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Original Article

Association between basal platelet count and all-cause mortality in critically ill patients with acute respiratory failure: a secondary analysis from the eICU collaborative research database

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Abstract: Background: Evidence regarding the correlation between platelet count and all-cause mortality in critically ill patients with acute respiratory failure (ARF) is limited. Therefore, the aim of the study was to evaluate whether platelet count was associated with all-cause mortality in critical patients with ARF by using the electronic intensive care unit (eICU) Collaborative Research Database (eICU-CRD). Methods: In this retrospective multicenter cohort study, the data of 26961 patients with ARF hospitalized in ICUs between 2014 and 2015 were collected. The independent variable was log2 basal platelet count, and the dependent variables were all-cause in-hospital and ICU mortality. Covariates including demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, supportive treatment, and comorbidities were collected. Results: In the fully adjusted model, log2 basal platelet count was negatively associated with all-cause mortality both in hospital [RR: 0.87, 95% CI: 0.84-0.91] and in ICU [RR: 0.87, 95% CI: 0.83-0.92]. A non-linear relationship between log2 basal platelet count and all-cause in-hospital and ICU mortality was identified by the nonlinearity test. The inflection points we got were 6.83 and 6.86 respectively (after inverse log2 logarithmic conversion, the platelet counts were 114×10^9/L and 116×10^9/L, respectively). On the right side of the inflection point, however, no association was observed between blood platelets and all-cause in-hospital (RR: 0.96, 95% CI: 0.88-1.03) and ICU mortality (RR: 0.97, 95% CI: 0.91-1.04). Conclusions: For patients with ARF in ICU, platelet count was negatively associated with all-cause in-hospital and ICU mortality when the platelet count was less than 114×10^9/L and 116×10^9/L respectively, but when the platelet count was higher, we failed to observe a correlation between them. The safe ranges of platelet count for hospital stay and ICU stay were 78×10^9/L-145×10^9/L and 89×10^9/L-147×10^9/L respectively.

Keywords: ICU, acute respiratory failure, platelet count, mortality

Introduction

Platelets are anucleate fragments derived from megakaryocytes [1]. Traditionally, platelets are considered to play a hemostatic role in response to vascular injury and endothelial disruption [2]. However, platelets have many other functions beyond that, among which participating in the inflammatory process is one of the most important [3]. In general, a large number of platelets are destroyed under the mediation of inflammatory factors and various toxins produced by acute diseases, leading to direct suppression of bone marrow proliferation, insufficient production of bone marrow megakaryocytes, and a decrease in the number of platelets [4]. Many studies have shown that platelets play a key role in the pathogenesis of various inflammation-related clinical diseases [3, 5, 6], involving respiratory system, rheumatic system, gastrointestinal system, etc. [7, 8]. Therefore, platelets can be used as a potentially important clinical indicator for monitoring disease progression. The most common complication of platelet abnormalities in the ICU is thrombocytopenia [9], which is a risk factor for organ failure and vascular leakage. The occurrence and development of thrombocytopenia is associat-

ed with increased mortality in critically ill patients [10-12].

Acute respiratory failure (ARF) is one of the common life-threatening complications in ICU patients, often accompanied by changes in platelet count [13]. The mechanism may be that part of platelets is originally derived from the lung tissue [13-15], indicated by (1) megakaryocytes are also found in the lung tissue [16], (2) platelet counts are higher in the left side of the heart than in the right side of the heart, suggesting platelet production in the pulmonary tissue [17], and (3) in many severe cases such as ARF, thrombocytosis often occurs first, followed by thrombocytopenia [18]. In recent years, the role of platelets in acute respiratory distress syndrome (ARDS) has been increasingly recognized, and its mechanism may be related to the involvement of inflammatory response and disseminated intravascular coagulation. Whereas, there are few studies on the role of platelets in ARF [19, 20]. Besides, the relationship between platelet count and prognosis of ARF patients has always been controversial, and due to methodological limitations, it is difficult to draw a real relationship.

