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ORIGINAL ARTICLE

Evaluating Neutrophil-to-albumin ratio Association with Clinical Outcomes in Acute Pancreatitis: A MIMIC-IV Based Retrospective Study

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ABSTRACT

Background: The Neutrophil-to-albumin ratio (NPAR), a novel inflammatory-nutritional composite index, has recently demonstrated prognostic utility across various pathological conditions. The relationship between NPAR and the severity or mortality of acute pancreatitis (AP) remains unclear, despite the increasing clinical importance of this condition.

Aim: To evaluate the relationship between NPAR levels and 28-day mortality outcomes among hospitalized acute pancreatitis patients.

Methods: This retrospective cohort study utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to evaluate how well NPAR predicts outcomes in acute pancreatitis. The key endpoint was mortality within 28 days, analyzed using multivariable Cox regression to evaluate the independent prognostic importance of NPAR after controlling for significant covariates. Stratified analyses further explored whether this relationship remained robust across clinically relevant subpopulations.

Results: Multivariable Cox regression analysis of 474 eligible acute pancreatitis patients, adjusted for age, sex, race, and comorbidities, demonstrated a significant dose-dependent association between elevated NPAR levels and 28-day all-cause mortality. Compared to the low- NPAR reference group (<25), patients in the intermediate-NPAR group (25-30.9) exhibited a 1.1-fold increased mortality risk (adjusted HR: 2.1; 95% CI: 1.1-4.02; p=0.025), while those in the high NPAR group (≥31) showed a 1.2-fold higher risk (adjusted HR: 2.2; 95% CI: 1.19-4.1; p=0.012). Kaplan-Meier analysis revealed significantly different survival curves among NPAR groups (log-rank p=0.037), with the highest NPAR group showing the poorest survival.

Conclusions: NPAR may serve as a novel prognostic biomarker for acute pancreatitis, although its clinical applicability still needs to be validated in a large number of prospective multicenter studies

Keywords: Acute pancreatitis, neutrophil-to-albumin ratio (NPAR), multiple parameters, mortality, prognosis, biomarkers

INTRODUCTION

Acute pancreatitis, characterized by sudden pancreatic inflammation, represents a leading cause of gastrointestinal hospitalization worldwide. While mild cases typically resolve spontaneously, severe acute pancreatitis (SAP) carries substantial mortality (15-20% in necrotizing forms) due to systemic complications[1,2]. Current prognostic systems (e.g., BISAP, APACHE-II) demonstrate limitations in early risk stratification, particularly in resource-limited settings[3]. NPAR has recently emerged as a potential prognostic marker, integrating both inflammatory response and nutritional status - two critical pathophysiological axes in AP progression. Unlike conventional biomarkers, NPAR offers the advantage of being derived from routine laboratory parameters without additional costs. Recent evidence suggests its predictive value in sepsis and critical illnesses, but its application in pancreatitis remains underexplored. This study investigates NPAR prognostic performance for 28-day mortality in AP patients. Our findings aim to address the pressing need for accessible, early prognostic

tools that can facilitate timely intensive care referrals and personalized treatment approaches for SAP patients.

Current prognostic scoring systems for AP, including the widely adopted APACHE-II and BISAP indices, present notable clinical implementation challenges despite their established use in severity assessment. These scoring systems incorporate multiple parameters, some of which lack direct relevance to AP pathophysiology. Furthermore, their complexity often delays timely assessment, particularly in emergency settings where rapid decision-making is crucial. This frequently results in missed opportunities for early intervention during the critical therapeutic window. Recent studies have highlighted these limitations, demonstrating suboptimal sensitivity (68-72%) for severe AP prediction within the first 48 hours of admission. Such diagnostic delays contribute significantly to poorer outcomes, emphasizing the need for more specific and efficient prognostic tools that can facilitate prompt risk stratification and guide early targeted therapies in AP management.

