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Research Paper

Long-term outcomes from pembrolizumab monotherapy in patients with advanced NSCLC, PD-L1 expression ≥ 50 %, and poor performance status: Transformer-based AI to characterize prognostic complexity

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ABSTRACT

Background: The use of first-line single agent immunotherapy in patients with advanced NSCLC and ECOG PS $\geq$ 2 remains controversial, as this frail population has been largely excluded from pivotal clinical trials. Real-world evidence suggests that although median survival is poor, a subset of these patients may achieve long-term benefit.

Methods: We analyzed data from the Pembro-Real 5Y registry, a global real-world dataset with > 5 years follow-up. The cohort included patients with advanced NSCLC, PD-L1 TPS $\geq$ 50 %, treated with first line pembrolizumab outside of clinical trials. Univariable analyses were conducted to identify descriptive characteristics associated with survival. To address the complexity of long-term outcome prediction, we integrated Elastic Net regression and a transformer-based AI model (NAIM). The Elastic Net model was employed to mitigate collinearity and select relevant prognostic factors, while NAIM was used to explore non-linear, time-dependent interactions between variables. Endpoints included overall survival (OS) and 5-year survival rates.

Results: Out of 1050 patients, 161 patients with ECOG PS $\geq$ 2 were included, showing a median OS of 5.4 months (95 % CI: 3.8–7.8), and a 5-year survival rate of 13.0 % (95 % CI: 8.1–19.9). Univariable analysis indicated that no single baseline variable was strongly predictive of 5-year survival, except for TMB, KRAS, and BRAF status, which were significantly limited by missingness. Elastic Net identified only two significant predictors of 5-year survival: high TMB (with unstable confidence intervals) and KRAS mutation. NAIM provided a dynamic perspective, confirming that bone metastases and baseline corticosteroid use were strong predictors of early mortality, whereas BMI increase and systemic health markers/host factors (e.g., hypertension and dyslipidemia) gained importance in long-term survivors. However, NAIM exhibited a notable performance drop from training to validation suggesting overfitting and the challenge of modeling long-term outcomes using baseline static variables.

Conclusions: Despite the overall poor prognosis, a subset of patients with ECOG PS $\geq$ 2 achieves long-term survival with pembrolizumab monotherapy, indicating that performance status alone should not preclude treatment in all cases. Our analysis highlights the limitations of traditional statistical approaches and AI-driven models in predicting long-term benefit in this heterogeneous population. Future efforts should focus on refining hybrid modeling strategies and incorporating prospective validation to better identify those who may benefit from immunotherapy beyond short-term expectations.

1. Introduction

Non-small cell lung cancer (NSCLC) treatment has been revolutionized by immune checkpoint inhibitors (ICIs), particularly in patients with high PD-L1 expression [1–5], for whom single-agent

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immunotherapy has become a standard first-line option. However, clinical trials leading to regulatory approval of ICIs largely enrolled patients with good performance status (Eastern Cooperative Oncology Group – Performance Status – ECOG PS 0–1), excluding those with ECOG PS $\geq$ 2. This exclusion created a significant knowledge gap, as a substantial proportion of patients with advanced NSCLC encountered in routine clinical practice present with an ECOG PS $\geq$ 2, often due to disease burden, comorbidities, or both [6].

The feasibility and efficacy of single-agent immunotherapy in this frail patient population remain a subject of debate. Real-world evidence and retrospective analyses have provided conflicting insights, with some studies reporting poor outcomes in patients with ECOG PS $\geq$ 2, while others have demonstrated survival benefits, particularly in select subgroups [7,8]. Meta-analyses have confirmed that ECOG PS $\geq$ 2 is an independent negative prognostic factor for overall survival (OS) and progression-free survival (PFS) in patients treated with ICIs [6].

A major challenge in assessing immunotherapy efficacy in patients with poor PS is the interplay between treatment response, patient frailty, and long-term outcomes. In a previous analysis of a large real-world (RW) repository with long term follow-up, we observed that there is a subset of patients with ECOG PS $\geq$ 2 who achieved remarkable long-term survival, remaining alive beyond five years [9]. These findings challenge the assumption that poor PS universally predicts worse outcomes and suggest that an integrated analytical approach is needed to identify those who derive durable benefit from immunotherapy.

Furthermore, in a prior analysis of the same dataset, we employed an Artificial Intelligence (AI)-based technique to capture the complex interplay between prognostic variables over time, focusing on their dynamic evolution [10]. Building on this foundation, the present study aims to specifically characterize the ECOG PS $\geq$ 2 population achieving long term survival from single agent pembrolizumab, dissecting the determinants of long-term survival and exploring how clinical and biological variables evolve over time in this challenging subgroup.

2. Methods

2.1. Study design

The objective of this study is to assess the long-term outcomes of patients with advanced-stage NSCLC, PD-L1 TPS $\geq$ 50 %, and ECOG-PS $\geq$ 2, treated with first-line pembrolizumab, leveraging on both conventional and AI-driven methodologies. Since the use of single-agent PD-L1 inhibition in this specific population has been widely debated, our approach aims to identify the determinants of long-term benefit in these frail patients and to delineate both expected and unexpected prognostic factors, providing a comprehensive understanding of patient trajectories.

The Pembro-real 5Y is a large real-world global dataset that includes 1,050 patients with stage IV NSCLC and PD-L1 TPS $\geq$ 50 %, treated with first-line pembrolizumab at 61 institutions across 14 countries, and has already been reported in detail [9,11]. The primary eligibility criteria included receiving first-line pembrolizumab monotherapy outside of clinical trials, having a PD-L1 TPS of $\geq$ 50 %, and starting treatment by May 31, 2018. To ensure at least five years of follow-up for long-term responders, the minimum data cut-off for patients still alive was set at May 1, 2023.

The endpoints of interest were the 5-year survival rate (proportion of patients alive five years post-treatment) and overall survival (OS), defined as time from treatment initiation to death or loss to follow-up, with survivors beyond five years censored at their last clinical follow-up. Additionally, we explored the cumulative incidence of "real-world" immune-related adverse events (rw-irAEs), classified per CTCAE v5.0.

We first described the distribution of a comprehensive set of baseline variables (detailed in the **supplementary methods**), including clinicopathologic characteristics, demographics, concomitant medications, and comorbidities, across the study population and stratified by 5-year survival status. Next, we evaluated clinical outcomes in the overall ECOG-PS $\geq$ 2 population using univariable analysis. We also categorized reasons for treatment interruption as progressive disease, toxicity-related discontinuation, treatment completion (defined as 2 years of therapy), other reasons (e.g., patient preference, clinical decision, or post-2-year interruption), and unknown/not reported. Additionally, we performed an exploratory analysis among patients who received treatment for at least 24 months.

To further leverage on the extended follow-up, we analyzed the safety profile of pembrolizumab monotherapy in this frail population. Specifically, we reported the cumulative incidence of real-world immune-related adverse events (rw-irAEs) in the entire cohort and those occurring beyond the first 2 years of treatment in patients with a minimum treatment duration of 24 months (detailed safety assessments are available in the **supplementary methods**).

For subgroup analyses and the exploration of long-term benefit determinants, we implemented a dual analytical strategy to address the dataset's complexity, characterized by long-term follow-up, extensive baseline data with inherent collinearity, and high proportion of missing values. We employed both conventional statistical modeling, using an Elastic Net regression framework, and a transformer-based AI model to evaluate OS and 5-year survival. **Supplementary** figure 1 reports the analytical framework.