The intensive care unit (ICU) mainly uses high-tech equipment and treatment means to provide continuous care and close monitoring for patients with life-threatening or serious diseases, so as to restore the physical function of patients to normal. Patients in the ICU are usually monitored for any changes in physiological status that may be related to disease deterioration. The bedside monitoring system for ICU patients generates a large amount of data, but only part of these data can be used as clinical documentation [21]. At the same time, massive amounts of data not only bring some challenges to collection, but also provide great opportunities for data archiving. The main difficulties of archiving include combining various information systems and managing different data types by organizing a popular network [22]. The electronic ICU (eICU) Collaborative Research Database (eICU-CRD) is a solution to archive these information, providing a wealth of valuable clinical information for ICU patients participating in the Philips eICU program [23]. In addition, there are other databases, such as the Medical Information Mart for Intensive Care (MIMIC), which stores clinical data of more than 50000 adult inpatients, including those in ICUs. The reason why we chose eICU-CRD is that it overcomes some of the limitations of other datasets such as MIMIC by including a larger number of ICU encounters from numerous hospitals, covering more of a contemporary time span (2014-2015) while MIMIC is relatively old, dating back as far as 2001 [24].

Therefore, we used eICU-CRD, a large sample library, to explore the relationship between platelet count and all-cause in-hospital and ICU mortality in patients with ARF. The innovation of this study is to investigate the relationships between platelet count and prognosis of ARF patients, confirming that platelet count has certain clinical significance as a prognostic indicator of patients with ARF.

Participants and methods

Data source

The data of our analysis came from the eICU-CRD. The dataset included 200,859 ICU admissions from 208 hospitals across the United States between 2014 and 2015. The eICU-CRD is a unique, publicly available multicenter database of ICU encounters with the potential to support advances in critical care data science and observational critical care research in general. The eICU-CRD data are of high quality, with most variables nearing complete and few omissions in the routinely collected fields [24]. These data are archived by Philips and converted into a research database by the eICU Research Institute [25]. The ethics activities of eICU have been approved. For details, please refer to the official website (https://eicu-crd.mit.edu). After completing a web-based training course and Protecting Human Research Participants examination (No. 36208651), we obtained permission to extract data from the eICU-CRD.

Study design

This is a secondary analysis based on a multicenter cohort dataset, in which the continuous variables, log2 basal blood platelet count, was served as an independent variable. The classified variables, hospital and ICU all-cause mortality, were served as dependent variable (0 survival, 1 non-survival). The study was