Neutrophils, as primary mediators of innate immunity, serve as sensitive indicators of systemic infection severity through their quantitative and functional responses[4,5]. Albumin, constituting 50-60% of plasma proteins, exhibits dynamic regulation through hepatic synthesis, intravascular-extravascular distribution, and catabolic rates[6,7]. The systemic inflammatory cascade of SIRS induces microvascular dysfunction, promotes enhanced endothelial albumin flux and subsequent interstitial edema formation[8,9]. This pathophysi- ological cascade arises through multiple concurrent mechanisms: cytokine-mediated vascular leakage, oxidative albumin modification, suppressed hepatic synthesis (negative acute-phase response) and enhanced lysosomal degradation[10,11]. The resultant hypoalbuminemia (<3.5g/dL) not only reflects inflammatory burden but also exacerbates tissue injury through compromised oncotic pressure and antioxidant capacity, creating a vicious cycle in critical illness. Emerging evidence indicates NPAR prognostic value extends across multiple pathological conditions, demonstrating significant associations with clinical outcomes in renal, neurological, cardiovascular, and infectious disease processes[10-15]. However, NPAR has not been reported to predict the clinical outcome of AP.

Thus, we conducted a retrospective cohort study to evaluate how well NPAR predicts 28-day mortality in patients with AP.

METHODS

Data Sources

This study utilized clinical data extracted from the MIMIC-IV database (version 2.2), which complies with HIPAA privacy standards by fully anonymizing all patient records. Obtain approval from the institutional Review Board before obtaining data

Study population and definition of NPAR

AP cases were detected using diagnostic codes from the International Classification of Diseases, Ninth Revision (ICD-9). The study cohort was restricted to adult patients (≥18 years) with first-time ICU admissions. Exclusion criteria comprised: (1) ICU stays <48 hours, and (2) absence of essential clinical data required for analysis. Patients were excluded for: (1) unavailable neutrophil percentage or serum albumin measurements during ICU admission, or (2) extensive missing data (>10% of key variables). NPAR was derived as the quotient of neutrophil percentage (obtained from complete blood count) and serum albumin concentration (g/dL), with both values extracted from the first available laboratory results following ICU admission. The final analytic cohort included 474 eligible patients after applying these criteria.

Data Extraction and Outcomes

We extracted demographic characteristics (age, sex), clinical parameters (SpO_2, mechanical ventilation, CRRT), and admission laboratory values (complete blood count, lactate, BE, AG, renal function tests, coagulation profile, albumin). Comorbid conditions included chronic organ diseases (kidney, liver, heart, lung) and diabetes mellitus. Disease severity was quantified using SAPS II and SOFA scores.

Definition and Endpoint

NPAR was computed as the neutrophil-to-albumin ratio using initial ICU laboratory results and categorized into tertiles for analysis. The primary endpoint was 28-day mortality.

Statistical Analysis

We examined potential nonlinear relationships using restricted cubic splines. Survival outcomes were compared using Kaplan-Meier analysis with log-rank tests. The NPAR-mortality association was assessed through Cox regression, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). Three progressively adjusted models were analyzed: (1) unadjusted, (2) demographic-adjusted, and (3) fully adjusted (including clinical covariates). Subgroup analyses evaluated consistency across age, race, sex, and comorbidity strata. All analyses utilized R 4.2.2 (R Foundation) and Free Statistics 2.1.1, with a two-tailed statistical significance level set at $\alpha=0.05$. Effect estimates are expressed in terms of hazard ratios and 95% confidence intervals.

RESULTS

Baseline characteristics of the study population

Our study cohort was derived from the MIMIC-IV database. From an initial pool of 1,700 acute pancreatitis cases, we applied the following exclusion criteria: (1) 420 patients without first-time ICU admissions; (2) 270 patients lacking complete neutrophil percentage or albumin measurements; and (3) 536 patients with either hospital or ICU stays shorter than 24 hours. After these exclusions, our final analytical cohort comprised 474 eligible participants. The complete selection process is illustrated in Figure 1 (exclusion flowchart).

The baseline features of the study group are detailed in Table 1, revealing an 18.8% (89/474) mortality incidence within the 28-day follow-up period. Participants had a mean age of 56.3±16.9 years, with male predominance (56.8%) and a majority Caucasian population (72.1%).Based on NPAR quantiles, we stratified patients into three groups: low (NPAR < 25), medium (25 ≤ NPAR < 31), and high (NPAR ≥ 31). Comparative analysis revealed that the high NPAR group demonstrated significantly elevated neutrophil percentages (85.1±6.7% vs 70.3±18.4%, p<0.001) and reduced albumin levels (2.2 ± 0.4 g/dLvs 3.3 ± 0.6 g/dL, p<0.001) compared to the low NPAR group. Clinically, the high NPAR group showed both higher 28-day mortality rates (24.7% vs 13.3%, p<0.05).