Given the high dimensionality of the dataset and multicollinearity among predictors, we applied a regularized regression approach to identify prognostic variables while mitigating overfitting. Moreover, the limited number of events and the overall sample size posed challenges for traditional regression models, making variable selection a critical step in enhancing model interpretability.

To complement conventional analysis, we employed NAIM (Not Another Imputation Method), a transformer-based AI model designed for robustness against missing data, previously validated for outcome prediction in patients with NSCLC [12–14] and already applied to the entire Pembro-Real 5Y study population [10]. To enhance interpretability, we applied explainable AI (XAI) techniques, specifically the SHAP (SHapley Additive exPlanations) method, to quantify the contribution of each feature to model predictions [15]. To further explore how individual features influence the risk of death over time, we visualized the cumulative sum of absolute SHAP values across four predefined time points (6, 12, 24, and 60 months) as previously done.

Statistical analysis details are reported as **supplementary methods**.

3. Results

3.1. Cohort characteristics

The Pembro-Real 5Y cohort has been thoroughly characterized in previous reports [9]. A total of 1,063 consecutive patients were initially enrolled in the registry (**Supplementary Table S1** details patient enrollment by each participating institution). After excluding 13 patients lost to follow-up, the final eligible population comprised 1,050 patients.

After the exclusion of 859 (81.8 %) patients with ECOG-PS 0–1 and 30 (2.9 %) with ECOG-PS unknown, 161 (15.3 %) patients with ECOG-PS $\geq$ 2 were included in the present analysis. Among the 161 patients with ECOG PS $\geq$ 2, the large majority had ECOG PS 2 at treatment initiation, while higher ECOG PS categories ($\geq$3) were not consistently reported across centers and therefore could not be reliably stratified.

Table 1 provides a comprehensive breakdown of the clinicopathologic characteristics of the study population, both overall and stratified by 5-year survival status. The median age was 70 years (range: 39–90), with a predominance of male (53.4 %) and white (78.9 %) patients. Most individuals had adenocarcinoma histology (73.3 %) and were either former (73.3 %) or current (18.6 %) smokers. With respect to body composition, 9.9 % of patients were underweight (BMI $<$ 18.5 kg/m^2),

Table 1
Patients' characteristics of the overall cohort and according to the 5 year survival. P-values were computed using chi-square and Fisher's exact test as appropriate. WHO: world health organizations; BMI: body mass index; NOS: not otherwise specified; PD-L1: programmed death-ligand 1; TPS: tumor proportion score; CNS: central nervous system; pred: prednisone; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ROS-1: proto-oncogene tyrosine-protein kinase ROS; KRAS: Kirsten rat sarcoma virus; Pred: prednisolone/prednisone; eq: equivalent. *p-value computed after the exclusion of missing data from the denominator. #Kurkas-Wallis was used test.

	Overall Study Population N° 161 (%)	Not alive at 5 years N° 140 (%)	Alive at 5 years N° 21 (%)	p-value
Age (years)				
Median (range)	70 (39–90)	71 (39–90)	67 (48–87)	0.211#
Sex				0.420
Female	75 (46.6)	63 (45.0)	12 (57.1)	
Male	86 (53.4)	77 (55.0)	9 (42.9)	
Ethnicity				0.204
White	127 (78.9)	113 (80.7)	14 (66.7)	
Black/African-American	5 (3.1)	4 (2.9)	1 (4.8)	
Asian	6 (3.7)	6 (4.3)	0 (0.0)	
Hispanic	2 (1.2)	1 (0.7)	1 (4.8)	
Others	2 (1.2)	2 (1.4)	0 (0.0)	
Unknow	19 (11.8)	14 (10.0)	5 (23.8)	
Smoking Status				0.384
Current smokers	30 (18.6)	28 (20.0)	2 (9.5)	
Former smokers	118 (73.3)	100 (71.4)	18 (85.7)	
Never smokers	13 (8.1)	12 (8.6)	1 (4.8)	
Who BMI category				0.066
Underweight	16 (9.9)	13 (9.3)	3 (14.3)	
Normal weight	76 (47.2)	71 (50.7)	5 (23.8)	
Overweight	35 (21.7)	31 (22.1)	4 (19.0)	
Obese	18 (11.2)	13 (9.3)	5 (23.8)	
Unknown	16 (9.9)	12 (8.6)	4 (19.0)	
Histology				0.478
Squamous	36 (22.4)	30 (21.4)	6 (28.6)	
Adenocarcinoma	118 (73.3)	103 (73.6)	15 (71.4)	
Others/NOS	7 (4.3)	7 (5.0)	0 (0.0)	
PD-L1 TPS				0.904
≥90 %	90 (55.9)	79 (56.4)	11 (52.4)	
50–89 %	47 (29.2)	40 (28.6)	7 (33.3)	
Not specified	24 (14.9)	21 (15.0)	3 (14.3)	
EGFR mutational status				0.565*
Wild type	140 (87.0)	120 (85.7)	20 (95.2)	
Mutant	2 (1.2)	2 (1.4)	0 (0.0)	
Not reported/not tested	19 (11.8)	18 (12.9)	1 (4.8)	
ALK translocation status				0.684*
Wild type	140 (87.0)	120 (85.7)	20 (95.2)	
Positive	1 (0.6)	1 (0.7)	0 (0.0)	
Not reported/not tested	20 (12.4)	19 (13.6)	1 (4.8)	
ROS-1 translocation status				–
Wild type	114 (70.8)	98 (70.0)	16 (76.2)	
Positive	–	–	–	
Not reported/not tested	47 (29.2)	42 (30.0)	5 (23.8)	
Tumor mutational burden				0.022*
Non-high	19 (11.8)	15 (10.7)	4 (19.0)	
High	2 (1.2)	0 (0.0)	2 (9.5)	
Not-tested	140 (87.0)	125 (89.3)	15 (71.4)	
KRAS mutational status				0.046*
Wild type	55 (34.2)	49 (35.0)	6 (28.6)	
Mutant	37 (23.0)	27 (19.3)	10 (47.6)	
Not reported/not tested	69 (42.9)	64 (45.7)	5 (23.8)	
BRAF mutational status				0.319*
Wild type	79 (49.1)	63 (45.0)	16 (76.2)	
Mutant	4 (2.5)	4 (2.9)	0 (0.0)	
Not reported/not tested	78 (48.4)	73 (52.1)	5 (23.8)	
Liver metastases				0.502
No	125 (77.6)	107 (76.4)	18 (85.7)	
Yes	36 (22.4)	33 (23.6)	3 (14.3)	
Bone metastases				0.260
No	101 (62.7)	85 (60.7)	16 (76.2)	
Yes	60 (37.3)	55 (39.3)	5 (23.8)	
Cns metastases				0.970
No	127 (78.9)	111 (79.3)	16 (76.2)	
Yes	34 (21.1)	29 (20.7)	5 (23.8)	
Pleural metastases				0.240
No	117 (72.7)	99 (70.7)	18 (85.7)	
Yes	44 (27.3)	41 (29.3)	3 (14.3)	
Adrenal metastases				1.000
No	124 (77.0)	108 (77.1)	16 (76.2)	
Yes	37 (23.0)	32 (22.9)	5 (23.8)	
Lung metastases				0.975
No	58 (36.0)	51 (36.4)	7 (33.3)	
Yes	103 (64.0)	89 (63.6)	14 (66.7)	
Other metastatic sites				0.925
No	133 (82.6)	115 (82.1)	18 (85.7)	
Yes	28 (17.4)	25 (17.9)	3 (14.3)	
Number of metastatic sites				0.389
≤ 3	140 (87.0)	120 (85.7)	20 (95.2)	
> 3	21 (13.0)	20 (14.3)	1 (4.8)	
Hypertension				0.793
No	73 (45.3)	64 (45.7)	9 (42.9)	
Yes	78 (48.4)	68 (48.6)	10 (47.6)	
Not reported	10 (6.2)	8 (5.7)	2 (9.5)	
Myocardial infraction				0.166
No	131 (81.4)	117 (83.6)	14 (66.7)	
Yes	20 (12.4)	15 (10.7)	5 (23.8)	
Not reported	10 (6.2)	8 (5.7)	2 (9.5)	
Other cardio-vascular conditions				0.349
No	100 (62.1)	88 (62.9)	12 (57.1)	
Yes	50 (31.1)	44 (31.4)	6 (28.6)	
Not reported	11 (6.8)	8 (5.7)	3 (14.3)	
Diabetes				0.789
No	121 (75.2)	106 (75.7)	15 (71.4)	
Yes	30 (18.6)	26 (18.6)	4 (19.0)	
Not reported	10 (6.2)	8 (5.7)	2 (9.5)	
Autoimmune diseases				0.797
No	143 (88.8)	125 (89.3)	18 (85.7)	
Yes	8 (5.0)	7 (5.0)	1 (4.8)	
Not reported	10 (6.2)	8 (5.7)	2 (9.5)	
Pulmonary disease				0.051
No	100 (62.1)	92 (65.7)	8 (38.1)	
Yes	51 (31.7)	40 (28.6)	11 (52.4)	
Not reported	10 (6.2)	8 (5.7)	2 (9.5)	
Dyslipidemia				0.170
No	99 (61.5)	90 (64.3)	9 (42.9)	
Yes	52 (32.3)	42 (30.0)	10 (47.6)	
Not reported	10 (6.2)	8 (5.7)	2 (9.5)	
Other comorbidities				0.337
No	87 (54.0)	75 (53.6)	12 (57.1)	
Yes	62 (38.5)	56 (40.0)	6 (28.6)	
Not reported	12 (7.5)	9 (6.4)	3 (14.3)	
Baseline proton pump inhibitors				0.680
No	81 (50.3)	71 (50.7)	10 (47.6)	
Yes	76 (47.2)	65 (46.4)	11 (52.4)	
Not reported	4 (2.5)	4 (2.9)	0 (0.0)	
Baseline statins				0.130
No	101 (62.7)	92 (65.7)	9 (42.9)	