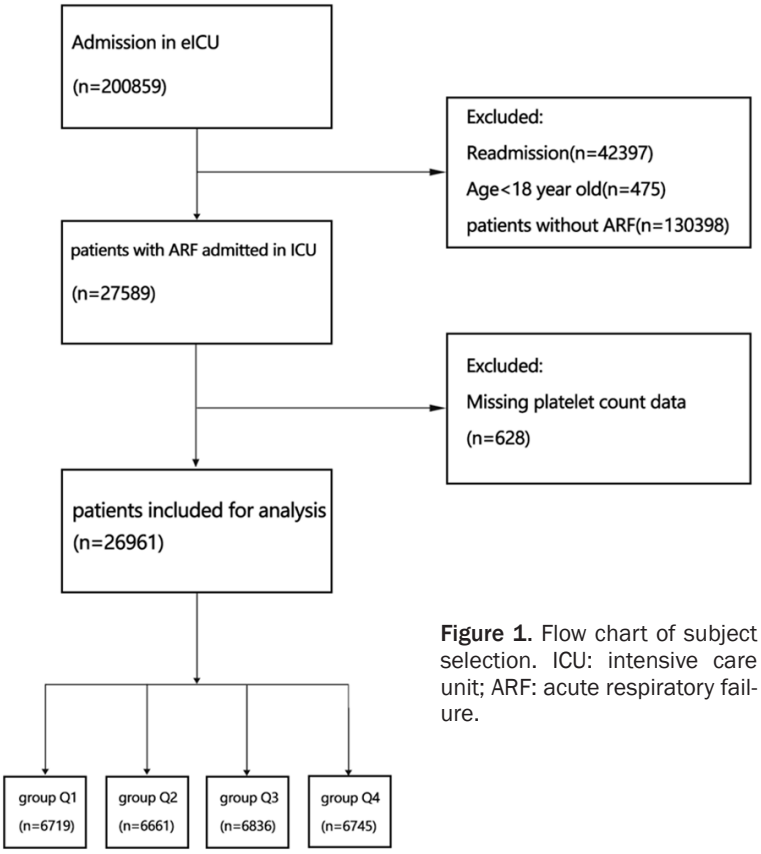

Figure 1. Flow chart of subject selection. ICU: intensive care unit; ARF: acute respiratory failure.

approved by the Institutional Review Board of our hospital.

Study population

The data of ARF were collected from 208 hospitals across the United States. To ensure the privacy of participants, database generators encode the patients' identity information into nontraceable codes. A total of 200,859 ICU patients were initially included, of whom 26961 were eventually screened for analysis (**Figure 1**). The collection of participants started in 2014 and ended in 2015. Patients were excluded for the following reasons: (1) Missing hospital mortality data, (2) Missing basal platelet count information.

Clinical variables and outcomes

In the present study, the independent variable was basal platelet count, and the target variables (dependent variables) were all-cause hospital and ICU mortality rates. The following variables were used as covariates: continuous variables included age (years), albumin (g/L), body mass index (BMI, kg/m^2), and the Acute Physiology and Chronic Health Evaluation (APACHE) IV score; Categorical variables included sex (male, female), race/ethnicity (African-American, Asian, Caucasian, Hispanic, U.S. native military, civilian, and Unknown), congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes, coagulation disease, mechanical ventilation, oxygen therapy, and antiplatelet drugs. In general, the covariates included demographic data, comorbidities, severity of illness, and life support interventions.

Statistical analysis

Given that the platelet count is a skewed distribution, we performed log2 transformation to make it close to a normal distribution. Continuous variables are expressed as mean ± standard deviation (SD) (Gaussian distribution) or median (range) (Skewed distribution), and categorical variables as number of cases and percentages (%). Chi-square test (categorical variables) or One-way ANOVA (continuous variables) was used to calculate the differences among different platelet count groups (quartile of log2 platelet count). The correlation of platelet count with in-hospital and ICU mortality in selected participants was investigated. The statistical analysis consisted of three major steps.

Step 1: Univariate and multivariate binary logistic regression models were employed. We constructed three distinct models: a non-adjusted model (with unadjusted covariates), a minimally-adjusted model (with adjusted social demography variables only), and a fully adjusted model (with adjusted covariates as shown in **Table 1**). Step 2: Considering that logistic regression cannot handle the nonlinear relationship, and the possibility of a nonlinear relationship between log2 platelet count and mortality cannot be ruled out, smooth curve fitting (penalized spline method) was used to address