Cox regression analysis

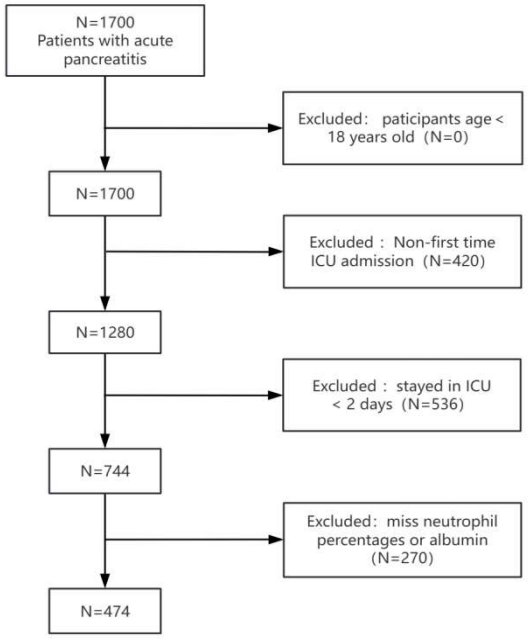
By employing multivariable Cox regression analysis, taking the low-NPAR group as a reference, we identified a notably increased risk of mortality linked to higher NPAR levels in ICU patients diagnosed with AP (Table 2).

In the crude model, the high-NPAR group exhibited a 97% higher mortality risk compared to the reference group (HR = 1.97; 95% CI: 1.16-3.34). The association persisted in models with sequential adjustment for potential confounding variables. Model I (minimally adjusted) revealed hazard ratios of 1.79 (95% CI: 0.95-3.39) for the mid-NPAR group and 2.23 (95% CI: 1.21-4.08) for the high-NPAR group. Following comprehensive adjustment in Model II, the corresponding HRs were 2.1 (95% CI: 1.1-4.02) and 2.2 (95% CI: 1.19-4.1) for the mid- and high-NPAR groups, respectively.

Restricted cubic splines analysis

We analyzed the NPAR-mortality relationship using restricted cubic splines to assess potential dose-response effects in acute pancreatitis patients. After full adjustment for potential confounders ,we observed a linear dose-response relationship between NPAR and mortality. (P for nonlinearity = 0.646; Figure 2). The linear trend persisted across the entire spectrum of NPAR values, suggesting a consistent mortality risk elevation with higher NPAR levels.

Fig. 1: Schematic diagram outlining participant enrollment, group allocation, and selection criteria. The flowchart delineates inclusion/exclusion processes, culminating in 474 eligible subjects with complete data for final analysis.



Kaplan–Meier analysis

The study included 474 acute pancreatitis patients, with 89 deaths (18.8%) occurring within 28 days (Table 1). Mortality rates differed significantly across NPAR tertiles (P=0.034), with the highest mortality observed in the high-NPAR group (24.7%, 39/158) compared to the mid-NPAR (18.4%, 29/158) and low-NPAR groups (13.3%, 21/158). The Kaplan-Meier analysis indicated a notably lower survival rate at 28 days among patients with high NPAR compared to the other groups (log-rank P=0.037; Figure 3).

Subgroup analyses

Given the significant heterogeneity in baseline characteristics across study groups, we conducted detailed subgroup analyses to assess the consistency of the NPAR-mortality association within clinically relevant strata, such as age, sex, and major comorbidities (Table 3). After full multivariable adjustment, elevated NPAR continued to show a robust association with increased 28-day mortality in most predefined subgroups. However, we identified significant effect modification by severe liver disease status (P for interaction = 0.012), indicating a differential mortality risk association in this subpopulation.

