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Pretreatment FIB-4 and Survival in Metastatic Solid Tumors Receiving Immune Checkpoint Inhibitor Monotherapy

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ABSTRACT

Objective: The fibrosis-4 index (FIB-4) is a readily available laboratory-based measure originally developed to assess liver fibrosis. Its prognostic relevance in patients receiving immune checkpoint inhibitors (ICI) remains uncertain. We investigated the association between pretreatment FIB-4 and survival in patients with metastatic solid tumours receiving ICI monotherapy.

Material and Methods: This retrospective, single-centre study included 408 patients treated at Ege University Medical Faculty Hospital between January 2015 and December 2024. We calculated pretreatment FIB-4 using age, aspartate aminotransferase, alanine aminotransferase, and platelet count. We categorised patients into low- and high-FIB-4 groups using an exploratory, overall survival-derived threshold. We evaluated overall survival (OS) and progression-free survival (PFS) using Kaplan-Meier estimates and Cox regression. Two multivariable models incorporating clinical covariates were fitted for each endpoint. We conducted exploratory subgroup analyses to assess potential heterogeneity across clinical strata.

Results: The cohort included 268 patients with low FIB-4 and 140 with high FIB-4. The most common malignancies were lung cancer (33.3%), melanoma (29.7%), and renal cell carcinoma (19.9%); 89.2% of patients received nivolumab. There were 290 deaths and 341 progression or death events. Low FIB-4 was associated with longer OS [unadjusted hazard ratio (HR): 0.729; 95% confidence interval (CI): 0.575-0.925; p=0.009]. This association persisted in both multivariable models, with adjusted HRs of 0.706 (95% CI: 0.554-0.899; p=0.005) and 0.710 (95% CI: 0.558-0.904; p=0.005). The association with PFS was not statistically significant (adjusted HR: 0.830; 95% CI: 0.661-1.040; p=0.110). Exploratory analyses provided no clear evidence of heterogeneity across evaluated subgroups.

Conclusion: Lower pretreatment FIB-4 was associated with longer OS, whereas its association with PFS remained inconclusive. These findings support further investigation of FIB-4 as a candidate prognostic marker, but do not establish its ability to predict immunotherapy benefit. Independent validation and analyses treating FIB-4 as a continuous variable are warranted.

Keywords: Fibrosis-4 index; immune checkpoint inhibitors; solid tumors; overall survival

INTRODUCTION

Immune checkpoint inhibitors (ICIs) targeting several pathways have become standard treatments for almost all metastatic solid tumours.[1] Nevertheless, survival outcomes vary considerably among patients receiving these agents.[2] Readily available pretreatment measures associated with prognosis could help characterise this variation in routine clinical practice.

The fibrosis-4 index (FIB-4), which was originally developed as a non-invasive tool for assessing liver fibrosis, is calculated from age, aspartate aminotransferase, alanine aminotransferase, and platelet count.[3] Because its components can also be influenced by cancer-related and other clinical conditions, FIB-4 in a heterogeneous oncology population should not be assumed to represent histological liver fibrosis.[4] Its potential association with survival during immunotherapy, therefore, warrants direct evaluation. Evidence concerning

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FIB-4 in patients receiving ICIs is limited and may vary by clinical setting. In a study of cholangiocarcinoma, higher FIB-4 was associated with shorter OS.[5] In patients with urothelial carcinoma, the FAN score, which combines FIB-4, the albumin-bilirubin (ALBI) grade, and the neutrophil-to-lymphocyte ratio, has also been shown to be independently associated with survival.[4]

Hepatic fibrosis can reshape the local immune environment through extracellular matrix deposition and altered cytokine signalling. In studies of hepatocellular carcinoma, transforming growth factor-β-associated fibrotic remodelling has been linked to reduced T-cell infiltration, while experimental work implicates interleukin-17A-driven inflammation in resistance to programmed death-ligand 1 (PD-L1) blockade.[6,7] More recently, a fibroinflammatory liver environment was associated with impaired $CD8^+$ T-cell effector function, including reduced interferon-γ and granzyme B activity, and poorer response to anti-programmed cell death protein-1 (PD-1) therapy in clinical samples and experimental models.[8] Together, these findings suggest that fibrosis-associated immune changes may weaken antitumor responses and limit the effectiveness of immune checkpoint inhibition. Evidence for this mechanism comes predominantly from liver cancer; whether it extends to other solid tumours remains to be established. We therefore evaluated the association between baseline FIB-4 and overall survival (OS) and progression-free survival (PFS) in patients treated with ICI monotherapy. We explored whether this association varied across selected clinical subgroups.

MATERIAL AND METHODS

Patients

This retrospective, single-centre cohort study included patients with histologically confirmed metastatic solid tumours who received anti-PD-1/PD-L1 monotherapy at the Ege University Medical Faculty Hospital outpatient clinic from January 2015 to December 2024. Eligible patients were aged 18 years or older, had solid-tumour diagnosis, and received anti-PD-1/PD-L1 monotherapy. We excluded individuals treated with combination regimens, adjuvant therapies, or anti-CTLA-4 agents from the analysis. Of 672 patients screened, 408 met the criteria and were included in the final analysis.

