The Neutrophil Percentage-to-Albumin Ratio is Associated with All-Cause Mortality in Critically Ill Patients with Acute Myocardial Infarction

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Abstract

Aim

In this study, we evaluated the utility of neutrophil percentage-to-albumin ratio (NPAR) in predicting in critically ill patients with acute myocardial infarction (AMI).

Methods

the information of patients were collected from Medical Information Mart for Intensive Care III (MIMIC III) database. Admission NPAR was calculated as neutrophil percentage divided by serum albumin. The endpoints of this study were 30-day, 90-day, 180-day, and 365-day all-cause mortality. Cox proportional hazards models and subgroup analyses were used to determine the relationship between admission NPAR and these endpoints.

Results

798 critically ill patients with AMI were enrolled in. After adjustments for age, race and gender, higher admission NPAR was associated with increased risk of 30-day, 90-day, 180-day, and 365-day all-cause mortality in critically ill patients with AMI. And after adjusting for possible confounding variables, two different trends have emerged. Stratified by tertiles, high admission NPAR was independently associated with 180-day and 365-day all-cause mortality in critically ill patients with AMI (tertile 3 vs. tertile 1: adjusted HR, 95%CI: 1.71,1.10-2.66, $p<0.05$; 1.66,1.10-2.51, $p<0.05$). In other hand, stratified by quartiles, highest admission NPAR levels were independently associated with 90-day, 180-day and 365-day all-cause mortality (quartile 4 vs. quartile 1: adjusted HR, 95% CI: 2.36,1.32-4.23, $p<0.05$; 2.58,1.49-4.47, $p<0.05$; 2.61,1.56-4.37, $p<0.05$). ROC test showed that admission NPAR had a moderate ability to predict all-cause mortality of critically ill patients with AMI. No obvious interaction was found by subgroup analysis in most subgroups.

Conclusions

admission NPAR was an independent predictor for 180-day and 365-day all-cause mortality in critically ill patients with AMI.

Introduction

As it is well known, acute myocardial infarction (AMI) as a common cardiovascular disease continues to be the leading cause of hospital admission and mortality rate worldwide in the past years(1). Although potent antiplatelet agents and early revascularization has greatly reduced the occurrence of major

adverse cardiovascular events in AMI patients(2), the prognosis of AMI patients is still an apparent problem worthy of our attention.

The inflammatory response participates in myocardial infarction (MI) area and left ventricular (LV) remodeling(3, 4). Neutrophil, the major participant in the inflammatory burst, mediates the inflammatory response to myocardial injury(3, 5). Albumin acts through its multiple binding sites and free radical-capture properties, involved in antioxidant activities (6). It has been confirmed that low albumin level has a significant effect on the mortality and prognosis of AMI (7–9).

According to the previous studies, admission neutrophil percentage-to-albumin ratio (NPAR) was an independent predictor of in-hospital mortality in patients with acute ST-segment elevation myocardial infarction (STEMI) (10). In the another study, in critically ill patients with coronary artery disease (CAD), the higher NPAR level was closely correlated with the higher rate of 30-day, 90-day, and 365-day all-cause death(11). However,there is no study yet that reported the association between admission NPAR level and the all-cause mortality in critically ill patients with AMI. For all the above reasons, in this study we hypothesized that admission NPAR level could be a prognostic predictor of all-cause mortality in critically ill patients with AMI.

Method

Source of data

We conducted a retrospective cohort study, where the data were collected from a large , single-center critical care database called Medical Information Mart for Intensive Care III (MIMIC III)(12). MIMIC III is a public and freely available database and integrates comprehensive clinical data of patients admitted to the intensive care units (ICU) at the Beth Israel Deaconess Medical Center between 2001 and 2012. This database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT). After successfully completing the National Institutes of Health (NIH) Web-based training course and the Protecting Human Research Participants examination (no. 40683764), we were given the permission to extract data from MIMIC III.

Population selection criteria

All ICU inpatients with AMI diagnosed by ICD-9 diagnosis code were enrolled in this study. Exclusion criteria were as follows: (1) multiple ICU admissions; (2) aged <18 years old; (3) had died before admission; (4) lack of the information of albumin and neutrophil percentage during ICU stay.

Data extraction and definition of NPAR

Data extraction from MIMIC III was accomplished using Structured Query Language (SQL) with the PostgreSQL tool (version 9.6). We extracted demographics, vital signs, comorbidities and medical history, laboratory parameters, scoring system, medication use, and clinical survival information. Age, gender and race were contained in demographics, and vital signs included heart rate, respiratory rate and mean blood

pressure (MBP). Comorbidities and medical history included CAD, prior MI, atrial fibrillation (AF), chronic heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and percutaneous transluminal coronary angioplasty/percutaneous coronary intervention (PTCA/PCI). Laboratory parameters consisted of neutrophils, albumin, hemoglobin, white blood cell (WBC), prothrombin time (PT), platelet, red cell distribution width (RDW), potassium, sodium, creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase peak (CK), MB isoenzyme of creatine kinase (CK-MB), and glucose. Scoring systems contain two important scoring scales—sequential organ failure assessment (SOFA) score (13) and simplified acute physiology score II (SAPS II) (14). In addition, the medication use of patients in this study would be shown in the baseline characteristics, including whether they have used aspirin, clopidogrel, metoprolol, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) or statins. The other extracted data have weight and urine output within 24 hours. All the laboratory parameters were firstly measured data after admission to the ICU. The endpoints of this study were 30-day, 90-day, 180-day, and 365-day all-cause mortality. We divided neutrophil percentage by albumin to get admission NPAR (10).