Table 1. Baseline characteristics of study participants stratified by NPAR quartiles

Characteristics	Total (n = 474)	Quartile of NPAR			P Value
		Quartile 1(n = 158) NPAR＜25	Quartile 2 (n = 158) 25≤NPAR＜31	Quartile 3 (n = 158) NPAR≥31	
Demographic					
Age（year）	56.3 ± 16.9	54.7 ± 18.3	54.8 ± 16.2	59.3 ± 15.8	0.02
Gender, n (%)					0.457
Female	205 (43.2)	62 (39.2)	72 (45.6)	71 (44.9)	
Male	269 (56.8)	96 (60.8)	86 (54.4)	87 (55.1)	
Race, n (%)					0.966
White	212 (44.7)	70 (44.3)	72 (45.6)	70 (44.3)	
Other	262 (55.3)	88 (55.7)	86 (54.4)	88 (55.7)	
Laboratory parameters					
BUN,（mg/dL）	22.0 (13.0, 39.8)	23.0 (12.0, 37.8)	23.0 (14.0, 39.8)	22.0 (13.0, 42.5)	0.947
Scr,（mg/dL）	1.1 (0.7, 2.2)	1.1 (0.7, 2.2)	1.1 (0.8, 2.2)	1.2 (0.7, 2.2)	0.995
Glucose,（mg/dL）	134.0 (104.0, 180.0)	131.0 (101.2, 182.5)	137.5 (107.5, 176.5)	135.5 (101.5, 179.5)	0.863
Albumin,(g/L)	2.8 ± 0.6	3.3 ± 0.6	2.9 ± 0.4	2.2 ± 0.4	< 0.001
Lymphocyte,（%）	7.3 (4.0, 12.0)	11.0 (7.5, 18.0)	6.2 (4.0, 10.0)	5.0 (3.0, 9.0)	< 0.001
Neutrophil,（%）	78.9 ± 14.0	70.3 ± 18.4	81.3 ± 9.6	85.1 ± 6.7	< 0.001
APTT, (s)	37.1 ± 18.9	36.8 ± 19.6	35.3 ± 16.1	39.1 ± 20.5	0.193
INR,(s)	1.6 ± 1.0	1.7 ± 1.0	1.7 ± 1.1	1.6 ± 0.9	0.879
PT, (s)	17.8 ± 10.2	17.9 ± 9.8	18.1 ± 12.1	17.4 ± 8.3	0.843
Lactate,(mmol/L)	1.8 (1.2, 3.3)	2.0 (1.3, 3.9)	1.6 (1.1, 2.8)	1.9 (1.1, 3.1)	0.108
AG, (mmol/L)	16.6 ± 5.6	17.6 ± 5.8	16.8 ± 6.0	15.3 ± 4.8	0.001
BE, (mmol/L)	-3.0 (-8.0, 0.0)	-3.0 (-8.0, 0.0)	-3.0 (-8.0, 0.0)	-3.0 (-8.0, 0.0)	0.95
Vital signs					
Spo2, (%)	95.9 ± 4.3	95.7 ± 4.8	95.8 ± 4.2	96.2 ± 3.8	0.602
Heart rate, (bests/min)	104.5 ± 22.7	102.6 ± 23.1	104.0 ± 20.7	106.9 ± 24.1	0.235
Treatment					
Crrt, n (%)					0.515
No	349 (73.6)	112 (70.9)	121 (76.6)	116 (73.4)	
Yes	125 (26.4)	46 (29.1)	37 (23.4)	42 (26.6)	
Ventilato, n (%)					
No	38 (8.0)	14 (8.9)	10 (6.3)	14 (8.9)	
Yes	436 (92.0)	144 (91.1)	148 (93.7)	144 (91.1)	0.633
Scoring systems					
SOFA	7.2 ± 4.3	7.6 ± 4.4	6.7 ± 4.2	7.4 ± 4.4	0.133
SAPS Ⅱ	42.1 ± 17.0	41.8 ± 18.0	39.2 ± 15.5	45.3 ± 17.1	0.006
Comorbidities					
Congestive heart failure, n(%)					0.594
NO	381 (80.4)	124 (78.5)	131 (82.9)	126 (79.7)	
Yes	93 (19.6)	34 (21.5)	27 (17.1)	32 (20.3)	
Chronic pulmonary disease, n (%)					0.512
NO	376 (79.3)	124 (78.5)	130 (82.3)	122 (77.2)	
Yes	98 (20.7)	34 (21.5)	28 (17.7)	36 (22.8)	
Diabetes, n (%)					0.433
NO	330 (69.6)	112 (70.9)	104 (65.8)	114 (72.2)	
Yes	144 (30.4)	46 (29.1)	54 (34.2)	44 (27.8)	
Renal disease					0.599
NO	385 (81.2)	128 (81)	132 (83.5)	125 (79.1)	
Yes	89 (18.8)	30 (19)	26 (16.5)	33 (20.9)	
Severe liver disease					0.513
NO	397 (83.8)	128 (81)	134 (84.8)	135 (85.4)	
Yes	77 (16.2)	30 (19)	24 (15.2)	23 (14.6)	

