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Prognostic significance of FIB-4 versus FIB-5 in non-ST-segment-elevation acute coronary syndrome

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Abstract

The fibrosis-4 (FIB-4) index captures advanced hepatic fibrosis and cardio-hepatic congestion, but its prognostic merit in non-ST-segment-elevation acute coronary syndrome (NSTE-ACS) relative to the newer fibrosis-5 (FIB-5) score is uncertain. In this single-centre retrospective cohort we evaluated 155 consecutive NSTE-ACS patients admitted between 2018–2022. FIB-4 index was dichotomised at the biopsy-validated threshold ≥3.25, whereas FIB-5 index was split at the cohort median −5.1. The primary composite end-point comprised all-cause death, heart-failure, acute kidney injury (AKI), rehospitalisation or revascularisation during a mean follow-up of 50±16 months. Multivariable logistic regression (adjusted for age and sex), receiver-operating-characteristic (ROC) analysis and interaction testing across diabetes, chronic kidney disease (CKD) and age ≥75 years were performed. Thirty-one patients (20 %) had FIB-4≥3.25. The composite end-point occurred in 64.5% vs 36.3% of high- and low-FIB-4 patients (p=0.006). FIB-4≥3.25 remained an independent predictor (adjusted OR 3.14, 95% CI 1.29-7.63; p=0.012) and outperformed FIB-5 (AUC 0.74 vs 0.58; p<0.001). Prognostic value was directionally preserved across diabetes, CKD and elderly strata (all interaction p>0.60). FIB-5 did not predict the composite or any individual component (p>0.30). An admission FIB-4≥3.25 triples the risk of mid-term mortality or major adverse events in NSTE-ACS, whereas FIB-5 is neutral. Incorporating FIB-4 into routine admission workflows could refine GRACE-based triage, spotlight extracardiac vulnerability and identify patients suited to intensified cardio-protective and decongestive strategies.

Keywords: Fibrosis-4 index, Fibrosis-5 index, non-ST-elevation acute coronary syndrome, prognostic biomarkers, risk stratification

Introduction

Non-ST-segment-elevation acute coronary syndrome (NSTE-ACS) remains a leading cause of morbidity and mortality despite contemporary guideline-directed medical therapy (GDMT). Although integrative scores such as Global Registry of Acute Coronary Events (GRACE) score capture ischaemic burden and haemodynamic compromise, residual risk persists, underscoring the need for additional, easily obtainable prognostic indices that reflect systemic pathobiology rather than coronary anatomy alone. Identifying patients at risk for adverse outcomes such as death, revascularisation, rehospitalisation, heart failure (HF), and acute kidney injury (AKI) is essential for effective clinical management. In recent years, liver fibrosis markers such as FIB-4 and FIB-5 have gained attention for their prognostic value beyond liver diseases, including cardiovascular risk prediction [1-4].

Fibrosis-4 (FIB-4) and Fibrosis-5 (FIB-5) are composite indices, not single biomarkers, originally devised to stage hepatic fibrosis. FIB-4 combines age, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet count; FIB-5 integrates albumin, alkaline phosphatase (ALP) , the AST/ALT ratio, platelets and age. Because these variables mirror senescence, hepatocellular injury, thrombopoiesis, and systemic inflammation, they plausibly link hepatic and cardiovascular physiology.

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Raised transaminases accompany myocyte necrosis, low platelets reflect heightened inflammatory consumption, and advancing age amplifies both hepatic and vascular vulnerability. Emerging data therefore situate liver-fibrosis indices at the intersection of the cardio-hepatic axis characterised by congestion, oxidative stress and low-grade inflammation. Consistent with this mechanistic overlap, elevated FIB-4 values have been linked to worse cardiovascular outcomes across several acute coronary syndrome (ACS) cohorts. Multiple Asian and European studies confirmed its independent association with natriuretic-peptide load, adverse remodelling on echocardiography, and a 2- to 3-fold rise in all-cause death after NSTE-ACS.

By contrast, evidence for FIB-5 in coronary populations remains limited. Although a low FIB-5 index independently predicts rehospitalisation and cardiovascular death in acute decompensated HF cohorts, its prognostic value in NSTE-ACS has not been directly compared with that of FIB-4 and therefore warrants investigation [5,6].

Accordingly, we sought to compare the prognostic performance of the FIB-4 versus the newer FIB-5 index for all-cause mortality in NSTE-ACS, and determine whether either index provides incremental value over established clinical scores. Grounded in the cardio-hepatic paradigm, we hypothesised that the inflammation-weighted FIB-4 would correlate more strongly with adverse outcomes than the albumin-weighted FIB-5.