Statistical Analysis

All the patients with AMI in the study were stratified in terms of admission NPAR tertiles. Data distribution of all continuous variables were tested using the Shapiro-Wilk test, and they were nonnormally distributed, and manifested as median and interquartile range (Q1–Q3). All categorical data was expressed as number and percentage. Kruskal–Wallis or Fisher's exact test was performed to evaluate statistical differences among different groups of NPAR.

Using Log-rank tests, survival rates of different groups were compared, and the Kaplan–Meier curves were built.

In order to evaluate the independent effect of admission NPAR on 30-day, 90-day, 180-day, and 365-day all-cause mortality, cox proportional hazard models were developed. The first tertile and quartile groups of admission NPAR were treated as the reference group, and the results were summarized as hazard ratios (HR) with 95% confidence intervals (CI). In model I, age, race and gender were incorporated into adjustment. In model II, we further adjusted for age, gender, race, respiratory rate, MBP, heart rate, ALT, AST, CK-peak, CK-MB-peak, glucose, PT, hemoglobin, RDW, creatinine, potassium, sodium, BUN, WBC, platelet, CAD, AF, COPD, hypertension, diabetes, prior MI, CHF, CKD, stroke, SOFA and SAPS II. And P for trend was calculated. Subgroup analysis was conducted to estimate the effect of admission NPAR on 180-day all-cause mortality. And we got the P value for interaction.

Receiver-operating characteristic (ROC) curve was performed to measure the sensitivity and specificity of admission NPAR, as well as SOFA score. Moreover, the area under the curve (AUC) was calculated to estimate the quality of admission NPAR as a predictor of 365-day all-cause mortality. Statistical analyses were performed using EmpowerStats version 2.0 (<http://www.empowerstats.com/cn/>, X&Y solutions, Inc., Boston, MA) and R software version 3.4.3; P value of <0.05 was considered to be statistically significant.

Result

Baseline characteristics of patients

After reviewing the data of 62,699 critically ill patients, a total of 798 patients with AMI were enrolled in our study (Figure 1). Based on tertiles of admission NPAR level, participants were categorized into three groups (tertile 1: <21.58 ; tertile 2: $\geq 21.58, <26.77$; and tertile 3: ≥ 26.77), and each group included 266 AMI patients. The baseline characteristics were displayed in Table 1. Patients in the highest tertile of admission NPAR level were older than other groups, and most of them were white. In addition, they reported more medical history of AF, but less comorbidities of CAD, hypertension and CHF. Moreover, patients in the highest tertile of admission NPAR level were less likely to use aspirin, clopidogrel, metoprolol, ACEI/ARBs and statin, and to receive PTCA or PCI. Finally, they had lower MBP, weight, albumin, hemoglobin, urine output in 24 hours, and higher values of heart rate, neutrophils, WBC, PT, RDW, creatinine, BUN, ALT, AST, SAPS II and SOFA.

Admission NPAR and outcome

As it had been shown in Table 2, the overall length of ICU stay (LOS) was 3.69 days, and the overall in-hospital, 30-day, 90-day, 180-day and 365-day all-cause mortality were 17.92%, 19.67%, 25.44%, 29.82% and 33.21%, respectively. Furthermore, as admission NPAR levels increased, the all-cause death rate of in-hospital, 30-day, 90-day, 180-day and 365-day were distinctly raised.

There were the survival curves of 30-day (log-rank, $p < 0.0001$), 90-day (log-rank, $p < 0.0001$), 180-day (log-rank, $p < 0.0001$) and 365-day (log-rank, $p < 0.0001$) all-cause mortality stratified by the tertiles of admission NPAR, which were manifested in Figure 2. The trends indicated that the higher NPAR level had a worse survival probability.

Admission NPAR as a predictor of the clinical endpoints

In cox regression models, admission NPAR levels were stratified by tertiles and quartiles, to appraise whether admission NPAR was related to 30-day, 90-day, 180-day and 365-day all-cause mortality (Table 3). In model I, after adjustments for age, race and gender, higher admission NPAR was associated with increased risk of all-cause mortality. In model II, age, gender, race, respiratory rate, MBP, heart rate, ALT, AST, CK-peak, CK-MB-peak, glucose, PT, hemoglobin, RDW, creatinine, potassium, sodium, BUN, WBC, platelet, CAD, AF, COPD, hypertension, diabetes, prior MI, CHF, CKD, stroke, SOFA and SAPS II were incorporated into the regression model. There was a prominent correlation between high admission NPAR, 180-day and 365-day all-cause mortality (tertile 3 vs. tertile 1: adjusted HR, 95% CI: 1.71, 1.10-2.66, $p < 0.05$; 1.66, 1.10-2.51, $p < 0.05$). However, the relationship between admission NPAR, 30-day and 90-day all-cause mortality was not as relevant as the other groups. Unexpectedly, a merely different trend was observed in admission NPAR levels stratified by quartiles; highest admission NPAR levels were independently associated with 90-day, 180-day and 365-day all-cause mortality (quartile 4 vs. quartile 1: adjusted HR, 95% CI: 2.36, 1.32-4.23; 2.58, 1.49-4.47; 2.61, 1.56-4.37, $p < 0.05$).