AKI, n (%)					0.225
NO	58 (12.2)	20 (12.7)	24 (15.2)	14 (8.9)	
Yes	416 (87.8)	138 (87.3)	134 (84.8)	144 (91.1)	
Outcomes					
28-day mortality					0.034
No	385 (81.2)	137 (86.7)	129 (81.6)	119 (75.3)	
Yes	89 (18.8)	21 (13.3)	29 (18.4)	39 (24.7)	

Table 2. The relationship between NPAR and 28-day mortality risk.

Variable	Crude model		Model I		Model II	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
NPAR as continuous	1.03 (1.01~1.05)	0.001	1.03 (1~1.05)	0.008	1.03 (1~1.05)	0.004
NPAR＜25	1(Ref)		1(Ref)		1(Ref)	
25≤NPAR＜31	1.41 (0.81~2.48)	0.229	1.79 (0.95~3.39)	0.073	2.1 (1.1~4.02)	0.025
NPAR≥31	1.97 (1.16~3.34)	0.012	2.23 (1.21~4.08)	0.01	2.2(1.19~4.1)	0.012

Crude Model was not Adjusted

Model I was adjusted forage+ gender+ race+BUN+Cr+glucose+ LYM+Lac+AG+BE+INR+PT+ APTT+heartrate+spo2+crrt.

Model II was adjusted for model 1 +sofa+sapsii+congestive heart failure+ chronic pulmonary disease+ diabetes+ severe liver disease+renal disease +AKI.

Figure 2. The smoothed curve was generated using generalized additive models with restricted cubic splines. There was a linear dose-response relationship between NPAR and mortality.