Methods

We extracted clinical and laboratory data from institutional electronic medical records, including demographics, tumour type, relevant biomarkers, Eastern Cooperative Oncology Group (ECOG) performance status, metastasis sites, treatment dates, and survival outcomes. Radiologic response was assessed using RECIST version 1.1. FIB-4 was calculated as age (years) × aspartate aminotransferase (U/L) / [platelet count (10^9/L) × √alanine aminotransferase (U/L)]. OS was defined as the time from immunotherapy initiation to death from any cause, with living patients censored at their last known follow-up. PFS was defined as the time from immunotherapy initiation to the first documented progression or death, whichever occurred first, with event-free patients censored at their last evaluable disease assessment.

Statistical Analysis

We summarised continuous variables using medians and interquartile ranges, and categorical variables using numbers and percentages. Percentages were calculated within each FIB-4 group using available data. We compared baseline categorical characteristics using Pearson's chi-square test, except for the immunotherapy agent, for which we used Fisher's exact test with Monte Carlo simulation. (Table 1). The FIB-4 threshold was selected using maximally selected log-rank statistics for OS, implemented in the maxstat package. The selected threshold was 0.85 with low FIB-4 defined as ≤0.85 and high FIB-4 as >0.85. This threshold was applied consistently to OS, PFS, and subgroup analyses. Because threshold selection and association testing were performed in the same cohort, the resulting estimates were considered exploratory. Unless otherwise specified, reported log-rank and Cox regression P values are nominal and do not account for cut point selection.

We estimated survival distributions using the Kaplan-Meier method and compared them using log-rank tests. Univariable Cox regression models were fitted separately for OS and PFS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported relative to the stated reference category. Two multivariable Cox regression models were fitted for each endpoint. Model A included FIB-4 group, sex, primary tumour type, disease setting, immunotherapy agent, treatment line, prior chemotherapy, and brain, lung, liver, and bone metastases. Model B retained FIB-4 regardless of its univariable association with the endpoint and included other covariates with an endpoint-specific univariable global p-value <0.05. Accordingly, the OS model B included FIB-4 group, primary tumour type, prior chemotherapy, and brain, lung, liver, and bone metastases, whereas the PFS model B included FIB-4 group, prior chemotherapy, and lung, liver, and bone metastases. Age was not entered separately because it is incorporated into FIB-4. Multivariable analyses used complete-case data for the variables included in each model, without imputation. Adjusted HRs and 95% CIs were reported for OS and PFS. We assessed the proportional

TABLE 1: Baseline characteristics by FIB-4 group.

Characteristic	Category	High FIB-4 (n=140)	Low FIB-4 (n=268)	p-value
Sex	Male	94 (67.1%)	193 (72.0%)	0.306
	Female	46 (32.9%)	75 (28.0%)	
ECOG	0-1	116 (82.8%)	207 (77.2%)	0.185
	2-3	24 (17.2%)	61 (22.8%)	
Age group	<65 years	106 (75.7%)	120 (44.8%)	<0.001
	≥65 years	34 (24.3%)	148 (55.2%)	
Age	Median (IQR), years	66.0 (59.0-70.0)	58.0 (59.0-64.0)	<0.001
ICI agent	Nivolumab	129 (92.1%)	235 (87.7%)	0.425
	Pembrolizumab	8 (5.7%)	25 (9.3%)	
	Atezolizumab	3 (2.1%)	8 (3.0%)	
Disease setting	*De novo* metastatic	59 (42.1%)	114 (42.5%)	0.939
	Recurrent metastatic	81 (57.9%)	154 (57.5%)	
Prior chemotherapy	No	72 (51.4%)	132 (49.3%)	0.677
	Yes	68 (48.6%)	136 (50.7%)	
ICI treatment line	Lines 1-2	106 (75.7%)	209 (78.0%)	0.604
	Line ≥3	34 (24.3%)	59 (22.0%)	
Diagnosis	Melanoma	50 (35.7%)	71 (26.5%)	0.012
	Lung cancer	53 (37.9%)	83 (31.0%)	
	RCC	22 (15.7%)	59 (22.0%)	
	Other	15 (10.7%)	55 (20.5%)	
Brain metastasis	No	122 (87.1%)	231 (86.2%)	0.790
	Yes	18 (12.9%)	37 (13.8%)	
Lung metastasis	No	62 (44.3%)	119 (44.4%)	0.982
	Yes	78 (55.7%)	149 (55.6%)	
Liver metastasis	No	120 (85.7%)	211 (78.7%)	0.087
	Yes	20 (14.3%)	57 (21.3%)	
Bone metastasis	No	95 (67.9%)	171 (63.8%)	0.415
	Yes	45 (32.1%)	97 (36.2%)	
AST, median U/L	Median (IQR), U/L	18.0 (15.0-24.0)	14.0 (11.0-18.0)	<0.001
Platelet count,	Median (IQR), $\times 10^3/\mu L$	338 (284.50-447.25)	230 (177.25-277.25)	<0.001
ALT,	Median (IQR), U/L	15.0 (9.8-21.0)	13.0 (10.0-22.0)	0.632
FIB-4	Median (IQR)	1.3 (1.1-1.8)	0.6 (0.5-0.7)	<0.001

Values are n (%); percentages are calculated within each FIB-4 group. Pearson chi-square tests were used, except for ICI agent, which used a Fisher's exact test with Monte Carlo simulation. FIB-4: Fibrosis-4 index; ICI: Immune checkpoint inhibitor; RCC: Renal cell carcinoma; ECOG: Eastern Cooperative Oncology Group; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; IQR: Interquartile range.

hazards assumption using Schoenfeld residual tests. The authors reported departures from proportional hazards and cautiously interpreted constant HRs when the proportional hazards assumption was not supported. The reported analyses did not show that time-varying coefficients or stratification resolved these departures.