The ROC test was employed to measure the sensitivity and specificity of admission NPAR with an AUC of 0.6421 (95% CI 0.6016–0.6826, $p < 0.0001$). Then the AUC area of admission NPAR was compared with SAPS II and SOFA score. There was no difference between NPAR and SOFA. Thus, it ascertained the quality of NPAR as a reliable predictor of 365-day all-cause mortality (Figure 3).

Subgroup Analysis

In most subgroups, no significant interaction between admission NPAR and 180-day all-cause mortality was observed (Table 4). Patients with high values of heart rate SAPS II, ICU LOS and age had higher risks of all-cause mortality for high admission NPAR.

Discussion

The study indicated that admission NPAR was an independent factor of 30-day, 90-day, 180-day, and 365-day all-cause mortality in critically ill patients with AMI, despite adjustment for age, race and gender. However, after adjustments for more potential confounders, admission NPAR was merely associated with 180-day, and 365-day all-cause mortality. Based on ROC curves, NPAR had a moderate ability to predict all-cause mortality of critically ill patients with AMI. Furthermore, subgroup analysis illustrated that there was no evident interaction in most subgroups.

Inflammation is a hallmark of atherosclerosis where immune cells, especially monocytes and white blood cells, together with cytokines and phospholipids contribute to trigger the inflammatory reaction(5, 15). The pervious study indicated that neutrophils, as an important member of white blood cells, played a significant role in coronary atherosclerosis and the formation of AMI(16, 17). Meissner, J. et al(18) found that high neutrophil count was associated with increased risk for AMI in patients presenting to the emergence department with chest pain. The findings hinted that neutrophil accumulation was a strong predictor of all-cause mortality in patients with AMI(18, 19)

All the time, albumin has been considered as an indicator of nutritional status. However, the current study showed that there was a certain correlation between albumin and inflammation(7, 20, 21). Serum albumin levels had been affirmed to be inversely related to occurrence of ischemic heart disease²¹. Low serum albumin level was an independent predictor of in-hospital mortality in patients with acute coronary syndrome (ACS)(7, 22). Furthermore, a significant interaction was found between low serum albumin level and first incident AMI(23) and there was a evident correlation between low serum albumin level long-term mortality in patients with STEMI undergoing PCI(24) and patients with unstable angina pectoris (UAP) or non-ST elevation myocardial infarction (NSTEMI)(25).

The previous studies has demonstrated the prognosis value of NPAR in other clinical events including severe sepsis or septic shock(26), acute kidney injury(27) and cardiogenic shock(28). Sun, T. N. et al(11) documented that NPAR was an independent risk factor in critically ill patients with CAD. In term of the above study, we were curious about that NPAR would have same outcomes in AMI as it did in chronic CAD. The previous study identified that admission NPAR was an independent predictor of in-hospital

mortality in patients with STEMI. Based on this, we investigated the impact of admission NPAR on the short-term and long-term risk of death in AMI patients. Our study showed that higher admission NPAR was only associated with increased risks of 180-day and 365-day all-cause mortality and may be an independent marker for long-term all-cause mortality in critically ill patients with AMI. According to the AUC area, admission NPAR had a moderate predictive ability in critically ill patients with AMI.

Compared with SOFA and SAPS II, the capacity of admission NPAR in predicting the risk of death was as well as SOFA though its effectiveness was not so adequate than SAPS II. But on account of the test methods for neutrophil percentage and albumin are economical and practical, admission NPAR would permit it possible to quickly evaluate the risk of death in critically ill patients with AMI. Especially, it has precious clinical utility for areas with underdeveloped economy and poor medical conditions.

Limitation

This study was a single-center retrospective study, the selection bias was inevitable. All data came from a publicly open clinical database, so it was difficult to extract some important variables, such as the history of smoking and drinking. Since both neutrophil percentage and albumin change dynamically, the study just chose admission NPAR measured at the first time after admission. Random error maybe inevitable. Due to missing values of more than 20%, it was difficult to obtain information about some important clinical or laboratory variables.

Conclusion

Our study suggests that higher admission NPAR was independently associated with 180-day and 365-day all-cause mortality in critically ill patients with AMI. NPAR may be a clinical maker to predict risk stratification in patients with AMI and further to offer the Individualized treatment services.

Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ALT, alanine aminotransferase; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; AUC, area under the curve; BUN, blood urea nitrogen; CAD, coronary artery disease; CDK, chronic kidney disease; CHF, chronic heart failure; CI, confidence interval; CK, creatine kinase-peak; CK-MB, MB isoenzyme of creatine kinase; COPD, chronic obstructive pulmonary disease; HR, hazard ratios; ICU, intensive care units; IRB, Institutional Review Boards; LOS, length of stay; MBP, mean blood pressure; MI, myocardial infarction; MIMIC III, Medical Information Mart for Intensive Care III; MIT, Massachusetts Institute of Technology; NIH, National Institutes of Health; NPAR, neutrophil percentage-to-albumin ratio; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; PT, prothrombin time; PTCA, percutaneous transluminal coronary angioplasty; RDW, red cell distribution width; ROC, receiver-operating characteristic; SAPS II, simplified acute physiology score II; SOFA,

sequential organ failure assessment; SQL, Structured Query Language; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris; WBC, white blood cell.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials

Not applicable.

Competing interests:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Authors' contributions:

Study concept and design: Ya Lin and Qianqian Zou;

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Drafting of the manuscript: Ya Lin and Yanhan Lin;

Statistical analysis: Ya Lin;

Study supervision: Juanqing Yue and Qianqian Zou;

All authors contributed to the manuscript for important intellectual content and approved the submission.

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Tables

Table 1: Characteristics of study patients by NPAR tertiles.

Characteristics	Tertile 1 (n=266) <21.58	Tertile 2 (n=266) ≥21.58, <26.77	Tertile 3 (n=266) ≥26.77	P value
Age (years)	67.50 (57.00-77.75)	69.00 (58.00-79.00)	73.00 (63.00-80.00)	0.001
Male, n (%)	179 (67.29%)	165 (62.03%)	160 (60.15%)	0.209
Race, n (%)				0.032
White	179 (67.29%)	160 (60.15%)	179 (67.29%)	
Black	21 (7.89%)	17 (6.39%)	8 (3.01%)	
Other	66 (24.81%)	89 (33.46%)	79 (29.70%)	
Heart rate (beats/minute)	95.77 ± 25.54	101.57 ± 26.39	105.51 ± 24.40	<0.001
MBP (mmHg)	73.15 ± 34.18	67.20 ± 28.90	62.95 ± 29.72	<0.001
Respiratory rate (beats/minute)	24.24 ± 8.82	24.33 ± 9.81	25.47 ± 9.94	0.240
Weight(kg)	81.94 ± 19.31	79.13 ± 19.65	77.97 ± 19.72	0.017
CAD	192 (72.18%)	207 (77.82%)	146 (54.89%)	<0.001
Prior MI	15 (5.64%)	18 (6.77%)	13 (4.89%)	0.645
AF	67 (25.19%)	80 (30.08%)	100 (37.59%)	0.008
Hypertension	136 (51.13%)	118 (44.36%)	91 (34.21%)	<0.001
Diabetes	75 (28.20%)	76 (28.57%)	80 (30.08%)	0.880
CHF	105 (39.47%)	136 (51.13%)	135 (50.75%)	0.009
CKD	29 (10.90%)	37 (13.91%)	42 (15.79%)	0.251
Stroke	6 (2.26%)	10 (3.76%)	14 (5.26%)	0.190
COPD	4 (1.50%)	2 (0.75%)	8 (3.01%)	0.131
PTCA/PCI	187 (70.30%)	173 (65.04%)	125 (46.99%)	<0.001
Laboratory parameters				
Neutrophil percentage (%)	71.20 (61.35-78.95)	84.00 (77.60-88.07)	86.00 (80.85-89.77)	<0.001
Albumin (g/dL)	3.80 (3.50-4.10)	3.50 (3.20-3.70)	2.70 (2.40-3.00)	<0.001
Hemoglobin (g/dL)	13.35 (11.90-14.57)	12.60 (11.10-14.10)	11.35 (10.10-12.97)	<0.001
WBC (10 ⁹ /L)	10.30 (7.50-13.80)	12.50 (9.60-16.70)	13.70 (10.10-	<0.001