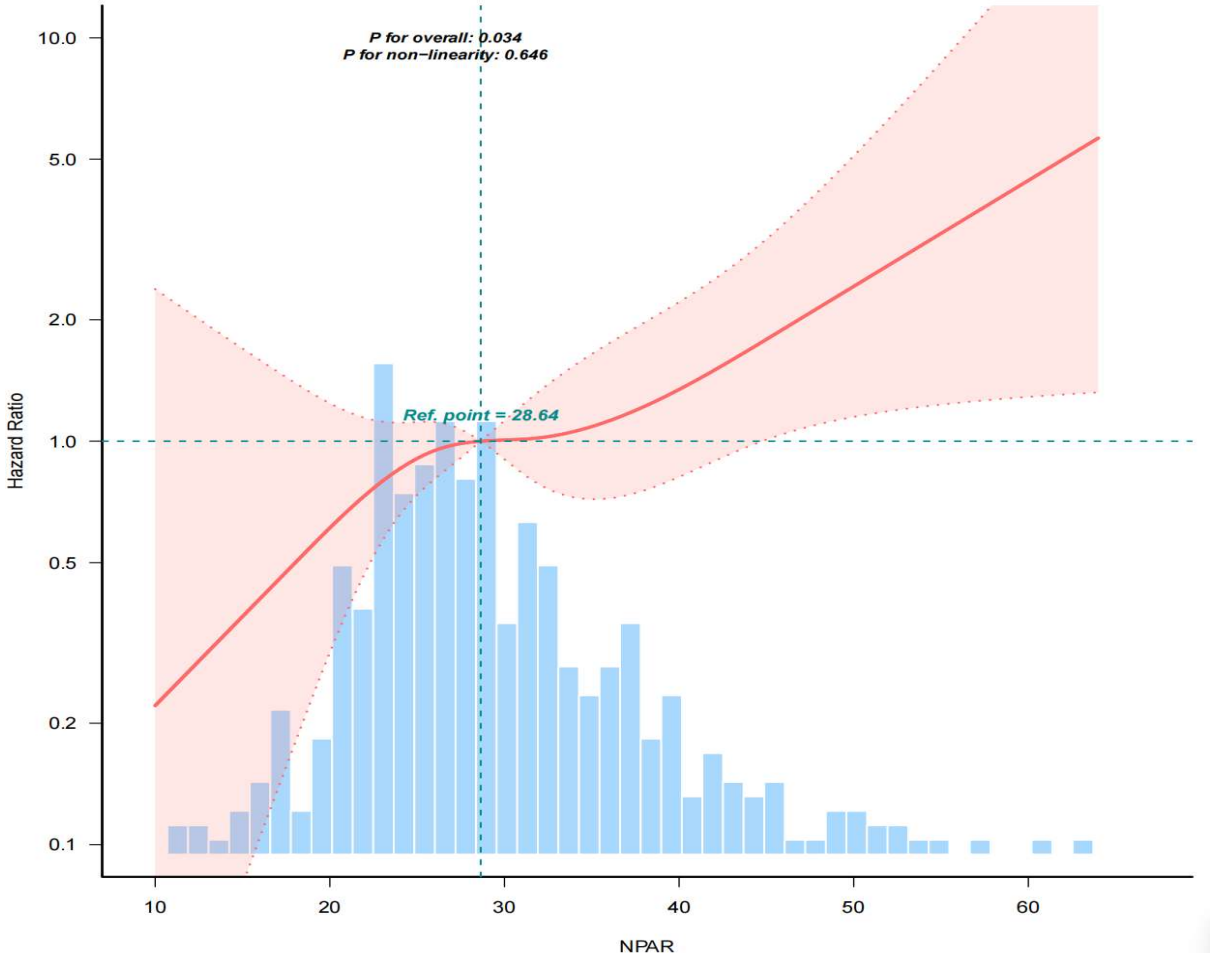


Figure 3. Kaplan-Meier survival analysis stratified by NPARtertiles in acute pancreatitis patients. The curves reveal significantly divergent 28-day survival patterns across NPAR categories (log-rank P=0.037)