Material and Methods

This is a single-center, observational and retrospective cohort study of 460 consecutive patients diagnosed with NSTE-ACS. Of the 460 consecutive ACS admissions, 305 (66.3%) were excluded owing to incomplete biochemical panels, leaving 155 patients for the final analysis. Between January 2018 and December 2022, we identified 155 patients with NSTE-ACS based on the 2020 ESC criteria, complete admission biochemistry (AST, ALT, platelets, ALP, albumin) and echocardiography, and ≥6-month follow up [7]. Patients with hepatitis, alcohol misuse, malignancy or missing data were excluded. Primary endpoints were death, revascularisation, rehospitalisation, HF and AKI.

FIB-4= (age × AST)/(platelets × √ALT); a cut-off of ≥3.25 defined the high-risk category as per prior cardiovascular literature [8].

FIB-5= (0.3 × albumin + 0.05 × platelets) – (0.014 × ALP + 6 × AST/ALT + 14); the cohort median (-5.1) was used to dichotomise low versus high scores, mirroring validation studies.

Continuous variables are expressed as mean±SD or median (IQR) and compared with Student-t or Mann-Whitney tests; categorical variables as counts (%), compared with χ^2/Fisher exact. Associations between FIB-4 (high vs. low) and outcomes were examined with univariable χ^2 tests and multivariable logistic regression adjusting for age and sex. Correlation between the The GRACE risk score and each hepatic index (FIB-4, FIB-5) was tested with Spearman rank coefficients (ρ), and between-index AUCs were compared by the DeLong method. Discrimination was evaluated with the area under the receiver-operating-characteristic curve (AUC). A two-tailed $P<0.05$ signified statistical significance. SPSS 28.0 was used for statistical analyses.

The study received ethics approval from the Demiroğlu Science University Medical Research Ethics Committee (approval No. 51016662/41201, dated 28 August 2024).

Results

Table 1 summarises demographic, clinical and biochemical variables stratified by FIB-4 category. Patients with FIB-4≥3.25 were older (72.6±10.9 vs 62.3±11.3 years), had higher AST, ALT and creatinine, and markedly lower platelet counts. Traditional cardiac risk factors and left ventricular ejection fraction (LVEF) were comparable between groups.

Table 1. Baseline characteristics according to FIB-4 category

Variable	FIB-4<3.2 (n=124)	FIB-4≥3.25 (n=31)	p-value
Age, ys (mean±SD)	62.3±11.3	72.6±10.9	<0.001
Female sex, n (%)	39 (31.5)	11 (35.5)	0.58
Hypertension, n (%)	64 (51.6)	20 (64.5)	0.14
Diabetes, n (%)	30 (24.2)	7 (22.6)	0.83
Platelet x 10^3/µL	226±62	170±83	<0.01
AST, uL	29 (17-46)	104 (67–145)	<0.01
ALT, uL	26 (15-39)	40 (21–60)	0.03
Serum creatinine, mg/dL	0.96±0.53	1.32±1.38	0.01
LVEF, %	52.5±8.4	49.7±8.7	0.07

ALT: alanine aminotransferase, AST: aspartate aminotransferase, LVEF: left ventricular ejection fraction, ys: years

Event rates for every component of the composite were numerically higher in high FIB-4 group (Table 2), but the gradient was most striking for all-cause mortality and the global composite endpoint. Specifically, 19.4% of high-FIB-4 patients died during the 24-month surveillance period compared with 4.0% in the low FIB-4 cohort, an absolute risk difference of 15.4% and a 4.9 fold unadjusted odds ratio (p=0.010). 64.5% of patients with FIB-4≥3.25 experienced at least one adverse outcome versus 36.3% in the reference group (p=0.006). Multivariable logistic regression confirmed the independent association: after adjusting for age and sex, high FIB-4 conferred a 3.1-fold increase in odds of the composite endpoints(adjusted OR 3.14, 95% CI 1.29-7.63, p=0.012) and 3.8-fold increase in

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odds of the mortality endpoints(adjusted OR 3.80, 95% CI 1.11-13.50, p=0.035).

