.11 to 1.77)	4.44 (0.94 to 23.66)
Others	0.96 (0.61 to 1.52)	0.42 (0.11 to 1.20)
Unknown	1.03 (0.75 to 1.39)	0.75 (0.39 to 1.39)
WHO BMI (13.7%)		
Normal weight	1	1
Underweight	1.31 (0.87 to 1.96)	0.89 (0.35 to 2.05)
Overweight	1.07 (0.89 to 1.29)	0.94 (0.63 to 1.38)
Obese	0.96 (0.76 to 1.20)	1.09 (0.69 to 1.72)
Unknown	0.98 (0.76 to 1.27)	1.25 (0.73 to 2.12)
ECOG-PS (2.9%)		
0–1	1	1
≥2	2.06 (1.67 to 2.52)	0.39 (0.23 to 0.65)
Unknown	1.31 (0.79 to 2.17)	0.70 (0.21 to 2.09)
Histology		
Squamous	1	1
Adenocarcinoma	1.06 (0.88 to 1.29)	1.18 (0.68 to 1.83)
Others/NOS	1.03 (0.66 to 1.62)	1.62 (0.74 to 3.77)
Smoking status (1.4%)		
Current smoker	1	1
Former smoker	1.04 (0.87 to 1.24)	0.81 (0.57 to 1.15)
Never smoker	1.35 (1.01 to 1.81)	0.57 (0.30 to 1.08)
Unknown	1.44 (0.77 to 2.69)	0.09 (0.01 to 0.60)
PD-L1 tumor proportion score (20.0%)		
50–89	1	1
≥90	0.95 (0.79 to 1.13)	1.08 (0.76 to 1.56)
Not reported	0.92 (0.74 to 1.13)	1.16 (0.24 to 1.76)
CNS metastases		
Yes vs No	1.04 (0.85 to 1.28)	0.90 (0.42 to 1.37)
Liver metastases		
Yes vs No	1.35 (1.07 to 1.69)	0.63 (0.47 to 1.06)
Bone metastases		
Yes vs No	1.32 (1.12 to 1.56)	0.67 (0.58 to 0.95)
Lung metastases		
Yes vs No	1.04 (0.88 to 1.23)	1.04 (0.94 to 1.48)
Pleural metastases		
Yes vs No	1.22 (1.02 to 1.45)	0.63 (0.61 to 0.93)
Adrenal glands metastases		
Yes vs No	1.11 (0.91 to 1.35)	0.95 (0.73 to 1.42)
Other metastatic sites		
Yes vs No	0.94 (0.75 to 1.18)	1.49 (0.11 to 2.24)
Number of metastatic sites		
>3 vs ≤3	1.12 (0.80 to 1.55)	0.68 (NA-1.47)
Corticosteroids at baseline		
No	1	1
<10 mg prednisolone or eq.	1.64 (1.28 to 2.06)	0.70 (0.41 to 1.18)
≥10 mg prednisolone or eq.	1.37 (1.04 to 1.81)	0.76 (0.46 to 1.36)
Baseline proton pump inhibitors (5.0%)		
No	1	1
Yes	1.20 (1.03 to 1.41)	0.85 (0.41 to 1.19)
Unknown	1.25 (0.71 to 2.21)	1.22 (0.64 to 3.49)
Baseline antibiotics		
Yes vs No	1.10 (0.86 to 1.41)	0.81 (0.37 to 1.39)
Baseline statins (5.3%)		
No	1	1
Yes	1.01 (0.80 to 1.25)	1.01 (0.30 to 1.58)
Unknown	0.99 (0.60 to 1.64)	0.83 (0.34 to 2.19)
Baseline metformin (3.7%)		
No	1	1
Yes	1.05 (0.78 to 1.41)	0.65 (0.58 to 1.22)
Unknown	0.70 (0.44 to 1.07)	1.35 (0.40 to 3.12)
Other glucose lowering medications (19.0%)		
No	1	1
Yes	1.27 (0.88 to 1.84)	0.73 (0.31 to 1.66)
Unknown	1.05 (0.83 to 1.34)	0.91 (0.55 to 1.47)
EGFR mutational status (13.4%)		
Wild type	1	1
Mutant	1.14 (0.64 to 2.04)	0.91 (0.26 to 2.87)
Not tested	1.42 (0.95 to 2.14)	0.64 (0.02 to 1.56)
ALK translocation status (15.3%)		
Wild type	1	1
Translocated	1.41 (0.55 to 3.58)	0.54 (0.37 to 3.99)
Not tested	1.08 (0.71 to 1.64)	0.91 (0.31 to 2.16)
ROS-1 translocation status (31.5%)		
Wild type	1	1
Translocated	0.68 (0.31 to 1.48)	1.65 (0.50 to 7.28)
Not tested	0.94 (0.73 to 1.18)	0.84 (0.38 to 1.40)
KRAS mutational status (47.3%)		
Wild type	1	1