Table 1. Baseline characteristics of participants 26961

log2 platelet count	Quarter 1	Quarter 2	Quarter 3	Quarter 4	*P*-value
N	6719	6661	6836	6745	
Age, mean ± SD, year	65.20±15.16	64.97±15.87	63.66±16.59	62.93±16.75	<0.001
BMI (kg/m^2)	27.31±8.74	27.92±8.67	27.62±8.69	26.89±8.54	<0.001
Albumin	2.84±0.72	3.09±0.69	3.14±0.72	3.00±0.77	<0.001
APACHE-IV score	78.55±32.03	69.95±29.35	69.39±28.84	70.21±28.58	<0.001
Gender (n, %)					<0.001
Male	4046 (60.24%)	3759 (56.45%)	3452 (50.51%)	3027 (44.89%)	
Female	2671 (39.76%)	2900 (43.55%)	3382 (49.49%)	3716 (55.11%)	
Race					<0.001
African-American	741 (11.11%)	731 (11.08%)	842 (12.40%)	697 (10.41%)	
Asian	91 (1.36%)	110 (1.67%)	99 (1.46%)	100 (1.49%)	
Caucasian	5020 (75.30%)	5069 (76.83%)	5074 (74.69%)	5184 (77.44%)	
Hispanic	411 (6.16%)	367 (5.56%)	426 (6.27%)	386 (5.77%)	
U.S. native military and civilian	87 (1.30%)	46 (0.70%)	49 (0.72%)	48 (0.72%)	
Unknown	317 (4.75%)	275 (4.17%)	303 (4.46%)	279 (4.17%)	
Congestive heart failure					<0.001
No	5694 (84.74%)	5481 (82.28%)	5698 (83.35%)	5703 (84.55%)	
Yes	1025 (15.26%)	1180 (17.72%)	1138 (16.65%)	1042 (15.45%)	
COPD					<0.001
No	5756 (85.67%)	5424 (81.43%)	5616 (82.15%)	5664 (83.97%)	
Yes	963 (14.33%)	1237 (18.57%)	1220 (17.85%)	1081 (16.03%)	
Mechanical ventilation					<0.001
No	2340 (34.83%)	2500 (37.53%)	2587 (37.84%)	2506 (37.15%)	
Yes	4379 (65.17%)	4161 (62.47%)	4249 (62.16%)	4239 (62.85%)	
Diabetes					0.013
No	5726 (85.22%)	5594 (83.98%)	5700 (83.38%)	5725 (84.88%)	
Yes	993 (14.78%)	1067 (16.02%)	1136 (16.62%)	1020 (15.12%)	
Sepsis					<0.001
No	4776 (71.08%)	5145 (77.24%)	5317 (77.78%)	4750 (70.42%)	
Yes	1943 (28.92%)	1516 (22.76%)	1519 (22.22%)	1995 (29.58%)	
Oxygen-therapy					0.940
No	4406 (65.58%)	4364 (65.52%)	4477 (65.49%)	4448 (65.95%)	
Yes	2313 (34.42%)	2297 (34.48%)	2359 (34.51%)	2297 (34.05%)	
Antiplatelet drugs					0.012
No	6317 (94.02%)	6184 (92.84%)	6343 (92.79%)	6304 (93.46%)	
Yes	402 (5.98%)	477 (7.16%)	493 (7.21%)	441 (6.54%)	
Coagulation disease					<0.001
No	6209 (92.41%)	6395 (96.01%)	6602 (96.58%)	6535 (96.89%)	
Yes	510 (7.59%)	266 (3.99%)	234 (3.42%)	210 (3.11%)	

Mean +/- SD for continuous variables: *P* value was calculated by weighted linear regression model. % for Categorical variables: *P* value was calculated by weighted chi-square test.

nonlinearity. When nonlinearity was detected, the recursive algorithm was first used to calculate the inflection point, followed by the identification of the range of the inflection point using the bootstrapping algorithm to calculate the confidence interval (CI), and then a two-phase linear regression model was constructed on both sides of the inflection point. We determined the best-fit model (linear regression model vs two-phase linear regression model)

Table 2. Results of univariate and multivariate analysis

Exposure	Non-adjusted model Effect size (95% CI)	Minimally-adjusted model Effect size (95% CI)	Fully-adjusted model Effect size (95% CI)
In-hospital mortality			
Log2 Platelets	0.73 (0.70, 0.75) <0.00001	0.72 (0.70, 0.75) <0.00001	0.87 (0.84, 0.91) <0.00001
Log2 Platelets group			
Q1	1.0	1.0	1.0
Q2	0.64 (0.59, 0.69) <0.0001	0.63 (0.58, 0.69) <0.0001	0.88 (0.79, 0.98) 0.0181
Q3	0.58 (0.53, 0.63) <0.0001	0.59 (0.54, 0.64) <0.0001	0.83 (0.74, 0.92) 0.0002
Q4	0.64 (0.59, 0.70) <0.0001	0.67 (0.61, 0.72) <0.0001	0.85 (0.76, 0.94) 0.0009
P for trends	<0.0001	<0.0001	0.0007
ICU mortality			
Log2 Platelets	0.71 (0.69, 0.74) <0.00001	0.71 (0.68, 0.74) <0.00001	0.87 (0.83, 0.92) <0.00001
Log2 Platelets group			
Q1	1.0	1.0	1.0
Q2	0.66 (0.60, 0.72) <0.0001	0.66 (0.60, 0.72) <0.0001	0.90 (0.80, 1.02) 0.0973
Q3	0.57 (0.52, 0.63) <0.0001	0.58 (0.52, 0.64) <0.0001	0.85 (0.75, 0.95) 0.0013
Q4	0.62 (0.56, 0.68) <0.0001	0.64 (0.58, 0.70) <0.0001	0.83 (0.74, 0.94) 0.0031
P for trends	<0.0001	<0.0001	0.0018