Exploratory subgroup analyses estimated unadjusted HRs for low versus high FIB-4 within selected tumour types and strata defined by sex, immunotherapy line, prior chemotherapy, and metastatic sites. Interaction P values were used to evaluate heterogeneity of the FIB-4 association across subgroup levels. An interaction result that was not estimable in the supplied output was reported as such, rather than interpreted as evidence of no heterogeneity. P values were treated as nominal and two-sided. Given exploratory threshold selection and multiple comparisons, we considered subgroup- and threshold-based findings to be hypothesis-generating. Statistical analyses were performed

using R software version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). The survival package was used for survival estimation, Cox regression, and assessment of the proportional hazards assumption, while the survminer package was used to generate Kaplan-Meier plots. The FIB-4 cut-off was determined using maximally selected log-rank statistics implemented in the maxstat package. Data management was performed using dplyr.

The study protocol was reviewed and approved by the Ege University Clinical Research Ethics Committee (approval number: 26-10T/61, date: 01.10.2026). The requirement for informed consent was waived by the ethics committee owing to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Patient Characteristics

The cohort comprised 408 patients, with 140 (34.3%) in the high-FIB-4 group and 268 (65.7%) in the low-FIB-4 group. Overall, 287 patients (70.3%) were male. The most common primary tumours were lung cancer (136, 33.3%), melanoma (121, 29.7%), and renal cell carcinoma (81, 19.9%). Nivolumab was administered to 364 patients (89.2%), and 315 patients (77.2%) received ICI treatment as first- or second-line therapy.

The proportion of patients younger than 65 years was higher in the high-FIB-4 group than in the low-FIB-4 group (75.7% vs. 44.8%; p<0.001). The primary tumour distribution also differed between groups (p=0.012). No statistically significant between-group differences were observed for sex, ECOG performance status, immunotherapy agent, disease setting, prior chemotherapy, treatment line, or the presence of brain, lung, liver, or bone metastases (Table 1).

Overall Survival

All 408 patients were included in the OS analysis, with 290 deaths: 110/140 in the high-FIB-4 group and 180/268 in the low-FIB-4 group. Kaplan-Meier analysis showed longer OS in the low-FIB-4 group (log-rank p=0.009; Figure 1).

In univariable Cox regression, low FIB-4 was associated with a lower hazard of mortality than high FIB-4 (HR: 0.729; 95% CI: 0.575-0.925; p=0.009). Prior chemotherapy and brain, lung, liver, and bone metastases were associated with increased mortality hazard. Primary tumour type was associated with OS in the overall test (p=0.022; Table 2).

The association between low FIB-4 and lower mortality persisted in both adjusted models: model A: adjusted HR: 0.706 (95% CI: 0.554-0.899; p=0.005); model B: adjusted HR: 0.710 (95% CI: 0.558-0.904; p=0.005). Brain, lung, liver, and bone metastases remained associated with higher mortality hazards in both models (Table 3).

TABLE 2: Univariable Cox regression for OS and PFS.

Characteristic and comparison	OS HR (95% CI)	p	PFS HR (95% CI)	p
FIB-4: low vs. high	0.72 (0.57-0.92)	0.009	0.85 (0.68-1.07)	0.164
Sex: female vs. male	0.92 (0.71-1.19)	0.523	1.05 (0.83-1.32)	0.695
Age: ≥65 vs. <65 years	1.19 (0.94-1.50)	0.147	0.93 (0.75-1.16)	0.529
Treatment: pembrolizumab vs. nivolumab	0.86 (0.54-1.38)	0.548	0.77 (0.50-1.19)	0.243
Treatment: atezolizumab vs. nivolumab	1.27 (0.65-2.48)	0.474	0.89 (0.46-1.73)	0.741
Recurrent vs. *de novo* metastatic disease	1.10 (0.86-1.38)	0.440	0.96 (0.77-1.20)	0.749
Prior chemotherapy: yes vs. no	1.61 (1.28-2.04)	<0.001	1.28 (1.03-1.58)	0.024
Immunotherapy line: ≥3 vs. 1-2	1.06 (0.81-1.39)	0.655	1.12 (0.87-1.44)	0.369
Primary tumor: lung vs. melanoma	1.34 (1.00-1.79)	0.049	1.24 (0.94-1.62)	0.122
Primary tumor: RCC vs. melanoma	0.80 (0.57-1.12)	0.195	1.14 (0.84-1.54)	0.400
Primary tumor: other vs. melanoma	1.09 (0.76-1.56)	0.631	1.07 (0.77-1.49)	0.682
Brain metastasis: yes vs. no	1.94 (1.41-2.68)	<0.001	1.35 (0.98-1.84)	0.059
Lung metastasis: yes vs. no	1.53 (1.21-1.94)	<0.001	1.32 (1.06-1.64)	0.011
Liver metastasis: yes vs. no	1.71 (1.30-2.26)	<0.001	1.82 (1.40-2.37)	<0.001
Bone metastasis: yes vs. no	1.43 (1.13-1.81)	0.003	1.56 (1.25-1.94)	<0.001