			17.50)	
PT (seconds)	13.30 (12.50-14.00)	13.70 (12.90-15.10)	14.50 (13.30-16.88)	<0.001
Platelet (10 ⁹ /L)	242.50 (188.25-301.75)	252.00 (192.25-299.00)	230.50 (170.25-302.75)	0.113
RDW (%)	13.60 (13.10-14.50)	13.70 (13.00-14.50)	14.20 (13.30-15.60)	<0.001
Potassium (mmol/L)	4.20 (3.90-4.60)	4.10 (3.80-4.50)	4.20 (3.80-4.70)	0.216
Sodium (mmol/L)	139.00 (137.00-141.00)	138.00 (135.25-141.00)	139.00 (134.25-141.00)	0.036
Creatinine (mEq/L)	1.10 (0.90-1.40)	1.10 (0.90-1.40)	1.20 (1.00-1.70)	<0.001
BUN (mg/dL)	20.00 (15.00-28.00)	21.00 (15.00-30.25)	27.00 (18.50-43.50)	<0.001
ALT (U/L)	30.21 (20.00-62.75)	37.00 (21.00-68.75)	42.33 (22.00-79.00)	0.024
AST (U/L)	52.00 (26.25-124.63)	74.50 (34.24-174.00)	77.70 (38.00-196.37)	0.001
CK-peak (U/L)	743.30 (292.70-1756.00)	1088.50 (329.25-2427.20)	702.00 (252.15-1983.00)	0.052
CK-MB-peak (U/L)	53.00 (14.00-181.00)	72.00 (13.00-227.50)	37.00 (11.00-150.00)	0.092
Glucose (mg/dL)	143.00 (115.25-191.75)	148.00 (122.25-207.25)	152.00 (119.25-213.75)	0.254
Scoring systems				
SAPS II	34.00 (25.00-44.00)	36.00 (28.00-48.00)	43.00 (35.00-54.00)	<0.001
SOFA	3.00 (1.00-2.00)	4.00 (3.00-5.00)	6.00 (7.00-10.00)	<0.001
Medication use, n (%)				
Aspirin	214 (80.45%)	221 (83.08%)	172 (64.66%)	<0.001
Clopidogre	132 (49.62%)	148 (55.64%)	117 (43.98%)	0.027
Metoprolol	209 (78.57%)	197 (74.06%)	156 (58.65%)	<0.001
ACEI/ARBs	156 (58.65%)	171 (64.29%)	100 (37.59%)	<0.001
Statin	201 (75.56%)	199 (74.81%)	156 (58.65%)	<0.001
Urine output (ml/24h)	2116.00 (1424.00-3074.00)	1825.00 (1090.00-2718.75)	1377.50 (812.25-2275.25)	<0.001

Continuous variables are presented as mean (SD) for normally distributed variables or median (interquartile range) for non-normally distributed variables, whereas categorical variables are presented as number (percentage).

MBP: mean blood pressure; CAD: coronary artery disease; prior MI: prior myocardial infarction; AF: atrial fibrillation; CHF: chronic heart failure; CDK: chronic kidney disease ;COPD: chronic obstructive pulmonary disease; PTCA/PCI: Percutaneous transluminal coronary angioplasty/percutaneous coronary intervention; WBC: white blood cell; PT: prothrombin time; RDW: Red Cell Distribution Width; BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CK-MB: MB isoenzyme of creatine kinase; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment score; ACEI/ARBs: angiotensin-converting enzyme inhibitor/angiotensin receptor blockers.

Table 2: Outcome of the study patients by NPAR tertiles.

outcomes	Total(n=798)	Tertile 1(n=266)	Tertile 2(n=266)	Tertile 3(n=266)	P value
		<21.58	≥21.58, <26.77	≥26.77	
ICU LOS (day)	3.69 (0.51-100.12)	2.57 (0.58-49.13)	3.71 (0.59-100.12)	5.33 (0.51-52.81)	<0.001
all-cause mortality					
In-hospital	143 (17.92%)	32 (12.03%)	38 (14.29%)	73 (27.44%)	<0.001
30-day mortality	157 (19.67%)	35 (13.16%)	48 (18.05%)	74 (27.82%)	<0.001
90-day mortality	203 (25.44%)	44 (16.54%)	58 (21.80%)	101 (37.97%)	<0.001
180-day mortality	238 (29.82%)	50 (18.80%)	73 (27.44%)	115 (43.23%)	<0.001
365-day mortality	265 (33.21%)	58 (21.80%)	84 (31.58%)	123 (46.24%)	<0.001

Data are expressed as count (percentage) for categorical variables and median (interquartile range) for continuous variables. ICU LOS: length of ICU stay.

Table 3: The association between all-cause mortality and NPAR.

	Non-adjusted		Model I		Model II	
NPAR	HR (95% CIs)	P value	HR (95% CIs)	P value	HR (95% CIs)	P value
30-day all-cause mortality						
Tertiles						
<21.58	1.0		1.0		1.0	
≥21.58, <26.77	1.38 (0.89, 2.13)	0.1506	1.27 (0.82, 1.96)	0.2917	0.99 (0.60, 1.66)	0.9826
≥26.77	2.29 (1.53, 3.43)	<0.0001	2.07 (1.38, 3.12)	0.0005	1.29 (0.77, 2.17)	0.3262
P for trend	<0.0001		0.0002		0.5418	
Quartiles						
<20.49	1.0		1.0		1.0	
≥20.49, <23.94	1.55 (0.91, 2.65)	0.1078	1.43 (0.84, 2.45)	0.1912	1.73 (0.91, 3.30)	0.0956
≥23.94, <28.33	2.07 (1.24, 3.45)	0.0056	1.96 (1.17, 3.28)	0.0109	1.50 (0.80, 2.83)	0.2101
≥28.33	2.87 (1.76, 4.69)	<0.0001	2.54 (1.54, 4.18)	0.0002	2.01 (1.05, 3.87)	0.0354
P for trend	<0.0001		<0.0001		0.2698	
90-day all-cause mortality						
Tertiles						
<21.58	1.0		1.0		1.0	
≥21.58, <26.77	1.34 (0.91, 1.98)	0.1439	1.22 (0.82, 1.81)	0.3200	1.06 (0.66, 1.70)	0.7952
≥26.77	2.59 (1.81, 3.68)	<0.0001	2.31 (1.61, 3.31)	<0.0001	1.54 (0.97, 2.46)	0.0701
P for trend	<0.0001		<0.0001		0.0893	
Quartiles						
<20.49	1.0		1.0		1.0	
≥20.49, <23.94	1.60 (1.00, 2.58)	0.0504	1.48 (0.92, 2.38)	0.1077	1.86 (1.04, 3.33)	0.0359
≥23.94, <28.33	1.85 (1.16, 2.94)	0.0099	1.75 (1.09, 2.79)	0.0195	1.41 (0.78, 2.53)	0.2512