Table 2. Endpoints by FIB-4 category

Outcome	FIB-4<3.25	FIB-4≥3.25	p-value
Death	5 (4.0%)	6 (19.4%)	<0.05
Heart failure	12 (9.7%)	7 (22.6%)	0.10
Rehospitalisation	31 (25.0%)	8 (25.8%)	0.94
Revascularisation	16 (12.9%)	2 (6.5%)	0.49
AKI	13 (10.5%)	5 (16.1%)	0.57
Composite	45 (36.3%)	20 (64.5%)	<0.05
	Mortality-adjusted OR	**95% CI**	**p-value**
Age (per year)	1.04	0.99-1.09	0.11
Female sex	10.06	1.06-95.5	<0.05
FIB-4≥3.25	3.80	1.11-13.50	<0.05
	Composite endpoint-adjusted OR	**95% CI**	**p-value**
Age (per year)	1.02	0.69–3.19	0.15
Female sex	1.48	0.69–3.19	0.31
FIB-4≥3.25	3.14	1.29–7.63	<0.05

AKI: acute kidney injury, CI: confidence interval, FIB-4: the fibrosis-4 index, OR: odds ratio

Table 3 summarises the prognostic performance of the FIB-5 index. When the cohort was dichotomised at the median value (-5.1), patients in the high FIB-5 group (≥-5.1) showed only a modest, non-significant excess of events: the multivariable model that adjusted for age and sex yielded an odds ratio of 1.23 for the composite endpoint (95% CI 0.64–2.38; p=0.54) and 1.74 for all-cause mortality (95% CI 0.46–6.62; p=0.41).

Table 3. Endpoints by FIB-5 category

Outcome	FIB-5<-5.1 (n=78)	FIB-5≥-5.1 (n=77)	p-value
Death	4 (5.1%)	7 (9.1%)	0.35
Heart failure	10 (12.8%)	9 (11.7%)	0.85
Rehospitalisation	9 (11.5%)	9 (11.7%)	0.97
Revascularisation	19 (24.4%)	20 (26.0%)	0.83
AKI	8 (10.3%)	10 (13.0%)	0.63
Composite	30 (38.5%)	35 (45.5%)	0.38

AKI: acute kidney injury, FIB-5: the fibrosis-5 index

At the validated cut-off FIB-4≥3.25, the sensitivity and specificity for the composite end-point were 71 % and 69%, respectively, whereas the cohort-median cut-off FIB-5≤-5.1 yielded a modest sensitivity of 583% and specificity of 52% (Figure 1).

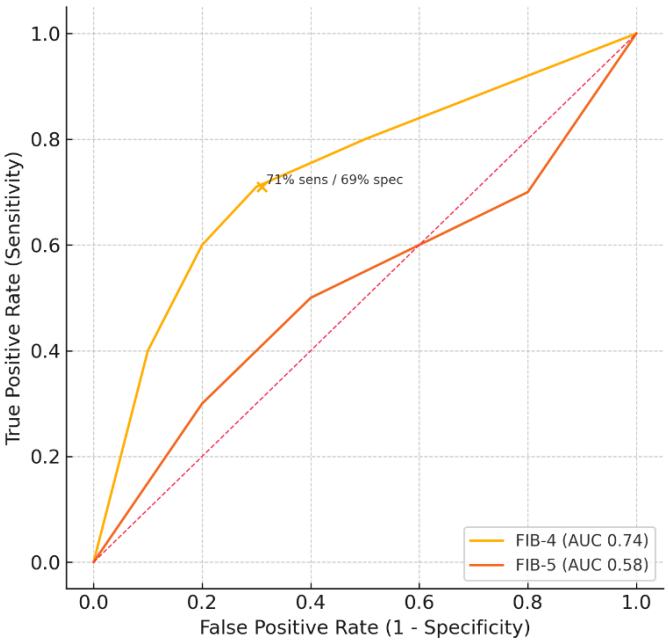

Figure 1. Receiver-operating-characteristic (ROC) curves comparing FIB-4 and FIB-5 for prediction of the composite end-point in 155 NSTE-ACS patients

In the correlation analysis, FIB-4 demonstrated a moderate, positive association with the GRACE score (Spearman ρ=0.42, p<0.001), whereas FIB-5 showed no significant correlation (ρ=0.07, p=0.28). Concordantly, FIB-4 provided superior discrimination for the composite outcome compared with FIB-5 (AUC=0.74 [0.67–0.81] vs 0.58 [0.50–0.66]; p<0.001) (Table 4).