(*continued on next page*)

Table 1 (*continued*)

	Overall Study Population N° 161 (%)	Not alive at 5 years N° 140 (%)	Alive at 5 years N° 21 (%)	p-value
Yes	55 (34.2)	44 (31.4)	11 (52.4)	
Not reported	5 (3.1)	4 (2.9)	1 (4.8)	
Baseline metformin				0.512
No	136 (84.5)	120 (85.7)	16 (76.2)	
Yes	19 (11.8)	15 (10.7)	4 (19.0)	
Not reported	6 (3.7)	5 (3.6)	1 (4.8)	
Baseline corticosteroids				0.654
None	109 (67.7)	93 (66.4)	16 (76.2)	
<10 mg pred or eq	34 (21.1)	31 (22.1)	3 (14.3)	
≥10 mg pred or eq	18 (11.2)	16 (11.4)	2 (9.5)	
Baseline antibiotics				0.724
No	131 (81.4)	115 (82.1)	16 (76.2)	
Yes	30 (18.6)	25 (17.9)	5 (23.8)	
Other glucose lowering medications				0.742
No	120 (74.5)	103 (73.6)	17 (81.0)	
Yes	13 (8.1)	12 (8.6)	1 (4.8)	
Not reported	28 (17.4)	25 (17.9)	3 (14.3)	

47.2 % had normal BMI (18.5–24.9 kg/m^2), and 32.9 % were overweight or obese (BMI ≥ 25 kg/m^2). Notably, corticosteroid use at baseline was recorded in 21.1 % of patients at doses < 10 mg and in 11.2 % at doses ≥ 10 mg of prednisolone or equivalent. Regarding molecular profiling, *EGFR* (Epidermal Growth Factor Receptor) mutation and *ALK* (Acute Leukemia Kinase) translocation statuses were not assessed in 11.8 % and 12.4 % of patients, respectively, while 1.2 % and 0.6 % were found to be EGFR- or ALK-positive. Data on *KRAS* (Kirsten Rat Sarcoma Virus) mutational status and tumor mutational burden (TMB) were missing for 42.9 % and 87.0 % of patients, respectively.

Comorbidities were frequently reported, with hypertension present in 48.4 % of patients, myocardial infarction in 12.4 %, and other cardiovascular conditions in 31.1 %. Additionally, type 2 diabetes (18.6 %), pulmonary disease (31.7 %), dyslipidemia (32.3 %), and pre-existing autoimmune disorders (5.0 %) were documented, while 38.5 % of patients had other comorbid conditions. None of the baseline variables were significantly associated with the 5-year survival at the univariable analysis, with the exception of TMB (non-high 10.7 % vs 19.%, high 0 % vs 9.5 %, not-tested 89.3 % vs 71.4 %), *KRAS* mutational status (wild type 35.0 % vs 28.6 %, mutant 19.3 % vs 47.6 %, not reported 45.7 % vs 23.8 %) and *BRAF* (B-raf) mutational status (wild type 45.0 % vs 76.2 %, mutant 2.9 % vs 0 %, not reported 52.1 % vs 23.8 %) (Table 1).

3.2. Clinical outcomes and safety

After a median follow-up of 72.5 months (95 % CI: 66.1–75.8) with 142 death events, the median OS for the study population was 5.4 months (95 % CI: 3.8–7.8). At the 5-year landmark, 21 patients remained alive, corresponding to a 5-year survival rate of 13.0 % (95 % CI: 8.1–19.9, Fig. 1A).

The median treatment duration was 2.1 months (95 % CI: 1.4–3.5). By the data cut-off, 160 patients had permanently discontinued treatment: 124 (77.5 %) due to disease progression, 19 (11.9 %) due to toxicity, 7 (4.4 %) following treatment completion, and 7 (4.4 %) for other reasons.

A total of 11 patients (6.8 %) received treatment for at least 24 months, 8 of whom were alive at the 5-year mark, resulting in a 5-year survival rate of 81.8 % (95 % CI: 39.0–93.9). Among these long-term responders, 3 (27.3 %) later discontinued treatment due to disease progression, 1 (9.1 %) due to toxicity, 5 (45.4 %) following treatment completion, and 1 (9.1 %) for other reasons. At the data cut-off, treatment was still ongoing in 1 patient (9.1 %) beyond the 2 years mark.