≥28.33	3.39 (2.21, 5.20)	<0.0001	2.97 (1.92, 4.58)	<0.0001	2.36 (1.32, 4.23)	0.0038
P for trend	<0.0001		<0.0001		0.0399	
180-day all-cause mortality						
Tertiles						
<21.58	1.0		1.0		1.0	
≥21.58, <26.77	1.50 (1.05, 2.15)	0.0273	1.38 (0.96, 1.98)	0.0821	1.36 (0.88, 2.11)	0.1660
≥26.77	2.67 (1.92, 3.73)	<0.0001	2.40 (1.71, 3.36)	<0.0001	1.71 (1.10, 2.66)	0.0165
P for trend	<0.0001		<0.0001		0.0272	
Quartiles						
<20.49	1.0		1.0		1.0	
≥20.49, <23.94	1.78 (1.15, 2.76)	0.0092	1.66 (1.07, 2.57)	0.0236	2.18 (1.27, 3.75)	0.0048
≥23.94, <28.33	1.91 (1.24, 2.95)	0.0036	1.80 (1.17, 2.79)	0.0080	1.66 (0.96, 2.88)	0.0698
≥28.33	3.54 (2.37, 5.29)	<0.0001	3.12 (2.08, 4.68)	<0.0001	2.58 (1.49, 4.47)	0.0007
P for trend	<0.0001		<0.0001		0.0150	
365-day all-cause mortality						
Tertiles						
<21.58	1.0		1.0		1.0	
≥21.58, <26.77	1.50 (1.08, 2.10)	0.0169	1.38 (0.99, 1.93)	0.0610	1.40 (0.93, 2.10)	0.1031
≥26.77	2.52 (1.85, 3.45)	<0.0001	2.22 (1.62, 3.04)	<0.0001	1.66 (1.10, 2.51)	0.0154
P for trend	<0.0001		<0.0001		0.0471	
Quartiles						
<20.49	1.0		1.0		1.0	
≥20.49, <23.94	1.76 (1.17, 2.65)	0.0064	1.64 (1.09, 2.46)	0.0182	2.20 (1.32, 3.66)	0.0024
≥23.94, <28.33	1.91 (1.27, 2.86)	0.0018	1.78 (1.18, 2.67)	0.0056	1.80 (1.08, 3.00)	0.0250
≥28.33	3.39 (2.33, 5.20)	<0.0001	2.92 (2.00, 4.58)	<0.0001	2.61 (1.56, 4.23)	0.0003

	4.95)	4.28)	4.37)
P for trend	<0.0001	<0.0001	0.0075

HR: hazard ratio; CI: confidence interval. Models were derived from Cox proportional hazard regression models.

Non-adjusted model adjust for: None

Adjust I model adjust for: Age; Gender; Race

Adjust II model adjust for: Age; Gender; Race; Respiratory rate; MBP; Heart rate; ALT; AST; CK-peak; CK-MB-peak; Glucose; PT; Hemoglobin; RDW; Creatinine; Potassium; Sodium; BUN; WBC; Platelet; CAD; AF; COPD; Hypertension; Diabetes; prior MI; CHF; CKD; STROKE; SOFA; SAPS II

Table 4: The association between three NPAR groups and 180-day all-cause mortality in subgroup analysis.

	N	NPAR <21.58 (reference)	21.58 ≤NPAR <26.77 HR (95% CIs)	NPAR≥ 26.77 HR (95% CIs)	P for interaction
AF					0.4736
No	551	1.0	1.42 (0.90, 2.23)	2.80 (1.85, 4.26)	
Yes	247	1.0	1.55 (0.86, 2.81)	2.19 (1.26, 3.82)	
CHF					0.1939
No	422	1.0	1.18 (0.68, 2.07)	2.89 (1.79, 4.67)	
Yes	376	1.0	1.60 (0.99, 2.59)	2.30 (1.45, 3.65)	
CKD					0.5369
No	690	1.0	1.54 (1.04, 2.27)	2.53 (1.76, 3.64)	
Yes	108	1.0	1.21 (0.47, 3.13)	3.12 (1.35, 7.22)	
COPD					0.9520
No	784	1.0	1.50 (1.04, 2.16)	2.62 (1.87, 3.67)	
Yes	14	1.0	2.42 (0.15, 39.05)	3.37 (0.40, 28.33)	
CAD					0.8694
No	253	1.0	1.72 (0.92, 3.23)	2.54 (1.48, 4.36)	
Yes	545	1.0	1.45 (0.94, 2.26)	2.49 (1.61, 3.83)	
Hypertension					0.3855
No	453	1.0	1.19 (0.74, 1.91)	2.34 (1.54, 3.55)	
Yes	345	1.0	1.95 (1.11, 3.41)	2.86 (1.64, 4.98)	
Diabetes					0.3603
No	567	1.0	1.36 (0.90, 2.06)	2.32 (1.58, 3.40)	