Continued

Table 2 Continued

Variable (data missingness)	Overall survival (risk of death)	5 year survival (probability of being alive)
	HR (95% CI)	OR (95% CI)
Mutant	0.83 (0.67 to 1.04)	1.34 (0.88 to 2.04)
Not tested	1.03 (0.78 to 1.33)	0.96 (0.56 to 1.65)
BRAF mutational status (50.7%)		
Wild type	1	1
Mutant	0.99 (0.61 to 1.57)	0.81 (0.26 to 2.19)
Not tested	1.15 (0.89 to 1.48)	0.88 (0.52 to 1.46)
Tumor mutational burden (89.6%)		
Non-high	1	1
High	0.60 (0.29 to 1.24)	2.99 (0.92 to 9.93)
Not tested	1.04 (0.76 to 1.40)	1.08 (0.62 to 1.97)
Hypertension (5.5%)		
No	1	1
Yes	1.01 (0.85 to 1.19)	0.78 (0.54 to 1.12)
Unknown	1.47 (0.41 to 5.36)	0.91 (0.08 to 12.17)
Myocardial infarction (6.1%)		
No	1	1
Yes	0.93 (0.73 to 1.18)	0.88 (0.52 to 1.46)
Unknown	1.32 (0.05 to 35.74)	0.81 (0 to NA)
Other cardiovascular conditions (6.1%)		
No	1	1
Yes	1.22 (1.01 to 1.46)	0.74 (0.49 to 1.10)
Unknown	1.14 (0.32 to 4.00)	1.05 (0.10 to 12.10)
Type 2 diabetes (6.1%)		
No	1	1
Yes	0.80 (0.59 to 1.09)	1.28 (0.70 to 2.32)
Unknown	0.29 (0.04 to 2.07)	1690577.00 (0.00 to NA)
Pulmonary disease (6.1%)		
No	1	1
Yes	0.87 (0.72 to 1.04)	1.01 (0.11 to 1.45)
Unknown	0.67 (0.22 to 2.01)	1.40 (0.91 to 19.44)
Dyslipidemia (6.7%)		
No	1	1
Yes	0.84 (0.67 to 1.04)	1.42 (0.11 to 2.24)
Unknown	0.78 (0.35 to 1.72)	0.70 (0.78 to 3.13)
Autoimmune diseases (6.1%)		
No	1	1
Yes	0.71 (0.50 to 1.01)	1.63 (0.84 to 3.11)
Unknown	6.04 (0.49 to 73.35)	0.01 (NA)
Other comorbidities (10.8%)		
No	1	1
Yes	0.92 (0.79 to 1.09)	1.07 (0.77 to 1.49)
Unknown	0.61 (0.41 to 0.88)	2.63 (1.25 to 5.53)

Continued

Table 2 Continued

Variable (data missingness)	Overall survival (risk of death)	5 year survival (probability of being alive)
	HR (95% CI)	OR (95% CI)

Missing values were reported as “unknown”, “not-specified” or “not-reported” as appropriate.
ALK, anaplastic lymphoma kinase; BMI, body mass index; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus; NOS, not otherwise specified; PD-L1, programmed death-ligand 1.

unit increase; 95% CI: 1.00 to 1.02). Conversely, Hispanic ethnicity (HR 0.28, 95% CI: 0.11 to 0.74) was identified as a protective factor while the absence of information on other comorbidities was associated with decreased risk of death (HR 0.60, 95% CI: 0.41 to 0.88). Variables with wide CIs were noted, reflecting statistical instability due to sparse events. Online supplemental figure 1 summarizes the ridge regression coefficients, ranking ECOG PS ≥2 as the most influential variable (coefficient: 0.39), followed by missing information on the smoking status (0.24) and low-dose steroid use (0.23), while Hispanic ethnicity (−0.47) and TMB-high (−0.24) were associated with the lowest coefficients.