Table 4. Correlation of FIB-4 and FIB-5 with the GRACE risk score and their ROC discrimination for the composite end-point

	Pearson r (vs GRACE)	Spearman ρ (vs GRACE)	p-value	ROC AUC (95% CI)
FIB-4	0.62	0.42	<0.001	0.74 (0.67–0.81)
FIB-5	0.09	0.07	0.28	0.58 (0.50–0.66)

AUC 0.74 vs 0.58; p<0.001; AUC: area under the curve, CI: confidence interval, FIB-4: the fibrosis-4 index, FIB-5: the fibrosis-5 index, GRACE: global registry of acute coronary events, ROC: receiver operating characteristic

Because an inappropriate threshold might obscure a true signal, we re-examined the data using the optimal Youden cut-off identified by ROC analysis (-4.7). This data-driven threshold increased the area under the ROC curve from 0.55 to 0.57, but discrimination remained poor and failed to reach statistical significance (p=0.21).

When the cohort was stratified by diabetes status, chronic kidney disease (CKD; serum creatinine≥1.3 mg/dL) and age≥75 years, the association between an admission FIB-4 score≥3.25 and the composite endpoint remained directionally consistent (Table 5). Point estimates for the odds-ratio (OR) ranged from 0.80

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to 2.00 across strata, but none of the interaction terms reached statistical significance (all p>0.60), indicating no evidence that the prognostic value of FIB-4 differed materially across these clinically relevant subgroups.

Table 5. Exploratory subgroup analysis: association of FIB-4≥3.25 with the composite endpoint within key clinical subgroups in NSTE-ACS

Subgroups	Absent FIB-4≥3.25 OR (95% CI)	Present FIB-4≥3.25 OR (95 % CI)	p-value
Diabetes	1.25 (0.51–3.07)	2.00 (0.38–10.58)	0.625
CKD	1.32 (0.55–3.15)	0.80 (0.06–11.50)	0.726
Age≥75 years	1.28 (0.44–3.72)	0.91 (0.23–3.62)	0.702

CI: confidence interval, CKD: chronical kidney disease, FIB-4: the fibrosis-4 index, OR: odds ratio

Discussion

Several recent cardiology focused papers have indeed stratified FIB-4 below the advanced fibrosis zone, most commonly using<1.30, 1.30–2.67 and >2.67 [2,9]. In a 3 100-patient ACS registry these bands comprised 2 899, 122 and 85 individuals, respectively; similar break-points were adopted in acute-MI cohorts. Such low thresholds maximise sensitivity for any hepatic insult yet dilute specificity when liver dysfunction is not the primary end-point.

Our aim was therefore to determine whether frank, biopsy-validated fibrosis (FIB-4≥3.25) amplifies risk in NSTE-ACS. The original derivation study showed that≥3.25 yields 97% specificity for advanced fibrosis, and NSTE-ACS cohorts using this cut-off reported higher NT-proBNP, more heart-failure admissions and excess mortality over ≈ 4 years [8]. However, the same threshold delivered lower specificity in our series (69%) because the reference standard differed: the hepatic study used histological stage, whereas we modelled cardiovascular events that also elevate AST and lower platelets after myocardial injury; this broader cardio-hepatic overlap inevitably increases sensitivity at the expense of absolute specificity. Given our older population (median age≥65 y) and the overlap between congestion, hepatic hypoperfusion and adverse cardiac outcomes, we prioritised a rule-in threshold that flags established fibrosis rather than mild transaminase leaks.

FIB-4≥3.25 identified patients with a 3-fold, age- and sex-adjusted increase in the composite end-point, driven chiefly by death and HF. That risk magnitude is comparable to the excess conferred by chronic kidney disease or a prior myocardial infarction in modern secondary prevention cohorts. Age integrates cumulative metabolic and inflammatory stress; AST records synchronous hepatocellular and cardiomyocyte necrosis; and thrombocytopenia reflects portal hypertension, systemic inflammation and impaired thrombopoiesis. Together these variables distil a cardio-hepatic vulnerability signal that liver-agnostic tools overlook [10]. Concordantly, a large heart failure with preserved ejection fraction (HfpEF) registry reported a 28% rise in right-ventricular dysfunction for every 1-point increment in FIB-4, underscoring shared haemodynamic pathways between venous congestion and fibrotic liver injury [11]. In NSTE-ACS, sub-endocardial ischaemia and raised right-sided pressures precipitate hepatic congestion and ischaemic hepatitis; these insults boost AST and depress platelet counts in a feed-forward loop that drives FIB-4 upward [12]. Unsurprisingly, elevated FIB-4 paralleled the SYNTAX score in predicting post-MI mortality while remaining entirely bedside-based [6]. Our post-hoc subgroup analysis confirmed that the excess risk associated with FIB-4≥3.25 persisted across diabetes, CKD and elderly strata (all p>0.60), reinforcing its applicability even in comorbidity-rich phenotypes. The ≥3.25 threshold itself comes from the original biopsy-validated derivation study, where it delivered 97% specificity for advanced fibrosis [8]. Its biological plausibility is strengthened by the high prevalence of metabolically driven NAFLD, oxidative stress and insulin resistance in ACS populations [13].