Non-adjusted model: we do not adjust for any covariates. Minimally-adjusted model: only sex, age, and race are adjusted. Fully-adjusted model: all covariates presented in **Table 1** are adjusted.

based on the *p* values of the log likelihood ratio test. Step 3: To ensure the robustness of data analysis, we converted the log2 platelet count into a categorical variable based on quartiles for sensitivity analysis to verify the results of log2 platelet count as a continuous variable.

The analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www. empowerstats.com, X&Y Solutions, Inc, Boston, MA). *P* values less than 0.05 (two-sided) were considered statistically significant.

Results

Baseline characteristics of participants

The distribution of baseline characteristics is shown in **Table 1**. The mean age of patients was (64.23±16.14) years old, and 53.00% were male. All-cause in-hospital and ICU mortality rates were 21.48% and 14.24%, respectively. All participants were divided into four groups according to the quarters of the year: Quarter 1 (January to March, Q1), Quarter 2 (April to June, Q2), Quarter 1 (July to September, Q3), Quarter 1 (October to December, Q4). Compared with patients in Q2-Q4, patients in Q1 were older, with more males, a higher Acute Physiology and Chronic Health Evaluation (APACHE) IV score, a higher proportion of mechanical ventilation, and a lower proportion of congestive heart failure, COPD, diabetes and use of anticoagulant drugs.

Blood platelet count and all-cause in-hospital and ICU mortality

The effect sizes and 95% CIs are listed in **Table 2**. Model 1, an unadjusted model, showed a negative correlation of all-cause in-hospital mortality (RR: 0.73, 95% CI: 0.70-0.75) and all-cause ICU mortality (RR: 0.71, 95% CI: 0.69-0.74) with log2 platelet count. These results were verified by sensitivity analysis. After adjusting for socio-demographic variables (age, sex, race/ethnicity), similar results were detected in model 2, i.e., log2 platelet count was negatively associated with all-cause in-hospital mortality (RR: 0.72, 95% CI: 0.70-0.75) and all-cause ICU mortality (RR: 0.71, 95% CI: 0.68-0.74). In model 3 (fully-adjusted model), log2 platelet count was still shown to be negatively correlated with all-cause in-hospital mortality (RR: 0.87, 95% CI: 0.84-0.91) and all-cause ICU mortality (RR: 0.87, 95% CI: 0.83-0.92) when all covariates presented in **Table 1** were adjusted.