All values are presented as hazard ratios (95% confidence intervals). P-values in the table refer to the indicated Cox coefficient. For factors with multiple levels, overall likelihood-ratio p-values were as follows: primary tumor type: OS 0.0216 and PFS 0.471; treatment: OS 0.640 and PFS 0.462.
For FIB-4, the coefficient p-values were 0.00925 for OS and 0.164 for PFS; overall likelihood-ratio p-values were 0.0103 and 0.168 for OS and PFS, respectively. The FIB-4 threshold was selected using OS in the same cohort. The reported Cox regression p values are nominal and do not account for cut point selection; threshold-based associations should therefore be interpreted as exploratory.
CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; RCC: Renal cell carcinoma; FIB-4: Fibrosis-4 index.

Progression-free Survival

The PFS analysis included 408 patients and 341 progression or death events: 119 of 140 patients in the high-FIB-4 group and 222 of 268 patients in the low-FIB-4 group. The Kaplan-Meier comparison was not statistically significant (log-rank p=0.16; Figure 2).

In univariable Cox regression, the estimated HR was lower in the low-FIB-4 group, although the CIs included the null value (HR: 0.854; 95% CI: 0.683-1.070; p=0.164). Prior chemotherapy and lung, liver, and bone metastases were associated with increased disease progression (Table 2).

Low FIB-4 was not significantly associated with PFS after adjustment. In model A, the adjusted HR was 0.830 (95% CI: 0.661-1.040; p=0.110); in model B, the adjusted HR was 0.833 (95% CI: 0.667-1.040; p=0.109). Liver and bone metastases remained associated with a higher hazard in both models (Table 4).

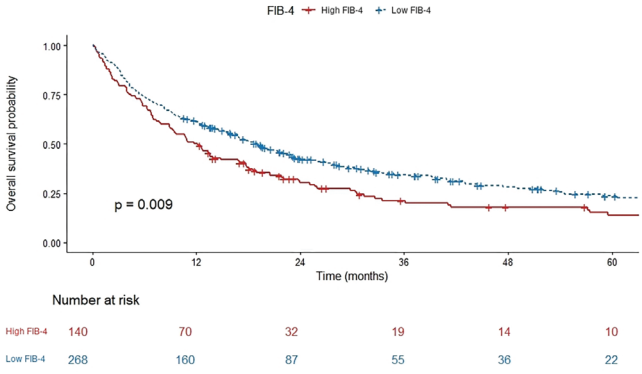

FIGURE 1: Overall survival according to pretreatment FIB-4 group. Kaplan-Meier estimates of overall survival in 408 patients with metastatic solid tumors receiving ICI, comparing low FIB-4 (n=268) with high FIB-4 (n=140). Tick marks indicate censoring, and numbers at risk are shown below the plot. Time was measured in months from the initiation of immunotherapy. Log-rank p=0.009.

FIB-4: Fibrosis-4 index; ICI: Immune checkpoint inhibitors.

Model Diagnostics and Exploratory Subgroup Analyses

Brain, lung, liver, and bone metastases remained associated with a higher mortality hazard in both adjusted OS models. Liver and bone metastases remained associated with higher progression in both adjusted PFS models; prior chemotherapy was additionally associated with a higher hazard in PFS Model B (adjusted HR: 1.250; 95% CI: 1.010-1.560; p=0.041). Exploratory subgroup analyses did not provide clear evidence that the association of FIB-4 with survival differed across the evaluated clinical strata. The interaction p-value for primary tumour type in the OS analysis was 0.353 (Figure 3). In the PFS analysis, the interaction p-values were 0.110 for sex and 0.187 for liver metastasis (Figure 4). Subgroup estimates were interpreted as exploratory.

TABLE 3: Multivariable Cox regression for overall survival.

Characteristic and comparison	Model A HR (95% CI)	p	Model B HR (95% CI)	p
FIB-4: low vs. high	0.70 (0.55-0.89)	0.005	0.71 (0.55-0.90)	0.005
Sex: female vs. male	0.93 (0.71-1.22)	0.613	—	—
Treatment: pembrolizumab vs. nivolumab	0.66 (0.35-1.25)	0.206	—	—
Treatment: atezolizumab vs. nivolumab	1.05 (0.48-2.27)	0.903	—	—
Recurrent vs. *de novo* metastatic disease	1.06 (0.83-1.35)	0.644	—	—
Prior chemotherapy: yes vs. no	1.38 (0.95-2.01)	0.090	1.35 (0.95-1.92)	0.092
Immunotherapy line: ≥3 vs. 1-2	0.95 (0.71-1.28)	0.764	—	—
Primary tumor: lung vs. melanoma	0.96 (0.65-1.42)	0.862	0.98 (0.68-1.43)	0.935
Primary tumor: RCC vs. melanoma	0.78 (0.54-1.13)	0.193	0.77 (0.54-1.10)	0.149
Primary tumor: other vs. melanoma	1.32 (0.76-2.29)	0.315	1.11 (0.73-1.68)	0.619
Brain metastasis: yes vs. no	1.88 (1.33-2.65)	<0.001	1.85 (1.32-2.59)	<0.001
Lung metastasis: yes vs. no	1.48 (1.15-1.91)	0.002	1.47 (1.14-1.89)	0.002
Liver metastasis: yes vs. no	1.59 (1.18-2.14)	0.002	1.61 (1.20-2.15)	0.001
Bone metastasis: yes vs. no	1.48 (1.15-1.90)	0.002	1.44 (1.13-1.85)	0.003