The ridge regression analysis for the 5-year survival state used an optimal lambda of 0.203, as determined by cross-validation. The model achieved an AUC of 0.72 (95% CI: 0.65 to 0.78), indicating acceptable discriminatory performance. Statistically significant predictors associated with decreased probability of being alive at 5 years included ECOG PS≥2 (OR 0.39; 95% CI: 0.22 to 0.65), increasing age (OR 0.97 per year; 95% CI: 0.96 to 0.99), bone (OR 0.67, 95% CI: 0.46 to 0.95) and pleural metastases (OR 0.62, 95% CI: 0.42 to 0.91). In addition, missing information on the smoking status was associated with a reduced probability of 5-year survival (OR 0.09, 95% CI: 0.01 to 0.60). Conversely, missing information on other comorbidities was associated with an increased probability of being alive at 5 years (OR 2.63, 95% CI: 1.25 to 5.53) (table 2). Ridge regression coefficients are reported as online supplemental figure 2; missing information on the smoking status was associated with the lowest coefficient (−0.67), followed by ECOG PS≥2 (−0.39) while Hispanic ethnicity (0.73) and TMB-high (0.51) were associated with the highest coefficients.

NAIM analysis

The NAIM model’s performance for predicting the risk of death was evaluated across four distinct time points (6, 12, 24, and 60 months) and through cumulative feature importance analysis. The NAIM model for risk of death, using all features, demonstrated a c-index of 62.98±2.11 on the training set and 61.24±2.15 on the all-feature evaluation set, indicating moderate predictive performance. While the training c-index suggests some degree of overfitting, the consistency between training and evaluation