A total of 161 patients were included in the safety population, with rw-irAEs of any grade occurring in 28.6 % of cases and G3/4 rw-irAEs in 7.5 % within the first two years of treatment. Among the 11 patients who

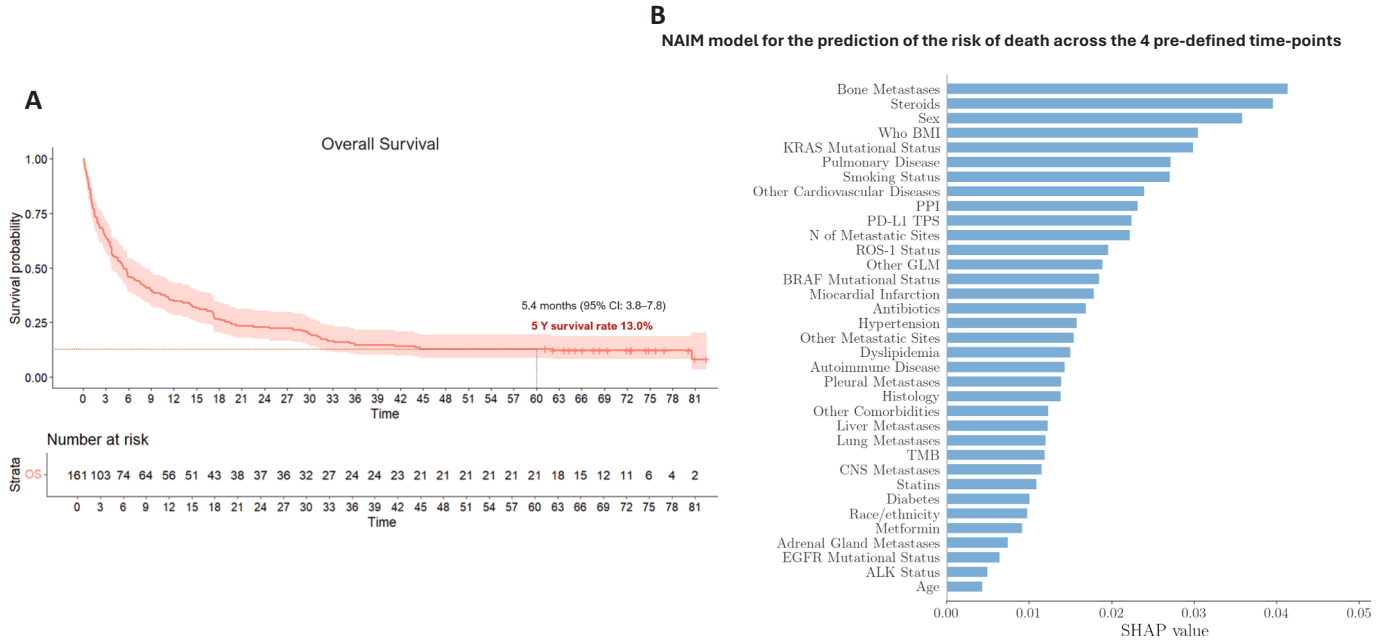

Fig. 1. A) Kaplan-Meier survival estimates for overall survival and 5-year survival rate. **B)** Histogram plot summarizing the cumulative SHAP values from the NAIM analysis for the risk of death across four predefined time points: 6 months, 12 months, 24 months, and 60 months. The length of each bar represents the SHAP value, indicating the relative importance of each variable within the model. Features were ordered by their absolute contribution. The c-index (% ± standard deviation) was 74.58 ± 9.61 on the training set and 52.39 ± 11.45 for the overall model..Variables definition and categorization details are reported in supplementary methods. Abbreviations: WHO BMI, World Health Organization Body Mass Index levels; NOS, Not Otherwise Specified; PD-L1, Programmed Death-Ligand 1; TPS, Tumor Proportion Score; CNS, Central Nervous System; pred, Prednisone; EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; KRAS, Kirsten Rat Sarcoma Virus; PPI, Proton Pump Inhibitors; GLM, Glucose Lowering Medications; TMB, Tumor Mutational Burden.

received treatment for at least 24 months and were included in the safety analysis for rw-irAEs beyond the two-year mark, the incidence was 54.5 % for rw-irAEs of any grade and 18.2 % for G3/4 rw-irAEs. A detailed breakdown of rw-irAEs by affected system/organ is provided in **Supplementary** Table S2.

3.3. Elastic net regression

The Elastic Net regression analysis for the risk of death was conducted using an optimal penalty parameter (λ) of 0.1, determined via cross-validation, prioritizing model stability and comprehensive variable selection. From the large baseline panel of variables, only a few key predictors had non-zero coefficients, as summarized in **Supplementary** Fig. 2. Among these, others/not otherwise specified (NOS) histology was the most influential variable associated with an increased risk of death (coefficient: 0.56), followed by low-dose corticosteroid use at baseline (0.51), missing *EGFR* mutational status (0.31), and high-dose corticosteroid use (0.14). Conversely, TMB-high (−1.05) and Hispanic ethnicity (−0.77) were associated with the lowest coefficients. The multivariate model, reported in Table 2, demonstrated moderate discriminatory ability with a c-statistic of 0.67 (95 % CI: 0.57–0.77). Significant predictors of increased mortality risk included increasing age (HR 1.03 per unit increase; 95 % CI: 1.01–1.04), male sex (HR 1.61; 95 % CI: 1.09–2.38), others/NOS histology (HR 2.91; 95 % CI: 1.14–7.36), low-dose corticosteroid use (HR 3.93; 95 % CI: 2.43–6.33), high-dose corticosteroid use (HR 2.16; 95 % CI: 1.19–3.92), and unknown *EGFR* mutational status (HR 2.97; 95 % CI: 1.65–5.31). Conversely, factors associated with a decreased risk of death included former smoking status (HR 0.46; 95 % CI: 0.30–0.71), hypertension (HR 0.34; 95 % CI: 0.41–0.91), prior myocardial infarction (HR 0.34; 95 % CI: 0.18–0.63), and pulmonary disease (HR 0.55; 95 % CI: 0.36–0.85).

The Elastic Net regression analysis for the 5-year survival status identified an optimal lambda of 0.089 through cross-validation, selecting only two variables with non-zero coefficients: TMB-high (coefficient: 1.44) and positive *KRAS* mutational status (coefficient: 0.13) (**Supplementary** Fig. 3). The multivariate model achieved an area under the receiver operating characteristic curve (AUC) of 0.65 (95 % CI: 0.53–0.76). *KRAS* positivity was associated with a higher probability of being alive at 5 years (OR 3.04, 95 % CI: 1.08–8.27), whereas the effect of TMB-high was uninterpretable due to the small sample size (OR 7.09 $\times 10^{-8}$, 95 % CI: 0.00–∞) (Table 2).

3.4. NAIM analysis

The performance of the NAIM model in predicting the risk of death was evaluated at four distinct time points (6, 12, 24, and 60 months). Using all available features, the model achieved a concordance index (C-index) of 74.58 ± 9.61 on the training set and 52.39 ± 11.45 on the evaluation set, indicating limited predictive performance.

In the cumulative feature importance analysis (Fig. 1B), the most influential variables across all time points were the presence of bone metastases, baseline corticosteroid exposure, sex, body mass index (BMI), pulmonary comorbidities, and smoking status. The time-specific SHAP analysis (Fig. 2A-D) revealed notable temporal variations in both the importance and directionality of individual predictors. Notably, the decreasing magnitude of SHAP values over time suggests a decline in the model's confidence or predictive strength at later time points (24 and 60 months).