Model A includes FIB-4 and all recorded baseline covariates except age group, because age is a component of FIB-4. Model B includes FIB-4 and covariates selected from the corresponding univariable OS analysis. Em dashes indicate covariates omitted from model B.
Proportional-hazards diagnostics indicated that prior chemotherapy (p=0.0325) and brain metastasis (p=0.0023) showed departures in model A; both also showed departures in model B (p=0.028 and p=0.002). FIB-4 did not show a departure (p=0.685 and 0.715); global p-values were 0.205 and 0.074. A stratified or time-varying sensitivity model is needed before final interpretation.
CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; RCC: Renal cell carcinoma; FIB-4: Fibrosis-4 index.

DISCUSSION

In this retrospective cohort of 408 patients with metastatic solid tumors who received ICI monotherapy, a lower pretreatment FIB-4 was associated with longer overall survival. The association persisted across two multivariable adjustment strategies, with adjusted HRs of 0.706 and 0.710 for low versus high FIB-4, respectively. In contrast, the corresponding PFS estimates were directionally consistent but did not reach statistical significance. Exploratory subgroup analyses provided no clear evidence of heterogeneity across the evaluated clinical strata, although their precision varied. These findings suggest that FIB-4 may capture aspects of prognosis that are not fully explained by the measured tumor and treatment characteristics. Nevertheless, the difference in statistical significance between OS and PFS does not itself establish that FIB-4 has different biological effects on these endpoints. These findings support a prognostic association between lower FIB-4 and longer OS in this ICI-treated cohort; they do not show that FIB-4 predicts a differential benefit from ICI therapy. The PFS association was not statistically significant and therefore remains inconclusive.

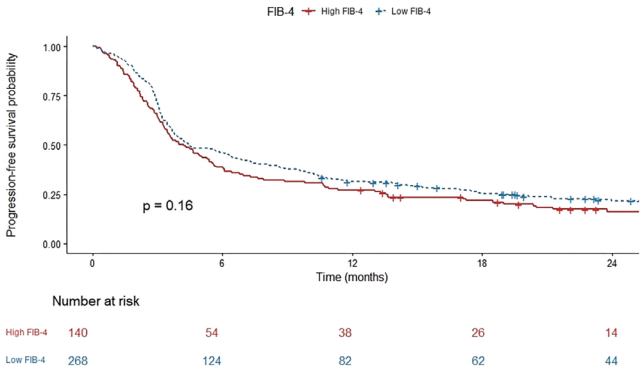

FIGURE 2: Progression-free survival according to pretreatment FIB-4 group. Kaplan-Meier estimates of progression-free survival in 408 patients with metastatic solid tumors receiving ICI monotherapy, comparing low FIB-4 (n=268) with high FIB-4 (n=140). Tick marks indicate censoring, and numbers at risk are shown below the plot. Time is measured in months from immunotherapy initiation. Log-rank p=0.16.

FIB-4: Fibrosis-4 index; ICI: Immune checkpoint inhibitors.

Previous studies have examined FIB-4 as a prognostic marker in selected populations receiving ICIs. In a retrospective study of 66 patients with cholangiocarcinoma, Zhang et al.[5] identified higher FIB-4 as an independent adverse prognostic factor for OS, whereas the factors associated with PFS differed. This provides a relevant parallel to our findings, although underlying hepatobiliary disease and differences in treatment regimens limit direct comparison. Kawashima et al.[4] evaluated patients with metastatic urothelial carcinoma treated with pembrolizumab and identified FIB-4, the albumin-bilirubin score, and the neutrophil-to-lymphocyte ratio as independent prognostic factors in a discovery cohort

TABLE 4: Multivariable Cox regression for progression-free survival.