Yes	231	1.0	1.99 (0.96, 4.13)	3.91 (1.99, 7.70)	
Prior MI					0.4050
No	752	1.0	1.54 (1.06, 2.25)	2.84 (2.01, 4.02)	
Yes	46	1.0	1.09 (0.33, 3.57)	1.20 (0.35, 4.13)	
Stroke					0.4004
No	768	1.0	1.52 (1.05, 2.20)	2.75 (1.95, 3.88)	
Yes	30	1.0	0.69 (0.16, 2.91)	0.92 (0.24, 3.58)	
Clopidogre					0.4357
No	401	1.0	1.22 (0.75, 1.99)	2.37 (1.55, 3.61)	
Yes	397	1.0	1.97 (1.14, 3.41)	3.04 (1.77, 5.20)	
Aspirin					0.4040
No	191	1.0	0.98 (0.47, 2.05)	1.93 (1.08, 3.46)	
Yes	607	1.0	1.73 (1.14, 2.62)	2.85 (1.90, 4.28)	
Metoprolol					0.8271
No	236	1.0	1.30 (0.72, 2.35)	1.98 (1.17, 3.35)	
Yes	562	1.0	1.53 (0.97, 2.41)	2.59 (1.68, 4.00)	
ACEI/ARBs					0.3793
No	371	1.0	1.33 (0.83, 2.14)	2.21 (1.48, 3.31)	
Yes	427	1.0	1.98 (1.13, 3.47)	2.19 (1.19, 4.03)	
Statin					0.2013
No	242	1.0	1.25 (0.73, 2.15)	1.68 (1.04, 2.72)	
Yes	556	1.0	1.67 (1.03, 2.71)	3.08 (1.94, 4.86)	

PTCA/PCI					0.2614
No	313	1.0	1.19 (0.71, 1.99)	1.73 (1.10, 2.74)	
Yes	485	1.0	1.69 (1.02, 2.80)	3.08 (1.89, 5.02)	
gender					0.7209
Female	294	1.0	1.37 (0.76, 2.47)	2.82 (1.65, 4.83)	
Male	504	1.0	1.57 (1.00, 2.47)	2.52 (1.65, 3.86)	
Race					0.5510
White	518	1.0	1.43 (0.88, 2.34)	2.84 (1.85, 4.38)	
Black	46	1.0	2.63 (0.66, 10.56)	6.29 (1.49, 26.52)	
Other	234	1.0	1.26 (0.70, 2.25)	1.99 (1.14, 3.48)	
ALT (U/L)					0.6194
<35.81	393	1.0	1.35 (0.80, 2.28)	2.88 (1.80, 4.64)	
≥35.81	405	1.0	1.57 (0.95, 2.58)	2.41 (1.51, 3.86)	
AST (U/L)					0.8455
<67.00	391	1.0	1.44 (0.82, 2.52)	2.84 (1.71, 4.73)	
≥67.00	407	1.0	1.45 (0.91, 2.32)	2.40 (1.55, 3.72)	
CK-peak (U/L)					0.9398
<823.00	397	1.0	1.46 (0.88, 2.41)	2.56 (1.64, 4.01)	
≥823.00	401	1.0	1.56 (0.93, 2.63)	2.81 (1.71, 4.62)	
CK-MB-peak (U/L)					0.9731
<48.00	398	1.0	1.54 (0.91, 2.60)	2.69 (1.68, 4.30)	
≥48.00	399	1.0	1.45 (0.89, 2.38)	2.66 (1.66, 4.28)	

Glucose (mg/dL)					0.7956
<148.00	395	1.0	1.53 (0.89, 2.61)	3.02 (1.85, 4.93)	
≥148.00	403	1.0	1.45 (0.89, 2.36)	2.35 (1.50, 3.70)	
PT (seconds)					0.2151
<13.70	388	1.0	1.96 (1.18, 3.27)	2.82 (1.67, 4.78)	
≥13.70	410	1.0	1.03 (0.62, 1.71)	2.00 (1.28, 3.13)	
Hemoglobin (g/dL)					0.7119
<12.40	394	1.0	1.20 (0.71, 2.03)	2.14 (1.34, 3.41)	
≥12.40	404	1.0	1.62 (0.98, 2.66)	2.47 (1.47, 4.15)	
RDW (%)					0.4510
<13.80	394	1.0	1.37 (0.77, 2.42)	2.84 (1.65, 4.88)	
≥13.80	404	1.0	1.55 (0.97, 2.47)	2.22 (1.45, 3.39)	
Creatinine (mEq/L)					0.6118
<1.10	303	1.0	1.76 (0.91, 3.42)	3.61 (1.91, 6.84)	
≥1.10	399	1.0	1.69 (1.05, 2.73)	2.58 (1.66, 4.02)	
BUN (mg/dL)					0.1007
<22.00	370	1.0	2.26 (1.21, 4.21)	3.86 (2.07, 7.20)	
≥22.00	414	1.0	1.11 (0.70, 1.75)	1.84 (1.23, 2.77)	
WBC (10 ⁹ /L)					0.3940
<12.00	383	1.0	1.38 (0.77, 2.46)	3.13 (1.85, 5.29)	
≥12.00	401	1.0	1.40 (0.85, 2.31)	2.10 (1.32, 3.35)	
Potassium (mmol/L)					0.5270