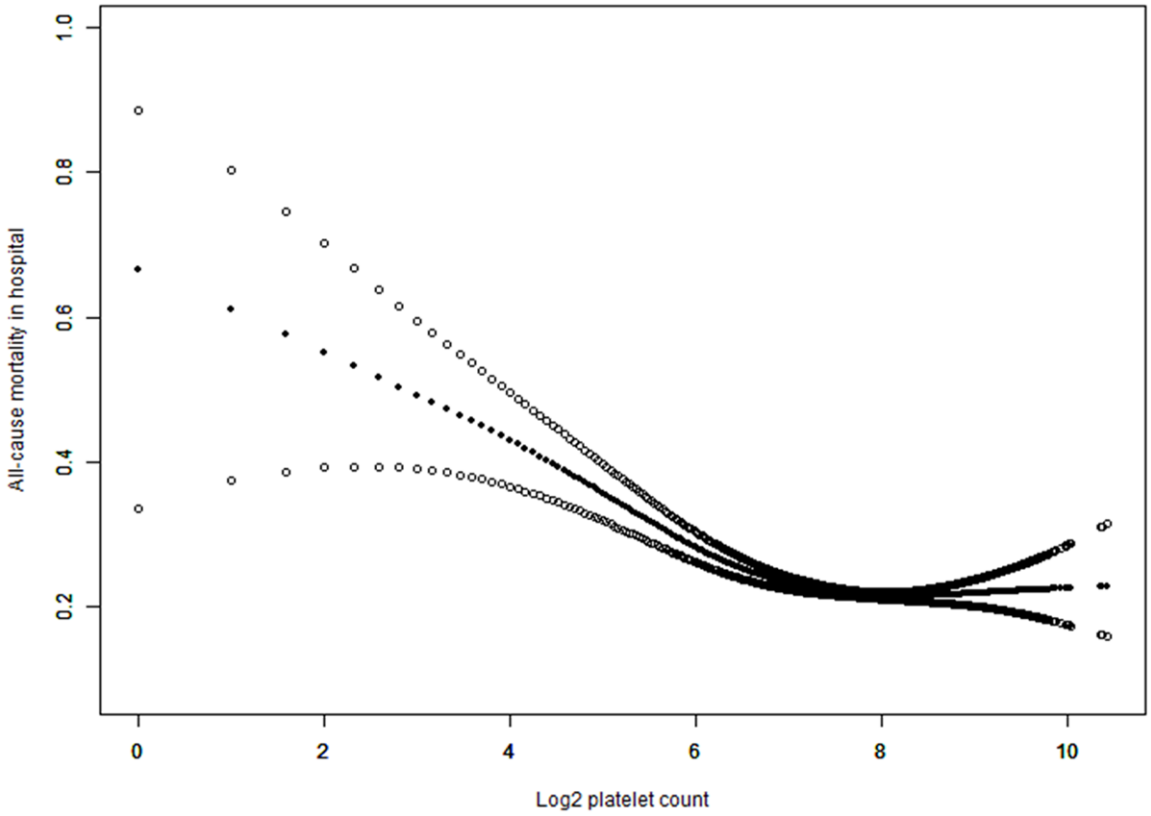

Figure 2. The correlation between log2 basal platelet count and all-cause in-hospital mortality in patients with ARF. The log2 basal platelet count had a non-linear relationship with the all-cause in-hospital mortality, and when the log2 platelet count was below the inflection point, it was negatively associated with the all-cause in-hospital mortality, with the inflection point between 6-8. On the right side of the inflection point, we failed to observe a correlation between log2 platelet count and all-cause in-hospital mortality.

The results on nonlinearity of log2 platelet count and all-cause in-hospital and ICU mortality are shown in **Figures 2**, **3** and **Table 3**, respectively. The inflection points of log2 platelet count (6.83 and 6.86) were obtained by recursive algorithm, and their CIs were 6.29-7.18 and 6.48-7.2 respectively. To facilitate clinical application, an inverse log2 logarithmic conversion was performed. The inflection points were found to be 114×10^9/L and 116×10^9/L, with the CIs of 78×10^9/L-145×10^9/L and 89×10^9/L-147×10^9/L respectively.

The two-phase Logistic regression model showed that to the left of the inflection point, each 1-unit increase in log2 platelet count was associated with a 25% reduction in the risk of in-hospital mortality (RR: 0.75, 95% CI: 0.68-0.83) and a 30% reduction in the risk of ICU mortality (RR: 0.70, 95% CI: 0.63-0.77). Conversely, on the right side of the inflection point, the log2 platelet count increase did not further reduce in-hospital mortality anymore (RR: 0.96, 95% CI: 0.88-1.03), prompting a saturation effect.