Characteristic and comparison	Model A HR (95% CI)	p	Model B HR (95% CI)	p
FIB-4: low vs. high	0.83 (0.66-1.04)	0.110	0.83 (0.66-1.04)	0.109
Sex: female vs. male	1.09 (0.85-1.38)	0.503	—	—
Treatment: pembrolizumab vs. nivolumab	0.58 (0.33-1.02)	0.058	—	—
Treatment: atezolizumab vs. nivolumab	0.66 (0.31-1.41)	0.287	—	—
Recurrent vs. *de novo* metastatic disease	0.98 (0.78-1.23)	0.890	—	—
Prior chemotherapy: yes vs. no	1.21 (0.86-1.69)	0.273	1.25 (1.01-1.56)	0.041
Immunotherapy line: ≥3 vs. 1-2	1.01 (0.77-1.32)	0.933	—	—
Primary tumor: lung vs. melanoma	1.08 (0.76-1.53)	0.669	—	—
Primary tumor: RCC vs. melanoma	1.15 (0.82-1.62)	0.413	—	—
Primary tumor: other vs. melanoma	1.47 (0.90-2.37)	0.117	—	—
Brain metastasis: yes vs. no	1.36 (0.97-1.90)	0.069	—	—
Lung metastasis: yes vs. no	1.19 (0.94-1.50)	0.138	1.19 (0.95-1.48)	0.127
Liver metastasis: yes vs. no	1.68 (1.27-2.22)	<0.001	1.66 (1.27-2.18)	<0.001
Bone metastasis: yes vs. no	1.48 (1.17-1.86)	<0.001	1.46 (1.16-1.82)	0.001

Model A includes FIB-4 and all recorded baseline covariates except age group; age is a component of FIB-4. Model B includes FIB-4 and covariates selected from the corresponding univariable PFS analysis. Em dashes indicate covariates omitted from model B.
Proportional hazards diagnostics indicated that brain metastasis departed from the assumption in model A (p=0.00049). FIB-4 showed no departure in models A or B (p=0.203 and 0.270); global p-values were 0.167 and 0.780. A sensitivity analysis model stratified by brain metastasis status should be considered for inclusion in model A.
CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; RCC: Renal cell carcinoma; FIB-4: Fibrosis-4 index. The FIB-4 cut-off was selected using OS in the same cohort; ordinary Cox p-values should be interpreted as exploratory alongside the cutpoint-search-adjusted results.