At 6 months, baseline corticosteroid use and the presence of bone metastases emerged as the strongest predictors of mortality, with high SHAP values underscoring their acute prognostic significance. However, their influence diminished markedly over time, as reflected in the reduced SHAP magnitude at 24 and 60 months. A similar trend was observed for pulmonary comorbidities and smoking status, both of which were initially associated with a decreased risk of death at 6 months but progressively lost importance as predictors over time. Sex

Table 2
Elastic Net fitted multivariable analyses for the risk of death (Overall Survival – using Cox proportional hazard regression) and the 5-year survival (using logistic regression). OR: odd ratio; HR: hazard ratio; 95%CI: 95% confidence intervals; WHO: world health organizations; BMI: body mass index; NOS: not otherwise specified; PD-L1: programmed death-ligand 1; TPS: tumor proportion score; CNS: central nervous system; pred: prednisone; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; KRAS: Kirsten rat sarcoma virus; Pred: prednisolone/prednisone; eq: equivalent.

	Overall Survival (risk of death) **HR (95 %CI)**	**5 Year Survival** (probability of being alive) **OR (95 %CI)**
Age		
(continuous)	1.03 (1.01–1.04)	–
Sex		
Male vs female	1.61 (1.09–2.38)	–
Ethnicity		
White	1	–
Black/African-American	–	
Asian	–	
Hispanic	0.04 (0.01–0.37)	
Others	0.13 (0.02–0.67)	
Unknow	0.51 (0.26–0.99)	
WHO BMI		
Normal weight	1	–
Underweight	–	
Overweight	–	
Obese	–	
Unknow	1.05 (0.53–2.09)	
Histology		
Squamous	1	–
Adenocarcinoma	–	
Others/NOS	2.91 (1.14–7.36)	
Smoking status		
Current smoker	1	–
Former smoker	0.46 (0.30–0.71)	
Never smoker	–	
PD-L1 tumor proportion score		
50–89	1	–
≥ 90	–	
Not reported	1.42 (0.83–2.42)	
CNS metastases		
Yes vs No	–	–
Liver metastases		
Yes vs No	–	–
Bone metastases		
Yes vs No	1.06 (0.69–1.62)	–
Lung metastases		
Yes vs No	–	–
Pleural metastases		
Yes vs No	1.49 (0.95–2.34)	–
Adrenal glands metastases		
Yes vs No	–	–
Other metastatic sites		
Yes vs No	–	–
Number of metastatic sites		
>3 vs ≤ 3	1.75 (0.92–3.33)	–
Corticosteroids at baseline		
No	1	–
< 10 mg pred. or eq.	3.93 (2.43–6.33)	
≥ 10 mg pred. or eq.	2.16 (1.19–3.92)	
Baseline proton pump inhibitors		
No	–	–
Yes		
Unknown		
Baseline antibiotics		
Yes vs No	–	–
Baseline statins		
No	1	–
Yes	1.03 (0.65–1.63)	
Unknown	0.25 (0.08–0.78)	
Baseline metformin		
No	–	–
Yes		
Unknown		

(*continued on next page*)

Table 2 (*continued*)

	Overall Survival (risk of death) **HR (95 %CI)**	**5 Year Survival** (probability of being alive) **OR (95 %CI)**
Other glucose lowering medications		
No	1	–
Yes	–	
Unknown	1.56 (0.92–2.64)	
EGFR mutational status		
Wild type	1	–
Mutant	–	
Not tested	2.97 (1.65–5.31)	
ALK translocation status		
Wild type	–	–
Translocated		
Not tested		
ROS-1 translocation status		
Wild type	–	–
Translocated		
Not tested		
KRAS mutational status		
Wild type	1	1
Mutant	0.94 (0.57–1.53)	3.04 (1.08–8.27)
Not tested	–	–
BRAF mutational status		
Wild type	–	–
Mutant		
Not tested		
Tumor mutational burden		
Non-high	1	1
High	7.09×10^{-8} (0.00-∞)	5.282334×10^{7} (0-NA)
Not tested	–	–
Hypertension		
No	1	–
Yes	0.61 (0.41–0.91)	
Unknown	–	
Myocardial infarction		
No	1	–
Yes	0.34 (0.18–0.63)	
Unknown	–	
Other cardio-vascular conditions		
No	–	–
Yes		
Unknown		
Diabetes		
No	–	–
Yes		
Unknown		
Pulmonary disease		
No	1	–
Yes	0.55 (0.36–0.85)	
Unknown	–	
Dyslipidemia		
No	–	–
Yes		
Unknown		
Autoimmune diseases		
No	–	–
Yes		
Unknown		
Other comorbidities		
No	–	–
Yes		
Unknown		

exhibited a bimodal trend: at 6 months, female sex ranked as the 7th most important determinant, with an increased risk of death. However, at 12 and 24 months, sex became the strongest predictor, with male and female patients showing distinct risk associations. By 60 months, its importance had declined significantly, ranking as the 10th most influential factor. Notably, BMI gained importance over time, transitioning from a marginal role at earlier time points to becoming the most significant predictor at 60 months, a trend also observed for *KRAS* mutations.

The 5-year survival state analysis (Fig. 3) provided insights into predictors of long-term survival. The NAIM model for predicting 5-year survival, using all features, demonstrated an AUC of 79.63 ± 9.73 on the training set and 58.29 ± 15.62 on the evaluation set. SHAP analysis identified several key predictors of long-term survival. The absence of hypertension emerged as the most impactful variable, strongly correlating with increased 5-year survival probability. Similarly, the presence of dyslipidemia, the absence of bone metastases, and the absence of other cardiovascular diseases were associated with a greater likelihood of survival at 5 years.

Interestingly, while pulmonary disease ranked as the 5th most important predictor for 5-year survival, its SHAP dot-plot did not exhibit a clear directional distribution. Smoking status, despite its initial relevance for short-term mortality risk, did not emerge as a strong determinant of long-term survival. Some variables that were highly predictive of short-term mortality, such as baseline corticosteroid exposure, were not among the most influential factors for 5-year survival. In contrast, increasing BMI displayed a strong association with long-term survival, in alignment with findings from the risk of death analysis.

4. Discussion

With a median survival of 5.4 months, the findings of this study contribute to the growing body of evidence highlighting the generally poor outcomes of immunotherapy in patients with advanced NSCLC and an ECOG PS ≥ 2. Nonetheless, the observed 5-year survival rate of 13 % indicates that a subset of patients may experience long-term benefit. This underscores the need to better identify those likely to achieve durable responses and supports the use of PD-1/PD-L1 monotherapy as a viable option for patients who are unfit for platinum-based chemotherapy. The feasibility of this approach is further supported by dedicated clinical trials, such as the IPSOS study, which confirm the role of PD-1/PD-L1 inhibition in this setting [16]. Notably, the 5-year survival rate in our study population appear numerically higher than those reported in KEYNOTE-407 and −189 for patients with PD-L1 negative tumors and good PS treated with chemotherapy plus pembrolizumab [1,2]. Despite these observations, access to pembrolizumab for patients with ECOG PS ≥ 2 remains restricted in many healthcare systems, as most regulatory approvals and reimbursement frameworks are based on clinical trials that excluded this population. As a result, treatment decisions are often discretionary and variable across institutions, leading to potential inequities in access to immunotherapy for frail patients. Our findings suggest that such restrictions may deny a meaningful minority of patients the chance of long-term clinical benefit.