< 4.20	388	1.0	1.22 (0.71, 2.08)	2.43 (1.48, 3.98)	
≥4.20	410	1.0	1.83 (1.13, 2.97)	2.90 (1.85, 4.54)	
Sodium (mmol/L)					0.8463
<139.00	384	1.0	1.64 (0.97, 2.78)	2.91 (1.77, 4.78)	
≥139.00	414	1.0	1.35 (0.82, 2.24)	2.46 (1.57, 3.85)	
Platelet (10 ⁹ /L)					0.9992
<241.00	399	1.0	1.50 (0.90, 2.49)	2.68 (1.70, 4.21)	
≥241.00	399	1.0	1.51 (0.91, 2.52)	2.62 (1.61, 4.29)	
Age (years)					0.0469
<70.00	394	1.0	1.26 (0.68, 2.32)	3.42 (1.99, 5.88)	
≥70.00	404	1.0	1.58 (1.01, 2.47)	2.05 (1.35, 3.12)	
Heart rate (beats/minute)					0.0023
<101.00	385	1.0	2.61 (1.43, 4.77)	5.12 (2.89, 9.07)	
≥101.00	413	1.0	0.92 (0.59, 1.45)	1.51 (1.00, 2.28)	
Respiratory rate (beats/minute)					0.8764
<26.00	368	1.0	1.44 (0.80, 2.58)	2.83 (1.65, 4.83)	
≥26.00	430	1.0	1.54 (0.98, 2.44)	2.56 (1.67, 3.90)	
MBP (mmHg)					0.4178
< 57.00	371	1.0	1.16 (0.70, 1.92)	2.23 (1.43, 3.46)	
≥57.00	427	1.0	1.87 (1.12, 3.13)	2.79 (1.68, 4.66)	
Weight (kg)					0.6674
< 78.00	392	1.0	1.76 (1.04, 2.97)	3.01 (1.84, 4.94)	

			2.97)	4.91)
≥78.00	406	1.0	1.26 (0.76, 2.08)	2.32 (1.46, 3.69)
ICU LOS (day)				0.0002
< 3.69	399	1.0	1.28 (0.73, 2.25)	4.33 (2.66, 7.03)
≥3.69	399	1.0	1.40 (0.87, 2.27)	1.59 (1.01, 2.52)
SAPS II				0.0010
< 31.00	247	1.0	8.90 (2.01, 39.44)	19.22 (4.30, 85.91)
≥31.00, <45	278	1.0	1.10 (0.58, 2.08)	1.33 (0.72, 2.45)
≥45	273	1.0	0.96 (0.60, 1.54)	1.44 (0.95, 2.18)
SOFA				0.0605
<3.00	247	1.0	2.17 (0.92, 5.11)	5.29 (2.19, 12.78)
≥3.00, <6.00	236	1.0	1.91 (0.96, 3.82)	1.75 (0.88, 3.50)
≥6.00	315	1.0	0.95 (0.58, 1.54)	1.53 (1.00, 2.33)
Urine output (ml/24h)				0.2991
<1805.00	399	1.0	1.26 (0.79, 2.01)	1.84 (1.21, 2.82)
≥1805.00	399	1.0	1.54 (0.87, 2.73)	3.20 (1.86, 5.50)

HR: hazard ratio; CI: confidence interval. AF: atrial fibrillation; CHF: chronic heart failure; CDK: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; prior MI: prior myocardial infarction; ACEI/ARBs: angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; PTCA/PCI: Percutaneous transluminal coronary angioplasty/percutaneous coronary intervention; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CK-MB: MB isoenzyme of creatine kinase; PT: prothrombin time; RDW: Red Cell Distribution Width; BUN: blood urea nitrogen; WBC: white blood cell; MBP: mean blood pressure; ICU LOS: length of ICU stay; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment score.

Figures

Figure 1

Flow chat of study selection. ICU: intensive care unit; AMI: acute myocardial infarction. MIMIC III: Medical Information Mart for Intensive Care III.

Figure 2

Survival probability and Kaplan–Meier curves of three admission NPAR groups. (a) 30-day. (b) 90-day. (c) 180-day. (d) 365-day. NPAR: neutrophil percentage-albumin ratio.

(a)

(b)

Figure 3

ROC curves for the prediction of 365-day all-cause mortality. (a) about NPAR. (b) about NPAR, SAPS II score, and SOFA score. NPAR: neutrophil percentage-albumin ratio; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment score.