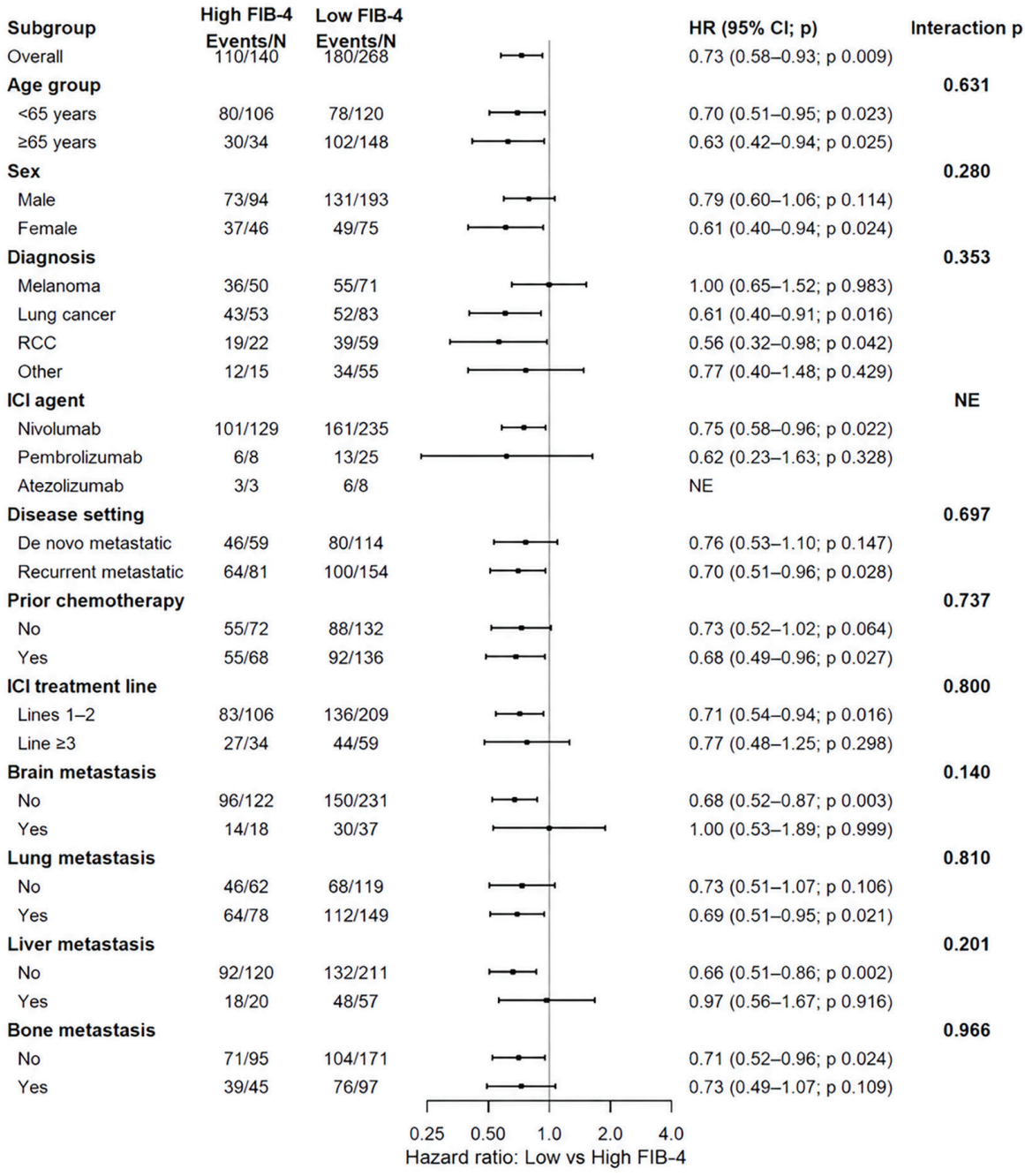

FIGURE 3: Exploratory subgroup analyses of overall survival. Squares and horizontal lines represent unadjusted Cox hazard ratios and 95% confidence intervals for low versus high pretreatment FIB-4 in the overall cohort of 408 patients and in clinical subgroups. The events/N columns indicate the number of deaths and of analysed patients in each FIB-4 group. Hazard ratios below 1 favour the low-FIB-4 group. The vertical dashed line indicates HR=1. Interaction p-values assess heterogeneity across subgroup levels. NE denotes that a value is not estimable. All subgroup analyses used the same OS-derived FIB-4 threshold and were exploratory.

FIB-4: Fibrosis-4 index; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival.

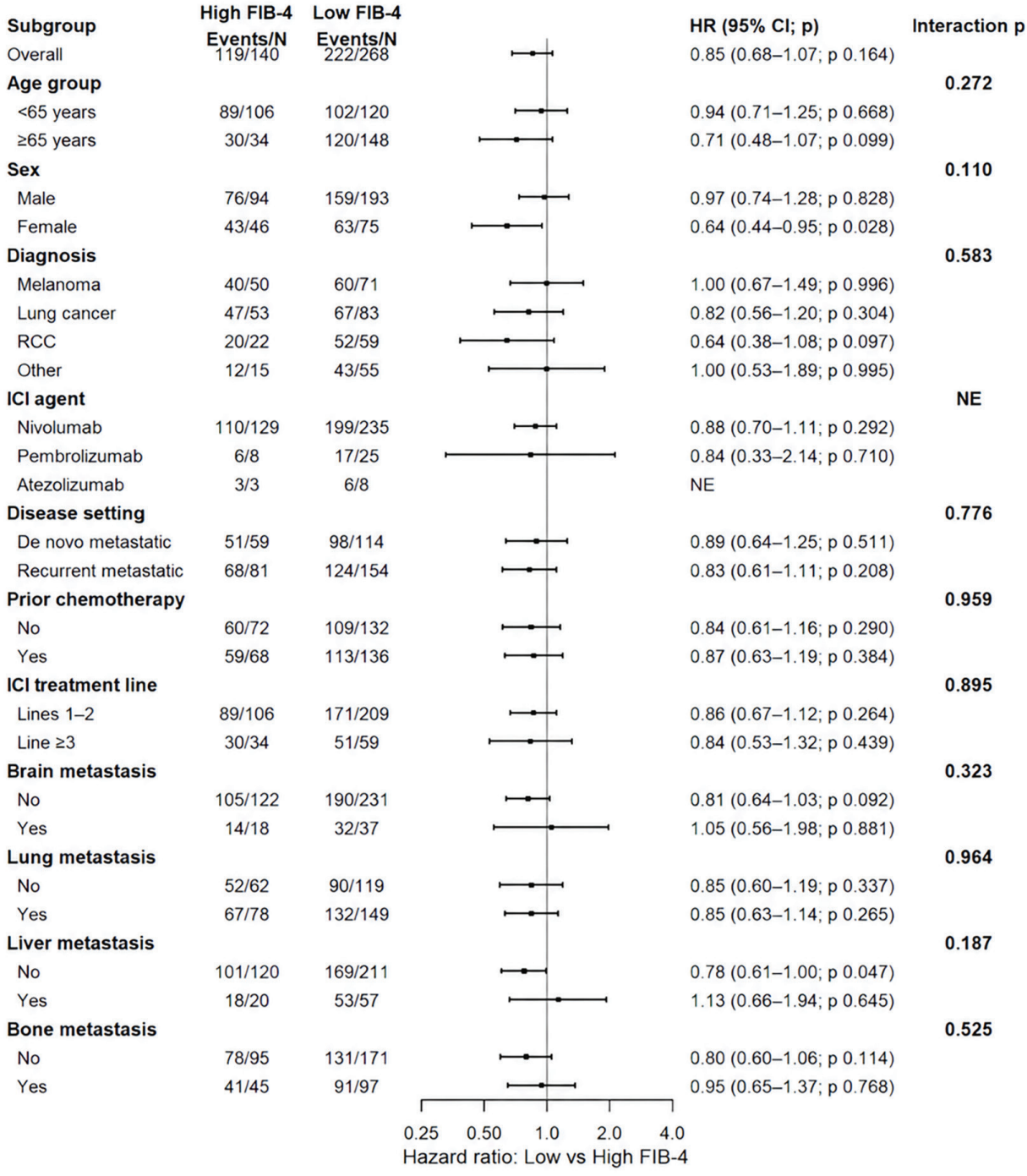

FIGURE 4: Exploratory subgroup analyses of progression-free survival. Squares and horizontal lines represent unadjusted Cox hazard ratios and 95% confidence intervals for low versus high pretreatment FIB-4 in the overall cohort of 408 patients and within clinical subgroups. The events/N columns indicate progression or death events and the number of analysed patients in each FIB-4 group. Hazard ratios below 1 favour the low-FIB-4 group. The vertical dashed line indicates HR=1. Interaction P values assess heterogeneity across subgroup levels. NE denotes not estimable. All subgroup analyses used the same OS-derived FIB-4 threshold and are exploratory.