The safety profile of pembrolizumab in patients with ECOG PS ≥ 2 appears comparable to that observed in the general population, with even a reduced incidence of adverse events, though this must be interpreted in the context of lower drug exposure due to early treatment discontinuation from disease progression or clinical deterioration.

From a descriptive standpoint, the overall characteristics of our cohort reflect the intrinsic frailty of this population, with a high prevalence of baseline corticosteroid use (>32 %) compared to the full registry population [11]. Other markers of frailty, such as smoking history, comorbidities, and concomitant medications, further reflect the inclusion of patients from the real-world setting in this cohort. Univariate analyses revealed that no specific baseline variable showed a significant association with long-term survival, except for TMB, *KRAS*, and *BRAF* status. However, these findings must be interpreted with caution given the high prevalence of missing values for these features.

To better understand long-term survival determinants, we employed both traditional statistical modeling and AI-driven approaches. The Elastic Net regression model identified plausible determinants of increased risk of death, including increasing age, sex, histology, and baseline corticosteroid use, while smoking history and pulmonary

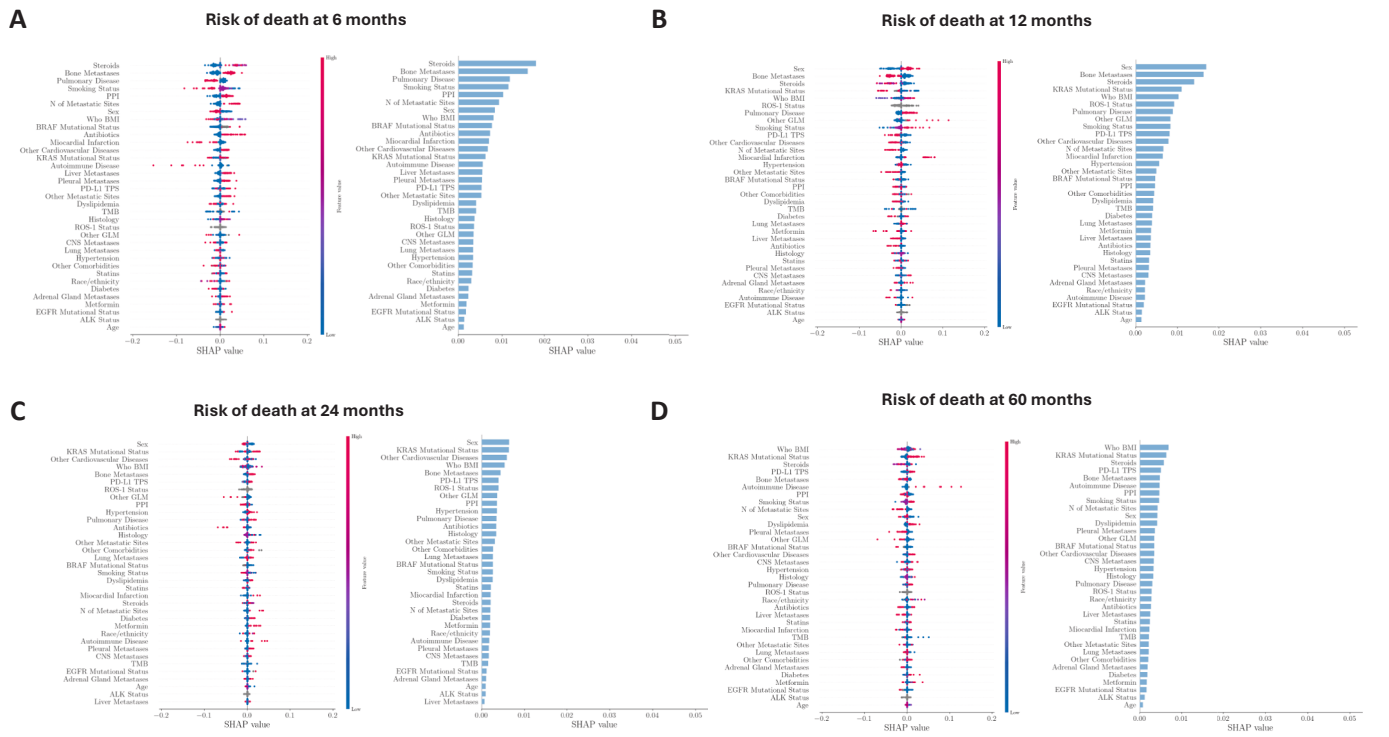

Fig. 2. Paired histogram and dot plots summarizing the SHAP values from the NAIM analysis for the risk of death at four predefined time points: A) 6 months, B) 12 months, C) 24 months, and D) 60 months. The length of each bar represents the mean absolute SHAP value, indicating the relative importance of each variable within the model. Features were ordered by their absolute contribution. In the dot plots, each dot represents a patient: red indicates higher feature values and blue indicates lower feature values (according to the original variable scale). The horizontal position reflects the direction of the association with outcome: dots shifted to the right indicate an increased predicted risk of death, while dots shifted to the left indicate a decreased predicted risk. Missing values were represented as gray dots. Readers should note that SHAP values are unitless measures of variable contribution; "high" or "low" refers to the underlying variable scale (e.g., high BMI, high PD-L1 expression). Variables definition and categorization details are reported in Supplementary Methods.. Abbreviations: WHO BMI, World Health Organization Body Mass Index levels; NOS, Not Otherwise Specified; PD-L1, Programmed Death-Ligand 1; TPS, Tumor Proportion Score; CNS, Central Nervous System; pred, Prednisone; EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; KRAS, Kirsten Rat Sarcoma Virus; PPI, Proton Pump Inhibitors; GLM, Glucose Lowering Medications; TMB, Tumor Mutational Burden.

disease were linked to a decreased risk of death, likely reflecting the well-documented association between smoking and immunotherapy benefit in NSCLC [17]. However, some variables yielded unexpected results, such as unknown *EGFR* status, prior myocardial infarction, and hypertension being associated with a reduced risk of death. While this could partially reflect selection biases, it may also be influenced by limitations of the Elastic Net regression. The regularization process, while effective in handling collinearity, can sometimes retain weak statistical signals, leading to spurious associations.

When assessing 5-year survival, Elastic Net identified only two significant predictors: TMB, which was challenging to interpret due to unstable confidence intervals and a high proportion of missing data, and *KRAS* status, which, despite its missingness, showed an association with survival. However, prior evidence linking *KRAS* mutations to immunotherapy response remains heterogeneous and context-dependent, as the prognostic impact likely varies based on specific co-mutations and the underlying *KRAS* mutation subtype [18]. In our dataset, only a small minority of patients underwent TMB testing, and just two individuals were classified as TMB-high, making any inference regarding TMB exploratory and unstable. Likewise, KRAS mutational subtype information (e.g. G12C, G12D, G12V) was not consistently available across centers and could not be analysed. This lack of molecular granularity limits the interpretability of these findings and reinforces their hypothesis-generating nature. These findings highlight the limitations of regularized regression in high-dimensional datasets with collinear features. Sparse events and wide confidence intervals further underline the statistical instability of these results, emphasizing the need for complementary analytical approaches.