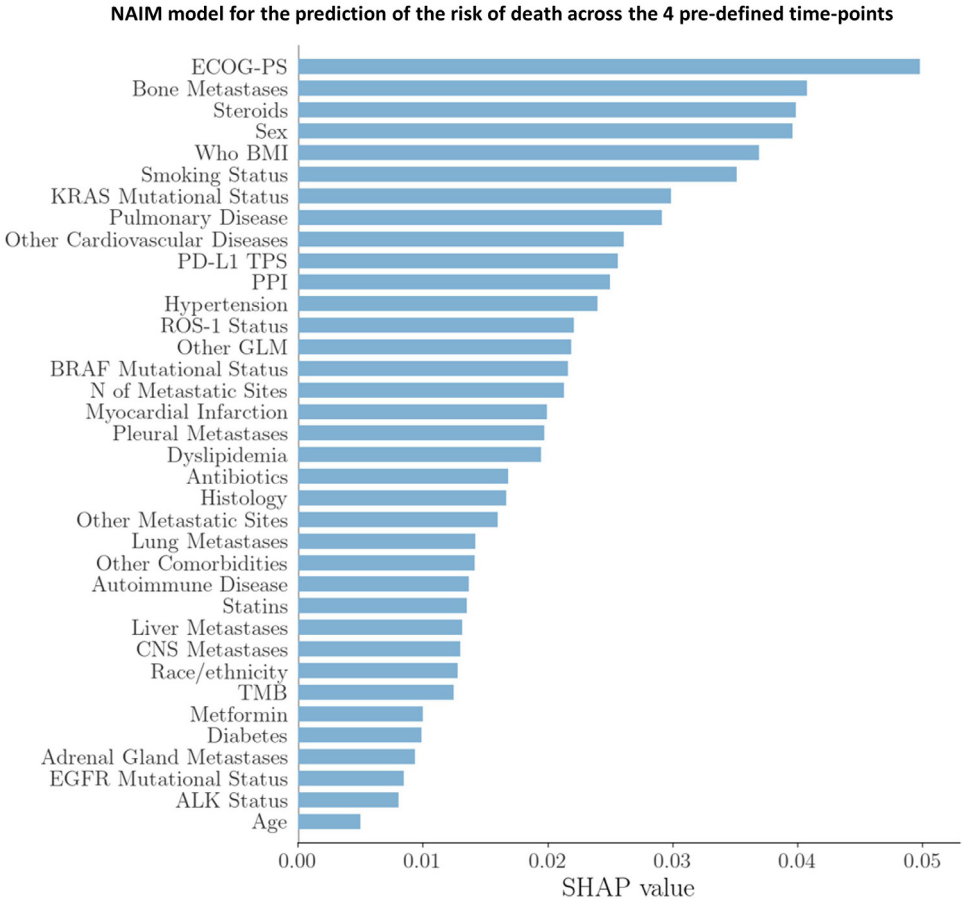

Figure 2 Histogram plot summarizing the cumulative SHAP values from the NAIM analysis for the risk of death. The length of each bar represents the SHAP value, indicating the relative importance of each variable within the model. Features were ordered by their absolute contribution. The c-index (% ±SD) was 79.76±2.44 for the training set and 62.98±2.11 for the overall model. Variable's definition and categorization details are reported in online supplemental methods. ALK, anaplastic lymphoma kinase; BMI, body mass index; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; GLM, glucose- lowering medications; NAIM, Not Another Imputation Method; NOS, not otherwise specified; PPI, proton pump inhibitors; pred, Prednisone; SHAP, SHapley Additive exPlanations; TMB, tumor mutational burden; TPS, Tumor Proportion Score.

results reinforces the robustness of the model's performance for this task.

For the cumulative importance (figure 2), the variables with the highest impact across all time points were ECOG-PS, steroid use, and the presence of bone metastases. These variables were consistently the strongest predictors of mortality, reflecting their clinical relevance in determining short-term and long-term risk. Further analysis of time-specific SHAP values (online supplemental figures 3–6) revealed notable temporal variations in the importance and directionality of individual variables. It must be noted that the decreasing magnitude of SHAP values over time may indicate reduced model confidence or predictive ability at intermediate time points (12 and 24 months). At 6 months, ECOG-PS ≥2 emerged as the strongest predictor of mortality, with high SHAP values underscoring its acute prognostic significance. Steroid use and bone metastases followed as key contributors, reflecting their impact on short-term outcomes. However, as time progressed to 12 and 24 months, the magnitude of SHAP values for these predictors decreased markedly, highlighting a diminishing influence on mortality risk over time. This decline suggests that short-term prognostic factors, such as ECOG-PS and steroids, lose relevance as other host-related or systemic variables gain prominence. Notably, variables such as PPI use and smoking status/pulmonary disease displayed dynamic trends over time. At 6 months, these factors had a more pronounced influence on mortality risk but showed variable contributions at later time points, reflecting evolving patterns of disease progression and competing risks. Meanwhile, BMI demonstrated increasing importance over time, transitioning from a marginal role at earlier time points to becoming a significant protective factor by 60 months.

The 5-year survival state analysis (figure 3) provided insights into predictors of long-term survival. The NAIM model for predicting the 5-year survival state, using all features, demonstrated an AUC of 60.52±3.71 on the evaluation set and 78.53±3.25 on the training set, indicating a notable degree of overfitting. Additional metrics for the evaluation set included an accuracy of 53.65±2.97, an F1-score of 45.43±23.10, an MCC of 10.72±8.35, and