FIB-4: Fibrosis-4 index; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival.

of 165 patients. Their combined FAN score was subsequently associated with cancer-specific survival and PFS in a separate validation cohort of 103 patients. These observations support the potential relevance of hepatic and inflammatory measures during immunotherapy, but validation of a composite score does not establish the performance of FIB-4 alone. Our study provides evidence from a broader population of patients with solid tumors treated with monotherapy and highlights the need to distinguish a reproducible prognostic association from a universally applicable threshold.

The association between lower FIB-4 and longer OS may reflect host characteristics that influence survival throughout the disease course, rather than initial tumor sensitivity alone. Relevant evidence comes from a multicenter study of metastatic RCC treated with nivolumab plus ipilimumab, in which the FAN score, incorporating FIB-4, ALBI, and NLR, was associated with OS and PFS2 but not with initial PFS.[9] This pattern raises the possibility that hepatic and inflammatory characteristics retain prognostic relevance beyond the first progression event, potentially through their relationship with physiological reserve, subsequent treatment eligibility, and the ability to continue systemic therapy. These pathways were not directly established in that study or in our cohort. Similarly, Takada et al.[10] found that ALBI grade was independently associated with survival in NSCLC patients receiving anti-PD-1-based therapy, without a significant association with overall tumor response. A complementary biological rationale is provided by Yu et al.[11] who demonstrated that liver metastases can suppress systemic antitumor immunity through macrophage-mediated elimination of activated $CD8^+$ T cells. The association of liver metastases with poorer long-term survival during nivolumab monotherapy in melanoma further supports the clinical relevance of hepatic involvement.[12] Nevertheless, hepatic metastases, functional reserve, and FIB-4 represent distinct features, and these findings do not establish that the OS association observed here is mediated by liver dysfunction or more durable immune responses.

The divergent OS and PFS findings may reflect differences in endpoint sensitivity rather than distinct biological effects. A meta-analysis of 61 randomized trials found only moderate trial-level concordance between PFS and OS treatment effects with ICI monotherapy (R^2=0.58).[13] In lung cancer, immune-related PFS correlated more closely with OS than conventional PFS, suggesting that progression definitions influence the capture of immunotherapy benefit.[14] These findings provide context, not direct evidence, for our biomarker association: FIB-4 may reflect host characteristics that shape the broader disease trajectory, while first-progression endpoints do not fully capture subsequent survival. Nevertheless, OS-based threshold selection may have amplified the apparent OS association. Because the PFS CI encompassed both a meaningful hazard reduction and no association, the result remains inconclusive and does not establish an OS-specific prognostic effect.

CONCLUSION

The strengths of this study include a clinically diverse cohort, substantial numbers of outcome events, restriction to ICI monotherapy, and assessment of both OS and PFS using two adjustment strategies. The availability of FIB-4 components in routine practice also makes the observed association suitable for further evaluation without requiring specialized assays. Several limitations temper its interpretation. The retrospective, single-center design introduces potential selection and information bias, while heterogeneity in tumor biology, treatment line, and subsequent care limits generalizability. Residual confounding remains particularly relevant because ECOG performance status was not included in the reported models, and age, which differed between groups, was not modeled separately. Because age is a component of FIB-4, the observed association should be interpreted as reflecting a composite index rather than an age-independent biomarker. Although the age distribution differed substantially between groups, patients in the high-FIB-4 group were more frequently under 65 years of age. This suggests that the observed association was not simply attributable to an older age distribution; however, the contribution of age cannot be separated from those of aspartate aminotransferase, alanine aminotransferase, and platelet count, and residual age-related confounding remains possible. The absence of direct fibrosis assessment, detailed characterization of chronic liver disease, and cytokine measurements prevents mechanistic interpretation. Complete-case analysis, outcome-driven dichotomization, univariable covariate selection, and multiple exploratory comparisons may also introduce bias or optimism. Departures from proportional hazards for some covariates used for adjustment further complicate the interpretation of constant HRs. Finally, without a non-ICI comparator or external validation, these findings cannot establish a treatment-specific predictive value or justify the clinical use of the selected threshold. Independent studies evaluating continuous FIB-4 and its incremental value beyond established clinical predictors are needed before its role in risk assessment can be defined.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Ege University Clinical Research Ethics Committee (approval number: 26-10T/61, date: 01.10.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Conceptualisation: H.Ç.Y., C.A., G.Ş., Methodology: H.Ç.Y., C.A., G.Ş., B.S.K., Investigation: P.F.A., Data Curation: P.F.A., C.A., G.Ş., Formal Analysis: H.Ç.Y., C.A., Validation: H.Ç.Y., Project Administration: B.S.K., Supervision: B.S.K., Writing - Original Draft: H.Ç.Y., C.A., Writing - Review & Editing: H.Ç.Y., C.A., G.Ş., P.F.A., S.T., B.S.K.

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