Discussion

This retrospective cohort study investigated the relationship between platelet count and all-cause in-patient and ICU mortality in patients with ARF. The results showed that after adjusting for age, sociodemographic factors, comorbidities, and interventions, the platelet count was found to be negatively correlated with the all-cause in-hospital and ICU mortality in severe ARF patients whose platelet count was below a certain range. However, the nonlinearity test demonstrated that the association between platelet count and mortality presented a saturation effect, that is, within a certain range, an increase in platelet count can reduce the risk of death, but when the platelet count was greater than 114×10^9/L and 116×10^9/L

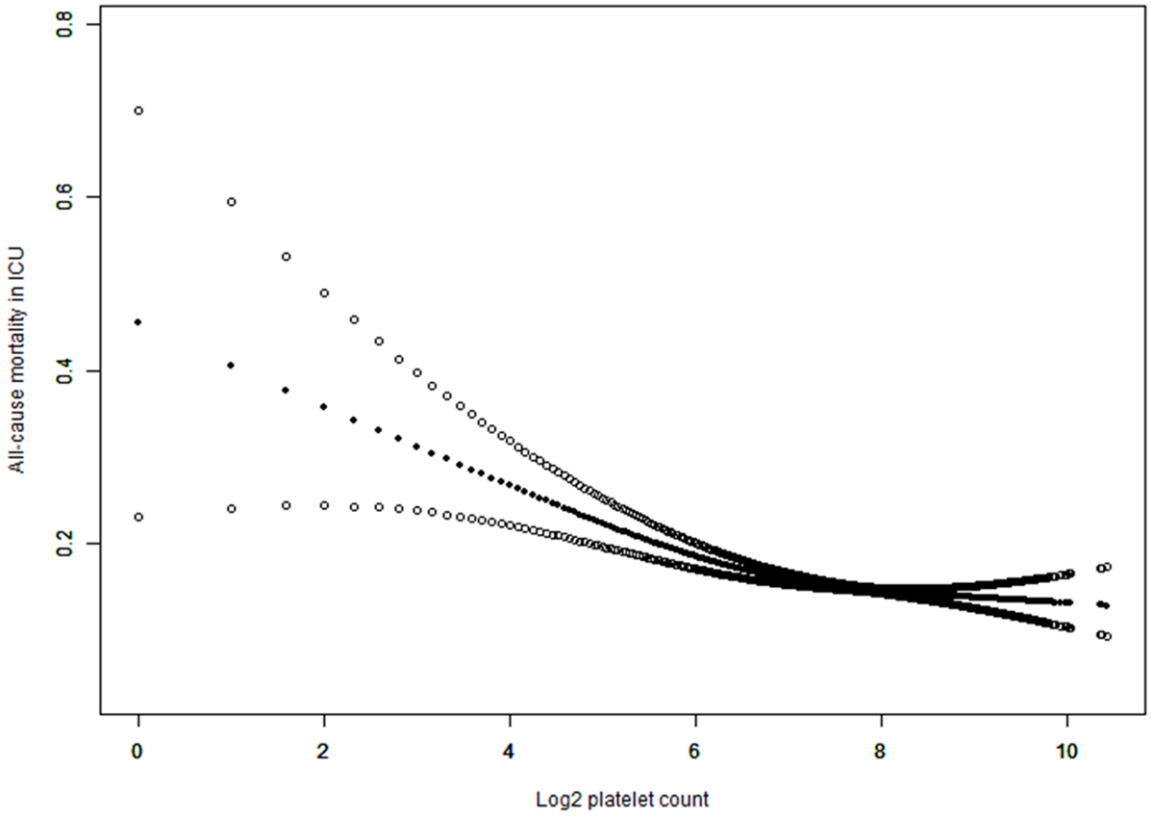

Figure 3. The correlation between log2 platelet count and all-cause ICU mortality in patients with ARF. The relationship between log2 basal platelet count and all-cause ICU mortality was nonlinear. The log2 platelet count was negatively associated with the all-cause ICU mortality when log2 platelet count was less than the inflection point, and the inflection point was visually to be between 6-8. On the right side of the inflection point, we failed to observe a correlation between log2 platelet count and all-cause ICU mortality.