Conversely, the NAIM model provided a more nuanced view of the prognostic landscape, enhancing interpretability through SHAP analysis. As expected, the presence of bone metastases and baseline corticosteroid exposure emerged as the strongest predictors of overall and early mortality, reinforcing clinically intuitive observations. Consistent with findings from the broader registry population [10], NAIM also identified time-dependent trends, with increasing BMI gaining importance beyond two years and other systemic health markers/host factors, such as hypertension and dyslipidemia, playing a key role in 5-year survival. Interestingly, smoking status and pulmonary comorbidities exhibited a heterogeneous prognostic role, likely reflecting their dual impact on tumor mutational burden and respiratory health [19,20].

These insights raise a critical question: who are the patients with ECOG PS $\geq$ 2 who survive long term? Taken together, our findings suggest that long-term survivors are not simply outliers, but rather represent a clinically and biologically distinct subgroup. They appear to be characterized by the absence of aggressive disease features (e.g., bone metastases), limited systemic inflammation/tumor burden (as inferred from the lack of corticosteroid use), and preserved host resilience, partially reflected in increased BMI. Baseline corticosteroid use may reflect underlying disease-related complications such as cancer cachexia, symptomatic CNS metastases, or lymphangitic carcinomatosis, acting as a surrogate of aggressive disease rather than a causal prognostic factor. Conversely, the association between higher BMI and long-term survival aligns with emerging evidence of an 'obesity – immunotherapy paradox,' whereby low-grade chronic inflammation in obesity may enhance anti-tumour immune responses [21]. Importantly, no single factor alone seems to be sufficient to discriminate this subgroup,

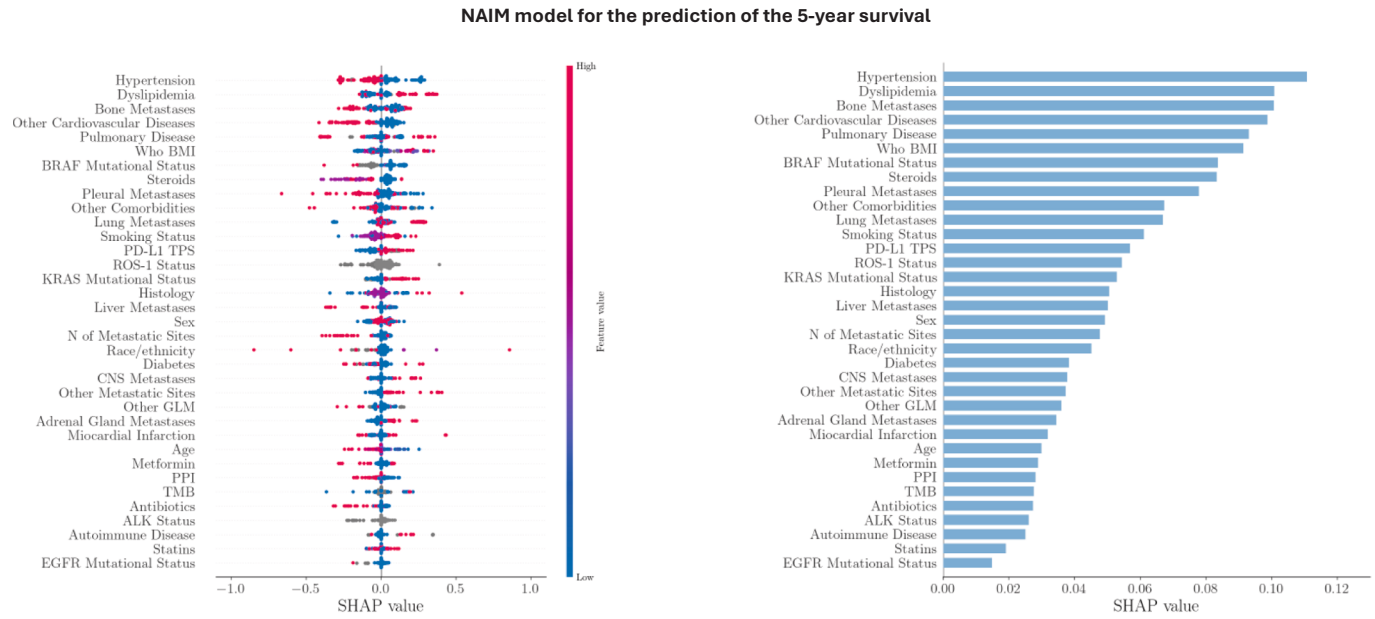

Fig. 3. Paired histogram and dot plots summarizing the SHAP values from the NAIM analysis for the prediction of 5-year survival. The length of each bar represents the mean absolute SHAP value, indicating the relative importance of each variable within the model. Features were ordered by their absolute contribution. In the dot plots, each dot represents a patient: red indicates higher feature values and blue indicates lower feature values, with the horizontal position reflecting the direction of the association. Dots shifted to the right indicate an increased predicted probability of being alive at 5 years, while dots shifted to the left indicate a decreased probability. Missing values were represented as gray dots. SHAP values are unitless measures of variable contribution; "high" or "low" refers to the original scale of the variable (e.g., high PD-L1 TPS vs. low TPS). Model performance was 79.63 ± 9.73 % C-index on the training set and 58.29 ± 15.62 % for the overall model. Variables definition and categorization details are reported in Supplementary Methods.. Abbreviations: WHO BMI, World Health Organization Body Mass Index levels; NOS, Not Otherwise Specified; PD-L1, Programmed Death-Ligand 1; TPS, Tumor Proportion Score; CNS, Central Nervous System; pred, Prednisone; EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; KRAS, Kirsten Rat Sarcoma Virus; PPI, Proton Pump Inhibitors; GLM, Glucose Lowering Medications; TMB, Tumor Mutational Burden.

highlighting the inadequacy of simplistic clinical triage in this setting. Instead, a multidimensional profile, encompassing tumor burden, systemic health, and host-tumor interaction, maybe necessary to individuate frail patients able to derive durable benefit from immunotherapy.

Despite these insights, both Elastic Net and NAIM models demonstrated only modest discriminatory ability (C-index/AUC around 0.6), reflecting the inherent challenges of prognostication in heterogeneous PS $\geq$ 2 populations. For NAIM in particular, the drop in performance from training to evaluation suggests overfitting, underscoring the limits of applying complex AI architectures to relatively small datasets. These shortcomings may stem from data heterogeneity, sample bias, or reliance on variables with limited predictive value across subgroups. Moreover, the dynamic nature of prognostic factors makes long-term survival prediction difficult to capture with static baseline variables alone. Although NAIM is able to handle missing data without imputation, missingness itself may still bias results. In our dataset, variables such as tumor mutational burden had high rates of non-reporting, which could have influenced model stability. Some associations identified by Elastic Net regression appeared counterintuitive, such as myocardial infarction, hypertension, or pulmonary disease being associated with improved outcomes. These signals may represent artifacts of penalized regression or residual confounding, and as such should be regarded as hypothesis-generating rather than definitive findings. Together, these limitations highlight the need for external validation in independent cohorts and further methodological refinement, while also emphasizing the intrinsic complexity of outcome prediction in frail, heterogeneous populations.

Our models were intentionally restricted to baseline variables to generate a prognostic 'snapshot' at treatment initiation. While this approach precludes incorporation of dynamic prognostic factors arising during therapy, it avoids the introduction of immortal time bias, which is a particular concern in survival analyses of longitudinal features. Future work may explore the integration of time-dependent or treatment-related variables within prospective study designs that allow proper handling of this complexity.