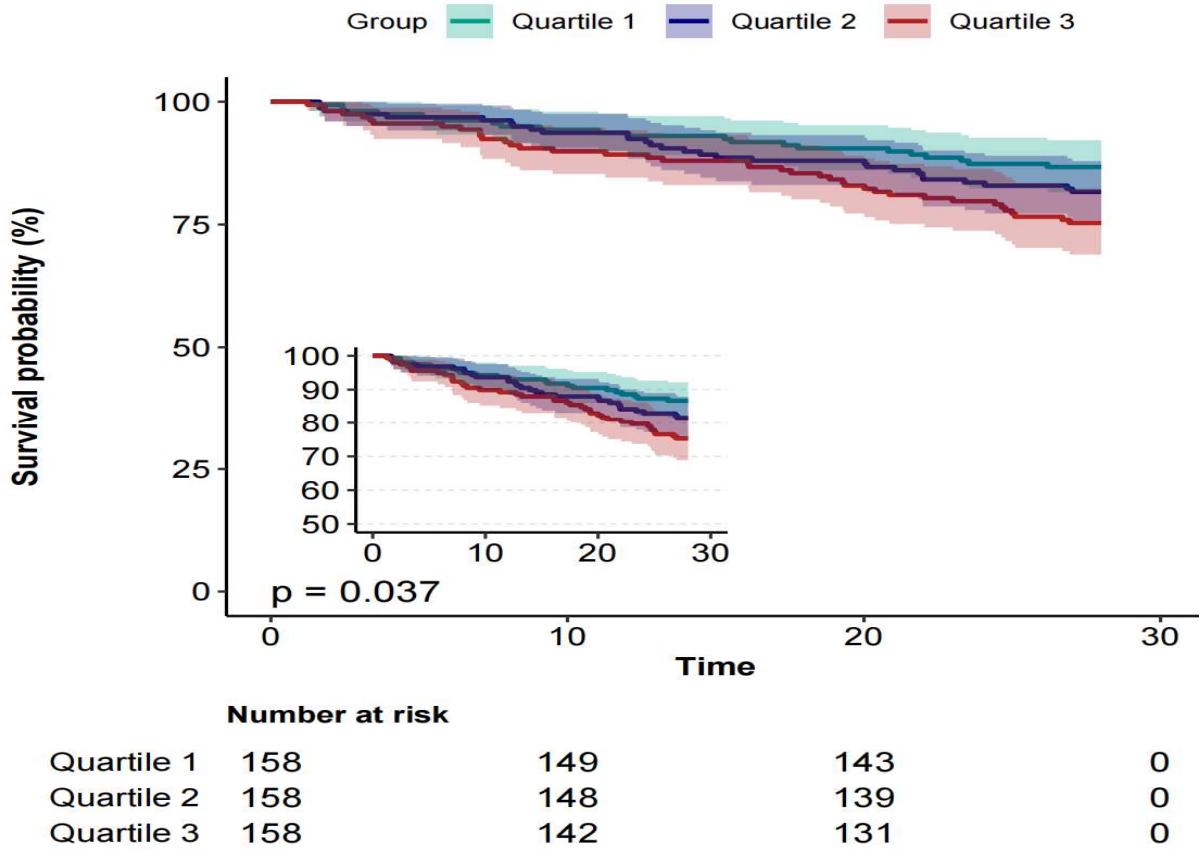


Table 3. Stratified analyses evaluating the association between NPAR and 28-day mortality across clinically relevant subgroups

Subgroup	n	Fully adjusted HR (95%CI)			P for interaction
		Quartile 1	Quartile 2	Quartile 3	
Gender					0.07
Female	205	1(Ref)	1.14(0.39~3.32)	1.48(0.48~4.5)	
Male	269	1(Ref)	2.91 (1.09~7.77)	2.23 (0.92~5.39)	
Race					0.208
White	212	1(Ref)	4.41 (1.46~13.28)	7.48 (2.72~20.56)	
Other	262	1(Ref)	1.35 (0.51~3.61)	1.39 (0.57~3.43)	
Age					0.537
＜65	326	1(Ref)	1.04(0.36~3.03)	2.39 (0.83~6.93)	
≥65	148	1(Ref)	4.33(1.58~11.87)	2.81(1.08~7.33)	
Congestive heart failure					0.399
NO	381	1(Ref)	1.76 (0.82~3.75)	1.66(0.78~3.53)	
Yes	93	1(Ref)	5.82 (1.1~30.7)	7.22 (1.35~38.64)	
Renal disease					0.599
NO	385	1(Ref)	2.25 (0.96~5.26)	3.01 (1.35~6.72)	
Yes	89	1(Ref)	5.98 (1.4~25.59)	2.89 (0.74~11.38)	
Severe liver disease					**0.012**
NO	397	1(Ref)	4.88 (1.93~12.33)	4.64 (1.89~11.39)	
Yes	77	1(Ref)	0.4 (0.05~2.89)	0.7 (0.15~3.16)	
CRRT					0.78
NO	349	1(Ref)	2.42 (0.76~7.72)	2.99 (1.01~8.9)	
Yes	125	1(Ref)	1.65 (0.65~4.24)	3.43 (1.15~3.03)	

DISCUSSION

This study is, to our knowledge, the first to systematically establish NPAR as an independent predictor of 28-day mortality in AP.Our study found a significant dose-dependent link between elevated NPAR levels and a higher risk of mortality, even after adjusting for demographic factors, clinical conditions, and illness severity. Restricted cubic spline analysis demonstrated a significant linear dose-response relationship between NPAR and mortality risk (P for nonlinearity =0.646) .Kaplan-Meier analysis corroborated these findings, demonstrating graded reductions in 28-day survival with increasing NPAR tertiles (log-rank P=0.037).