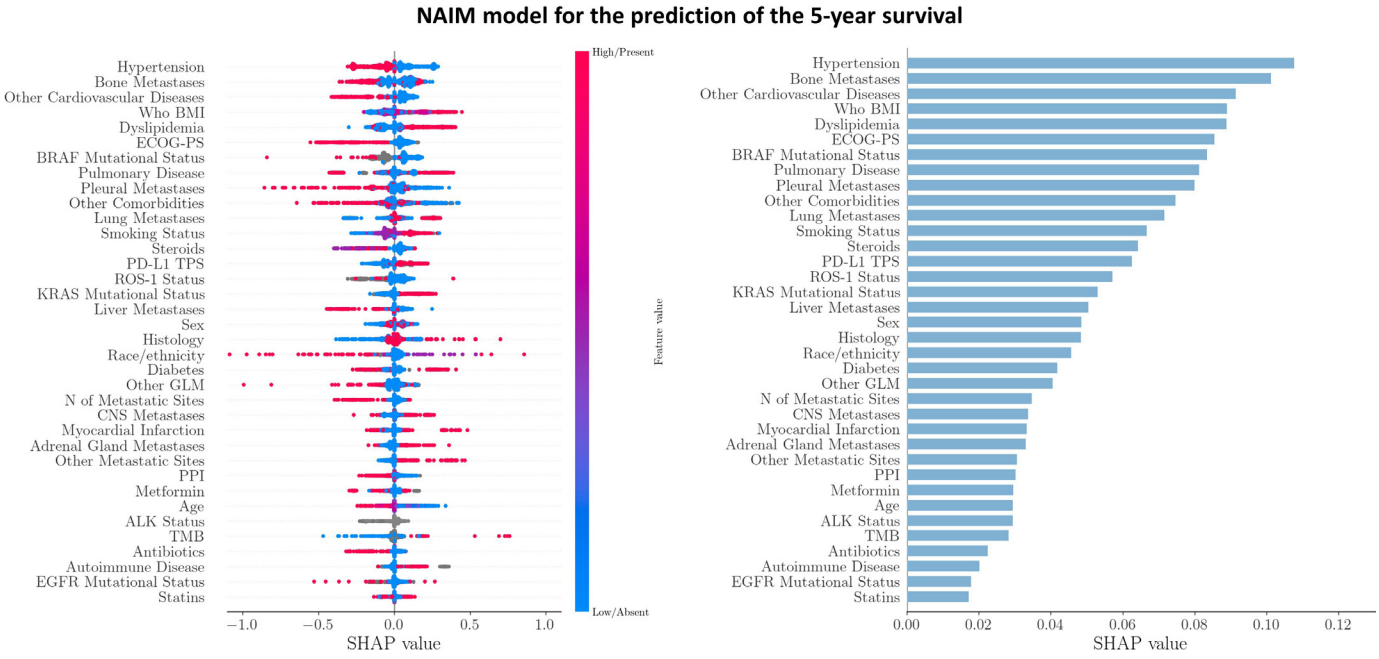

Figure 3 Paired dot plot and histogram and plot summarizing the SHAP values from the NAIM analysis for the 5-year survival. Features were ordered by their absolute contribution, with high values (red) and low values (blue) positioned to indicate their influence on outcomes. For instance, red dots on the right side of the plot imply a positive association with the probability of being alive at 5 years, while blue dots on the right side imply a negative association. Missing values were represented as gray dots. The length of each bar represents the SHAP value, indicating the relative importance of each variable within the model. The metrics for the model (% ±SD) were as follows: the training set achieved an AUC of 78.53±3.25, an accuracy of 74.41±2.56, an F1-score of 71.38±2.82, an MCC of 47.34±3.41, and a G-Mean of 64.89±3.17. In the evaluation set, the model demonstrated an AUC of 60.52±3.71, an accuracy of 53.65±2.97, an F1-score of 45.43±23.10, an MCC of 10.72±8.35, and a G-Mean of 36.71±7.61. Variables definition and categorization details are reported in online supplemental methods. ALK, anaplastic lymphoma kinase; AUC, area under the curve; BMI, body mass index; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; GLM, glucose-lowering medications; NAIM, not another imputation method; NOS, not otherwise specified; PPI, proton pump inhibitors; pred, Prednisone; Matthews correlation coefficient: MCC; SHAP, SHapley Additive exPlanations; TMB, tumor mutational burden; TPS, Tumor Proportion Score.

a G-mean of 36.71±7.61. The SHAP analysis identified several key predictors of 5-year survival. The absence of hypertension emerged as the most impactful variable, demonstrating a strong positive association with long-term survival. Similarly, the absence of other cardiovascular diseases and the presence of dyslipidemia were also strongly associated with an increased likelihood of being alive at 5 years. The absence of bone metastases further emerged as a significant predictor of long-term survival. In contrast, variables such as ECOG-PS≥2 and steroid use were negatively associated with 5-year survival but were not prioritized among the most influential variables. Interestingly, BMI displayed a strong association with 5-year survival, with increasing BMI being linked to a higher likelihood of long-term survival, despite its mixed distribution in the SHAP plots.