An additional limitation of our analysis is the imbalance between the relatively modest size of the ECOG PS $\geq$ 2 cohort and the extensive number of baseline variables explored. Although we applied regularized regression and transformer-based AI to mitigate the impact of collinearity and reduce overfitting, the risk of multiple testing and statistical instability cannot be excluded.

All this emphasizes the need for hybrid modeling strategies that integrate conventional statistical rigor with AI-driven flexibility. Future research should focus on refining AI architectures to better account for evolving host-tumor interactions over time.

Our findings reaffirm that patients with ECOG PS $\geq$ 2 face a poor overall prognosis, and treatment decisions should carefully weigh the cost-benefit ratio of PD-1/PD-L1 monotherapy in this setting. While the majority of patients derive limited benefit, a subset, approximately 13 %, achieves long-term survival, suggesting that absolute exclusion of this population from immunotherapy should be reconsidered. This observation reinforces the concept that impaired PS alone should not preclude the use of PD-1/PD-L1 monotherapy in carefully selected individuals.

From a healthcare policy perspective, patients with ECOG PS $\geq$ 2 may warrant specific health technology appraisal pathways. Standard HTA frameworks, largely based on pivotal clinical trial evidence, often fail to reflect the heterogeneity and vulnerabilities of frail patients who are underrepresented in trials. Tailored appraisal strategies could better account for the unique balance of risks, benefits, and resource utilization in this subgroup, ultimately informing more equitable access and reimbursement decisions.

Given that no clear baseline features were able to reliably identify these long-term survivors, prospective trials should aim for broad

inclusion of patients with PS $\geq$ 2 to better characterize this population and ensure that treatment opportunities are not denied based solely on functional status. In parallel, our findings support moving beyond ECOG PS as a binary decision-making tool, advocating for a more nuanced and biologically informed framework to guide immunotherapy use in frail patients with advanced NSCLC in routine practice.

In conclusion, while our findings highlight the possibility of durable benefit with immunotherapy even in frail patients with ECOG PS $\geq$ 2, they also underscore the broader challenge for the oncology community: to systematically account for comorbidities in both real-world research and clinical trial design, ensuring that treatment decisions remain patient-centered and evidence-based.

Authors' contributions.

All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. Alessio Cortellini serves as the guarantor for data integrity.

Ethics approval and consent to participate.

The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki.

The Pembro-real IT cohort Institutional Review Board (IRB) approval reference is "Comitato Etico per le province di L'Aquila e Teramo, verbale N.15 del 28 Novembre 2019)". For Italian institutions participating to the Pembro-real 5 years cohort the IRB reference is "Comitato Etico Fondazione Policlinico Universitario Campus Bio-Medico, IRB ID approval N.PAR 70.23 OSS, 17 May 2023, registry number: SC 2023.0682" (written informed consent was obtained for patients alive at the time of data collection). For the non-Italian institutions participating to the Pembro-real 5 years cohort the IRB reference is "Health Research Authority approval of the 22nd of November 2023, REC reference 23/HRA/4467" (written informed consent was waived due to the retrospective and observational nature of the study).

Consent for publication

The co-authors give permission for the work and data shown herein to be published.

Availability of data and material

The dataset used for this study contains patient-level data that cannot be made available to third parties, although anonymized. Third party research proposals will be assessed by the study investigators and performed by the study team if accepted. Requests can be made to AC (a.cortellini@policlinicocampus.it).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (OpenAI) in order to assist with language editing and improvement of textual flow. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Alessio Cortellini: Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Edoardo Garbo:** Writing – review & editing, Data curation. **Giulia La Cava:** Writing – review & editing, Data curation. **Fabrizio Citarella:** Data curation. **Valentina Santo:** Data curation. **Leonardo Brunetti:** Data curation. **David J Pinato:** Writing – original draft, Visualization. **Jarushka Naidoo:** Writing – review & editing, Visualization, Validation. **Monica Loza:** Data curation. **Carlo Genova:** Data curation. **Scott Gettinger:** Data curation. **So Yeon Kim:** Data curation. **Ritujith Jayakrishnan:** Data curation. **Talal El Zarif:** Data curation. **Marco Russano:** Data curation. **Federica Pecci:** Data curation. **Alessandro Di Federico:** Data curation. **Michele Montrone:** Data curation. **Dwight H Owen:** Data curation. **Diego Signorelli:** Data curation. **Mingjia Li:** Data curation. **Andrea Camerini:** Data curation. **Balazs Halmos:** Data curation. **Bruno Vincenzi:** Data curation. **Giulio Metro:** Data curation. **Sai Yendamuri:** Data curation. **Francesco Grossi:** Data curation. **Eleni Josephides:** Data curation. **Bartłomiej Tomasik:** Data curation. **Raffaele Giusti:** Data curation. **Emilio Bria:** Data curation. **Martin Sebastian:** Data curation. **Maximilian Rost:** Data curation. **Fabian Acker:** Data curation. **Lorenza Landi:** Data curation. **Francesca Mazzoni:** Data curation. **Alessandro Morabito:** Data curation. **Alessandro Leonetti:** Data curation. **Luca Cantini:** Data curation. **Giannis Mountzios:** Data curation. **Sukumar Kalvapudi:** Data curation. **David O'Reilly:** Data curation. **Eleni Karapanagiotou:** Data curation. **Isabelle Monnet:** Data curation. **Javier Baena:** Data curation. **Marianna Macerelli:** Data curation. **Margarita Majem:** Data curation. **Aida Piedra:** Data curation. **Diego L Cortinovis:** Data curation. **Giuseppe Tonini:** Visualization, Validation. **Gabriele Minuti:** Data curation. **Laura Mezquita:** Data curation. **Teresa Gorria:** Data curation. **Teresa Beninato:** Data curation. **Giuseppe Lo Russo:** Data curation. **Arsela PrelaJ:** Data curation. **Andrea De Giglio:** Writing – review & editing, Visualization, Validation. **Federica Biello:** Data curation. **Frank Aboubakar Nana:** Data curation. **Anne-Marie C. Dingemans:** Data curation. **Joachim GJV Aerts:** Data curation. **Roberto Ferrara:** Writing – review & editing, Visualization. **Taher Abu Hejleh:** Data curation. **Kazuki Takada:** Writing – review & editing, Visualization, Validation, Supervision. **Abdul R Naqash:** Writing – review & editing, Visualization, Validation. **Marina C Garassino:** Writing – review & editing, Visualization. **Heather A. Wakelee:** Writing – original draft, Visualization, Data curation. **Amin Nassar:** Writing – review & editing, Data curation. **Biagio Ricciuti:** Writing – review & editing, Data curation. **Paolo Soda:** Writing – review & editing, Validation, Supervision. **Camillo Maria Caruso:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Conceptualization. **Valerio Guarrasi:** Writing – review & editing, Visualization, Validation, Software, Formal analysis, Conceptualization.

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Alessandro Leonetti has been on advisory board for AstraZeneca, BeiGene, Novartis and Sanofi; consultant's fee for Amgen; has attended editorial activities sponsored by Eli Lilly, Novartis and Roche and has received travel support from MSD, Novartis, Roche and Takeda. Francesca Mazzoni received honoraria for advisory board/speaker fees from MSD, ROCHE, AMGEN, REGENERON, J&J.

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Appendix A. Supplementary data

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