Why did FIB-5 fail? Its equation rewards albumin and platelets but subtracts alkaline-phosphatase (ALP) and the AST/ALT ratio, and it omits any age term. Albumin and ALP evolve slowly in the acute phase; they mainly reflect chronic mal-nutrition, cholestasis or micro-vascular hepatic congestion rather than the abrupt haemodynamic insult of plaque rupture. Consequently, the score compresses toward the mean and loses granularity when early triage is critical. A meta-analysis showed that albumin discriminates risk only when values are already<3.5 g/dL [14]; in our cohort most patients presented with normal albumin, so the positive coefficient (0.3 × albumin) pushed FIB-5 values toward the null. Elevated ALP, although independently linked to in-hospital death after PCI, failed to improve the GRACE model in >6 000 ACS patients [15]. Similar null findings have been reported in transcatheter-aortic-valve-replacement populations, where FIB-5 was non-prognostic whereas FIB-4 retained independent predictive value [16]. Lacking age or inflammatory weighting, FIB-5 under-represents frailty and systemic stress, explaining its lack of discrimination in our series.

The GRACE score remains the benchmark for early NSTE-ACS risk-stratification (c-statistics ≈ 0.80) [17-19]. In our data GRACE correlated moderately with FIB-4 (ρ=0.42) but not with FIB-5, indicating that the age–AST–platelet triad supplies incremental information on systemic vulnerability and venous congestion while dovetailing with variables already embedded in GRACE. A Spanish registry likewise showed higher GRACE scores and doubled in-hospital mortality among patients with FIB-4>2.67 [2]. Collectively, these data position FIB-4 as a simple, inexpensive adjunct that can refine GRACE-based triage in contemporary NSTE-ACS.

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Routine calculation of FIB-4 at admission offers a rapid, cost-free gauge of extracardiac frailty. An electronic flag for FIB-4≥3.25 could prompt early optimisation of GDMT, including timely initiation and aggressive up-titration of SGLT2 inhibitors, ARNIs and high-intensity statins [20,21]. The same phenotype may enrich mechanistic or therapeutic trials targeting systemic inflammation, hepatic congestion or modulation of the cardio-renal-hepatic axis. Embedding FIB-4 in discharge summaries could also alert primary-care teams to latent NAFLD, triggering lifestyle counselling and hepatology referral.

Prospective, multicentre studies with serial FIB-4 sampling, at baseline, 48 h and pre-discharge combined with cardiac MRI for infarct quantification are warranted to map temporal dynamics and causality. Machine-learning models that integrate FIB-4 with continuous haemodynamic telemetry, natriuretic peptides and high-sensitivity CRP may enable precision risk-profiling [22]. Finally, interventional trials should test whether therapeutic strategies that lower FIB-4, through aggressive decongestion, SGLT2-mediated natriuresis or emerging anti-fibrotic agents, translate into hard outcome gains [23,24], thereby moving FIB-4 from a passive marker to an actionable treatment target.

Conclusion

In this real-world NSTE-ACS cohort, an admission FIB-4≥3.25 tripled the odds of all-cause death and major adverse cardiovascular events, whereas the albumin-weighted FIB-5 index was prognostically neutral despite its reported value in HF populations. By demonstrating that FIB-4, but not FIB-5, adds independent, cardio-hepatic information on top of traditional scores such as GRACE, our study broadens the clinical relevance of liver-derived biomarkers in ischaemic heart disease. Because FIB-4 is cost-free and calculated from routine chemistry, embedding an automatic FIB-4 alert in admission workflows could flag vulnerable patients earlier, prompt more aggressive guideline-directed therapy, and offer a practical enrichment strategy for future trials targeting inflammation or venous congestion.

Study Limitations

This study has several limitations. First, because it is a retrospective, single-centre analysis, hidden confounders cannot be ruled out. Because cardio-hepatic physiology may vary across healthcare systems and ethnicities, a prospective multicentre study with harmonised laboratory timing and adjudicated outcomes is now warranted. Second, we had only one FIB-4 measurement per patient, so we could not see whether the score rises or falls after discharge. Finally, we did not have liver imaging, so we could not link FIB-4 values to actual structural changes.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study received ethics approval from the Demiroğlu Bilim University Medical Research Ethics Committee (approval No. 51016662/41201, dated 28 August 2024).

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