DISCUSSION

Our study is unique in its application of both conventional and advanced AI-based methodologies to a large, granular dataset with long-term follow-up, capable of capturing and describing unconventional and non-proportional baseline variable impacts over time. With one in three patients surviving beyond 5 years in the setting of NSCLC with PD-L1 TPS ≥50%,[5 7] a comprehensive approach to care becomes essential, underscoring the growing importance of systemic health in the survivorship phase.

Previous studies leveraging AI and machine learning in advanced NSCLC have predominantly focused on static baseline factors and short-term outcomes.[25 26] In contrast, our approach stands out by being the first to examine long-term outcomes and their temporal evolution in patients treated with ICIs.

The AI-based NAIM model and ridge regression provide complementary approaches for analyzing clinical outcome; each method offers unique strengths and limitations, reflecting their distinct capabilities to address the complexity of real-world data: long-term follow-up, extensive baseline granularity, significant missing data, and variable collinearity.

While ridge regression provides a static, interpretable estimate of the relative prognostic weight of each variable, the NAIM model allows for a dynamic view of how the relevance of individual features evolves over time.

By combining these methods, we aimed to gain deeper insights into both static and dynamic predictors of patient outcomes, uncovering temporal trends and unexpected patterns that inform personalized management in the evolving oncology landscape. For instance, the prognostic relevance of ECOG-PS and corticosteroid use is well-established in the immunotherapy setting, the emergence of dyslipidemia and the absence of cardiovascular disease as features associated with long-term benefit is a novel observation. These findings may reflect underlying systemic resilience and deserve further validation across diverse therapeutic contexts.

Ridge regression provides interpretable metrics essential for clinical translation. ECOG-PS≥2, increasing age, metastatic burden, exposure to steroids, and PPI were associated with the risk of death and inversely associated with the 5-year survival state. These findings align with the known impact of PS, age, and metastatic sites on prognosis.[9] However, the wide CIs of some variables reflect statistical instability due to low event rates or multicollinearity, undermining the robustness of these estimates. In addition, the observation that missing variables (other comorbidities "unknown" and smoking status "unknown") and under-represented subgroups, such as Hispanic ethnicity, have a statistically significant impact on outcomes warrants careful interpretation as these estimates may reflect pre-existing correlations rather than true causal effects. Although prior studies have suggested potential biological or socioeconomic factors contributing to improved outcomes in Hispanic populations,[27 28] these findings require further investigation. Moreover, while the ridge regression coefficients allow for ranking variables by magnitude, it is critical to note that variables with large coefficients but no significant impact may lead to misinterpretations of their true value, as their statistical insignificance could result from factors such as multicollinearity, limited event rates, or noise in the dataset rather than a genuine prognostic association.

The NAIM model provides insights into how prognostic factors influence outcomes not just at baseline, but at different time points during follow-up. This ability to capture temporal dynamics helps identify variables whose importance may increase, decrease, or shift over time, offering a more flexible and realistic understanding of patient trajectories under immunotherapy. The use of SHAP values offers a broader perspective by capturing the relative importance and directionality of variables across multiple predictions, unveiling non-proportional effects. However, the decreasing magnitude of SHAP values over time may indicate reduced model confidence or predictive ability at intermediate time points (12 and 24 months). This trend suggests that while the model effectively captures early predictors of mortality, its ability to sustain strong predictive insights diminishes as the follow-up period extends.

NAIM confirmed several classical prognostic variables while revealing their time-dependent trends, such as ECOG-PS and steroid exposure. ECOG-PS≥2 emerged as the strongest determinant of mortality risk within the first 6 months but diminished over time. By contrast, patients with ECOG-PS 0–1 exhibited increased mortality at 12, 24, and 60 months, reflecting the early dominance of poor PS in acute settings. A similar trend was observed for steroids, strongly associated with early mortality but reversing direction over time. By 5 years, non-steroid exposure was associated with survival, suggesting a diminishing prognostic role as disease trajectories stabilize. Similarly, the presence of bone metastases was confirmed as one of the strongest determinants, following a time-dependent pattern as well. Initially strongly associated with early mortality, its relevance diminished over time, while the absence of bone metastases remained a significant determinant of the 5-year survival state. Interestingly, NAIM revealed that bone metastases were the most significant metastatic site influencing outcomes, while other sites such as liver or CNS metastases, or the overall burden of disease, played a less prominent role.