Acute pancreatitis (AP) represents a profoundly inflammatory condition characterized by dysregulated systemic immune activation. The underlying pathophysiology involves dysactivation of white blood cells, triggering a cascade of pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) leading to systemic inflammatory response syndrome (SIRS)[16-18]. Notably, this inflammatory milieu promotes robust neutrophil chemotaxis to pancreatic tissue, where these cells exacerbate local damage through multiple mechanisms: (1) release of proteolytic enzymes, (2) excessive reactive oxygen species production, and (3) pathological neutrophil extracellular trap (NETs) formation. These processes collectively contribute to the progression from localized pancreatic injury to multiorgan dysfunction syndrome (MODS), particularly in severe AP cases. Neutrophils serve as primary effector cells of innate immunity, playing a pivotal role in systemic inflammatory responses to infection[19-21].

As key effector cells of innate immunity, neutrophils mediate diverse immune and inflammatory processes while orchestrating integrated host defense responses[22]. Leukocyte infiltration amplifies the inflammatory cascade through enhanced chemokine and cytokine secretion, exacerbating systemic inflammation. Substantial clinical evidence implicates neutrophil infiltration as a primary driver of multiple organ dysfunction in acute pancreatitis (AP)[23].

Albumin, a key plasma protein, serves dual roles as both a nutritional marker and a critical regulator of systemic inflammation. Beyond maintaining oncotic pressure, it modulates inflammatory responses by transporting pro- and anti-inflammatory mediators, exhibits potent antioxidant activity through free radical scavenging, neutralizes endotoxins and preserves endothelial integrity. These multifunctional properties make albumin a clinically significant biomarker, particularly in inflammatory conditions where its levels reflect both nutritional status and disease severity[24]. Levels of serum albumin act as indicators for nutritional status as well as liver synthetic function, whereas systemic inflammation further inhibits albumin production by causing a cytokine-mediated reduction in hepatic synthesis[25-26].

NPAR integrates two established clinical parameters-neutrophil-driven inflammation and nutritional/ anti-inflammatory status-demonstrating strong prognostic value across multiple critical conditions, including sepsis, acute kidney injury (AKI), septic shock, and ST-elevation myocardial infarction (STEMI)[27-29]. In this study, both the mid- and high-NPAR groups exhibited significantly higher mortality risk compared to the low-NPAR group , indicating that elevated NPAR levels are associated with worse clinical outcomes in critically ill acute pancreatitis patients. Our analysis demonstrated a linear dose-response relationship between NPAR and 28-day mortality risk. However, the prognostic performance of NPAR was significantly attenuated in patients with severe liver disease (interaction P=0.012), indicating reduced discriminative power in this subpopulation. In severe liver disease, neutrophil functional responses undergo dynamic modification over time, potentially disrupting the critical equilibrium between immunotolerance and effective host defense mechanisms[30]. Consequently, severe liver disease may impair the liver's coordinated immunoregulatory response to systemic infections. This pathophysiological mechanism could explain the attenuated prognostic utility of NPAR observed in acute pancreatitis patients with concurrent hepatic dysfunction in our cohort

Strengths and Limitations

This study provides the first large-scale validation of NPAR as an independent prognostic biomarker in AP, with robust associations demonstrated in a critically ill ICU population. There are, however, a few limitations to note: the single-center retrospective design naturally involves risks of selection and confounding biases; the exclusive focus on ICU patients may limit generalizability to less severe cases; missing data despite the routine availability of neutrophil and albumin measurements may affect result reliability; and the use of admission NPAR values (within 24 hours) precludes assessment of its dynamic behavior, optimal detection timing, or treatment-related variations. These findings warrant validation through prospective multicenter studies incorporating serial NPAR measurements to fully evaluate its clinical utility.

CONLUSION

In critically ill patients with acute pancreatitis, elevated NPAR was significantly associated with a greater risk of

death. These results position NPAR as a clinically actionable prognostic biomarker for acute pancreatitis severity. Rospective multicenter studies with extended follow-up are needed to validate these findings.

DECLARATION

Author's contribution

Each author of this article fulfilled following Criteria of Authorship:

1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

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Availability of data and materials

The datasets created and/or examined in this study can be obtained from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no competing interests, financial or otherwise, related to this work.

Ethics Approval and consent to participate Institutional Review Board Statement: The Institutional Review Boards at the Massachusetts Institute of Technology and BIDMC have ethically approved the MIMIC-IV database, which does not include protected health information.

Consent for publication

Before the study findings were published, written informed consent was acquired from all participants or their legal representatives.

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