Table 3. Nonlinearity explanation on log2 platelet count and all-cause in-hospital and ICU mortality using the two-phase linear model

	ICU mortality Effect size (95% CI) *P* value	In-hospital mortality Effect size (95% CI) *P* value
Fitting model using		
I model	0.87 (0.82, 0.91) <0.00001	0.86 (0.82, 0.89) <0.00001
Fitting model using two-piecewise linear model		
Inflection point (log2 platelet count)*	6.83 (6.29-7.18)	6.86 (6.48-7.2)
< Inflection point	0.75 (0.68, 0.83) <0.0001	0.70 (0.63, 0.77) <0.0001
> Inflection point	0.96 (0.88, 1.03) 0.2608	0.97 (0.91, 1.04) 0.5190
P for log likely ratio test	<0.001	<0.001
Inflection point (platelet count)#,*	114 (78-145)	116 (89-147)

The adjustment strategy is the same as the fully-adjusted model. #the inflection point of the platelet count is obtained by log2 inverse logarithmic conversion. *the true value of platelets needs $\times 10^9$/L.

respectively, the negative relationship of in-hospital and ICU mortality with platelet count would disappear.

Clinical studies have shown that patients with ARF are often accompanied by thrombocytopenia, which is associated with an increased risk of adverse events and death. Matthew et al. found a strong relationship between hematologic failure (manifested as thrombocytopenia) and mortality in ARF patients treated with mechanical ventilation [26]. The PROTECT trial

enrolling 3721 patients showed that compared with patients without thrombocytopenia, those with moderate and severe thrombocytopenia were more likely to experience subsequent bleeding and received transfusions and, more importantly, were more susceptible to death during ICU or hospital stay [27]. Juan et al. reported in a prospective observational study that ARF patients with H1N1 influenza complicated with thrombocytopenia had a lower in-hospital survival rate [28]. Our results were consistent with those of the above studies. However, these studies have explored a linear rather than a nonlinear correlation between platelet count and mortality, which, we believe, is inconsistent with the real situation in the human body. Instead, we used a nonlinear model to analyze the relationship between platelet count and all-cause mortality in ARF patients, and the results demonstrated that platelet count was negatively correlated with in-hospital and ICU mortality only when the platelet count was less than 114×10^9/L and 116×10^9/L respectively. Once the patient's platelet count exceeded these ranges, the negative correlation disappeared. From the correlation analysis figures, we detected that the safe range of platelet count was 78×10^9/L-145×10^9/L for hospital stay and 89×10^9/L-147×10^9/L for ICU stay.

The mechanisms of thrombocytopenia in patients with ARF are associated with the following aspects: (1) suppression of stem cell/progenitor cell function in the hematopoietic system [29-32]; (2) decreased thrombopoietin production; (3) increased platelet clearance and platelet consumption; (4) bone marrow microenvironment dysfunction and; (5) lung damage [15, 33, 34].

Our research has certain advantages. First, the sample size of this research is relatively large. Second, the subjects of the study were from multicenter ICUs, making the findings applicable to general ICU patients with ARF. Third, to ensure the robustness of data analysis, we performed sensitivity analysis by converting log2 platelet count into categorical variables using quartiles. Finally, a two-phase linear regression model was used to observe the saturation effect between log2 platelet count and all-cause in-hospital and ICU mortality. These advantages make our conclusions more valuable and meaningful in critical situations.

However, this study also has some shortcomings. First, there are some certain regional or national biases as the study population was mainly from the United States. Second, as in other clinical studies, some unmeasured confounders were not adjusted in our data, which inevitably affected the analysis results. Third, this research is a secondary mining of a public database, in which the adjustment strategy of covariates is limited by the database.

Conclusions

Our results demonstrated that platelet count was negatively associated with all-cause in-hospital and ICU mortality in critically ill patients with ARF when the platelet count was less than 114×10^9/L and 116×10^9/L respectively. For AFR patients, the safe ranges of platelet count for hospital stay and ICU stay were 78×10^9/L-145×10^9/L and 89×10^9/L-147×10^9/L, respectively.

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Disclosure of conflict of interest

None.

Abbreviations

ARF, acute respiratory failure; APACHE, Acute Physiology and Chronic Health Evaluation; eICU-CRD, eICU of Collaborative Research Database; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

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