NAIM also revealed unexpected patterns that differed from conventional expectations and underscored the unique capacity of the model to detect complex relationships. Before delving into technical details, it is worth noting that NAIM identified predictors whose prognostic importance evolved over time or emerged unexpectedly, such as cardiovascular health, metabolic factors, and smoking history. These findings suggest that some features gain relevance only at later stages of survivorship or through interactions not captured in traditional modeling frameworks. Unlike ridge regression, which retains increasing age as a significant prognostic factor, the NAIM analysis does not identify it as a relevant predictor over time. This discrepancy may stem from NAIM's ability to account for collinearity, possibly allowing comorbidities to emerge as stronger determinants of long-term outcomes. Hypertension and the absence of other cardiovascular diseases gained disproportionate importance at 60 months, reflecting the cumulative impact of cardiovascular health on survivorship. Never-smokers and those without pulmonary disease were associated with increased mortality risk at 6 months, a finding linked to the historical association of smoking with good outcomes in immunotherapy due to inflammatory tumor microenvironments and higher TMB levels.[29 30] By 12 and 24 months, these risks reversed, likely reflecting competing risks and evolving dynamics. BMI and dyslipidemia transitioned from marginal roles to significant factors over time, partially aligning with the "obesity paradox" in immune-oncology but suggesting a credible impact in the long term.[12–15 31 32]

Taken together, this integrative modeling approach enhances clinical interpretability by combining the transparency of traditional regression with the flexibility of deep learning, allowing for a more nuanced understanding of patient trajectories under immunotherapy. Concordant predictors across both models (eg, ECOG-PS, corticosteroid use, and tumor burden) can guide baseline risk stratification and treatment discussions, offering clinicians interpretable, stable

markers for early decision-making. In parallel, time-varying signals captured only by NAIM (eg, BMI, dyslipidemia, or cardiovascular comorbidities) may inform longitudinal patient monitoring, survivorship planning, or tailored follow-up strategies as prognostic relevance shifts over time. Together, these complementary insights foster a layered interpretation of risk, supporting both immediate clinical action and long-term care strategies in a real-world setting.

This study has several limitations. First, it is based on a retrospective, observational dataset, which may carry inherent confounding and selection biases. However, this design reflects the real-world clinical setting in which pembrolizumab is routinely administered to patients with advanced NSCLC and allowed the inclusion of a large, multinational population across 61 centers. To mitigate these biases, we employed rigorous statistical methods, including penalized regression, multivariable adjustment, and an AI-based framework designed to handle incomplete and non-linear data structures. Second, this study did not include a comparator arm treated with chemotherapy or targeted agents. This choice was deliberate: our aim was not to assess the relative efficacy of pembrolizumab but to characterize the time-varying impact of baseline clinical features within a homogeneous, real-world immunotherapy cohort. Including patients treated with alternative therapies would have introduced substantial clinical and molecular heterogeneity (eg, PD-L1-negative tumors, oncogene-addicted subtypes), thus reducing the internal validity of the predictive models. This rationale guided our cohort definition and is a key aspect of our study design.

Missing data remain a pervasive challenge in real-world datasets, arising from various causes such as human error, non-response, or systematic loss. The NAIM model showed moderate predictive performance, with metrics such as c-index of 61.2, an AUC of 60.5–78.5 and low F1-score and MCC values, reflecting a degree of overfitting and limited generalizability. These findings underscore the need for further validation and potential refinement before clinical application. Future studies should validate these findings in external datasets with more complete and diverse representation.

Despite the mentioned limitations, the nuanced, time-dependent insights revealed by the AI-based NAIM model complement the static interpretability of ridge regression, together providing a robust framework for understanding the interplay of oncologic, systemic, and temporal factors. Over the course of a 5-year follow-up, the risk of death in patients with NSCLC treated with immunotherapy evolves to increasingly include non-cancer-related factors. This shift underscores the growing importance of systemic health and holistic care in the survivorship phase. With nearly one-third of patients surviving beyond 5 years in this setting, modern oncology must adopt comprehensive management strategies that address comorbidities, support metabolic and nutritional health, and incorporate time-sensitive interventions.

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