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: There is limited evidence on the correlation between platelet counts and all-cause mortality in critically ill patients with acute respiratory failure (ARF). The aim was to evaluate whether platelet count was associated with all-cause mortality in critical patients with ARF by using the eICU Collaborative Research Database.

Methods: Using a retrospective multicenter cohort dataset, data of 26961 patients with ARF in ICU between 2014 and 2015 were collected. The independent variable was log2 basal platelet count, and the dependent variables were all-cause mortality in hospital and in ICU. Covariates included demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, supportive treatment, and comorbidities.

Results: In 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] or in ICU [RR: 0.87, 95% CI:0.83, 0.92]. By nonlinearity test, the relationship between log2 basal platelet count and all-cause mortality in hospital and in ICU were nonlinear. The inflection point we got was 6.83 and 6.86 (after inverse log2 logarithmic conversion, the platelet count are $114 \times 10^9/L$ and $116 \times 10^9/L$). There was no a correlation between blood platelets and all-cause mortality in hospital on the right side of the inflection point, (RR:0.96, 95% CI: 0.88-1.03) and in ICU (RR:0.97, 95% CI: 0.91-1.04).

Conclusions: For patients with ARF in ICU, platelet count was negatively associated with all-cause mortality in hospital and in ICU when platelet count is less than $114 \times 10^9/L$ and $116 \times 10^9/L$ respectively, but when the platelet count was higher, we failed to observe a correlation between them. The safe ranges of platelet count we detected were $78 \times 10^9/L$ - $145 \times 10^9/L$ and $89 \times 10^9/L$ - $147 \times 10^9/L$ respectively.

Introduction

Platelets are unnucleated fragments derived from megakaryocytes¹. Traditionally, platelet is regarded as to be responsible for hemostasis in response to vascular injury and endothelial disruption². However, besides that, platelets have many other functions, among which participating in the inflammatory process is one of the most important functions³. Many studies have proved that platelets participate in the pathogenesis of many inflammation-related clinical diseases³⁻⁵, including respiratory system, rheumatic system, gastrointestinal system and other diseases^{6,7}. Therefore, platelets can be used as potentially important clinical indicators for the monitoring of disease progression. The most common complication of platelet abnormalities in ICU is thrombocytopenia⁸, which is a risk factor for the development of organ failure and vascular leakage. Occurrence and development of thrombocytopenia is associated with increased mortality in critically ill patient^{9,10,11}.

Acute respiratory failure (ARF) is one of the common life-threatening complications in intensive care unit patients, often accompanied by changes in platelet count¹². The mechanism may be that part of platelets

is originally derived from the lung tissue^{12–14}, indicated by 1) megakaryocytes are also found in the lung tissue¹⁵, 2) platelet counts are higher in the left side of the heart than in the right side of the heart, implying platelet genesis in the pulmonary tissue¹⁶, and 3) in many severe cases such as ARF, thrombocytosis is often occurred first, and then followed by thrombocytopenia¹⁷.

However, the relationship between platelet count and prognosis in ARF patients has been controversial, and the real relationship was actually difficult to be drawn because of the limited methodology. Therefore, we used the large sample library of eICU to explore the relationship between platelet count and all-cause mortality in hospitals and in ICU for patients with ARF.

Participants And Methods

Data source

The data of our analysis came from the eICU of Collaborative Research Database (eICU-CRD). The dataset included 200,859 ICU admissions between 2014 and 2015. These patients were collected from 208 hospitals across the United States. The data contained in the eICU-CRD are of high quality. Most variables are close to complete, with little missingness in the routinely collected fields^{18,19}. The ethics of eICU has been approved. For details, please refer to the official website (<https://eicu-crd.mit.edu>). After finishing the web-based training courses and Protecting Human Research Participant 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. The target independent variable is log2 basal blood platelet count and recorded as a continuous variable. The outcome variables are all-cause mortality in hospital and in ICU, respectively. Both are recorded as binary variables (0 survival, 1 non-survival)

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 patient's identity information as nontraceable codes. A total of 200,859 ICU patients were initially included, of whom 26961 were eventually screened to be analyzed. (Fig. 1). The collection time of participants started 2014 and ended in 2015, respectively. 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 dependent variable was basal platelet count data. Targeted independent variables were all-cause mortality in hospital and in ICU. Covariates were used as follows : continuous variables consisted of age (years), albumin (g/L), body mass index (BMI, kg/m²), APACHE IV score.

Categorical variables consist of sex, race / ethnicity, congestive heart failure, COPD, diabetes, coagulation disease, mechanical breathing, oxygen therapy, antiplatelet drugs. In general, the covariates included demographic data, comorbidities, severity of illness, and life support interventions, etc.

Statistical analysis

Given that the platelet count is a skewed distribution, we log2 transform it to be close to a normal distribution. We use mean $\pm$ standard deviation (SD) to represent continuous variables, median (range) (skew distribution), no. (%) to represent categorical variables). Chi-square test (categorical variables) or One-way ANOVA (continuous variables) were employed to calculate the differences among different platelet count groups (quartile of log2 platelet count). We investigated whether the platelet count is related to the mortality of selected participants in hospitals and ICUs. Our statistical method is divided into 3 steps.

Step 1: We used Univariate and multivariate binary logistic regression models and constructed three distinct models: including non-adjusted model (no covariates were adjusted), minimally-adjusted model (only social demography variables were adjusted), and fully adjusted model (adjusted the covariates 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 death cannot be ruled out, we used the smooth curve fitting to address the nonlinearity. We use a recursive algorithm to calculate the inflection point, if non-linearity is detected, the range of the inflection point using bootstrapping to calculate the credible interval, and construct two piecewise linear regression models on both sides of the inflection point. The determination of the best fit model (linear regression model and two-stage linear regression model) was based on the P value of the log-likelihood ratio test. Step 3: We did a sensitivity analysis by converting the log2 platelet count into a categorical variable by quartile to ensure the robustness of data.

Table 1
Baseline characteristics of participants 26961

log2 platelet count	Q1	Q2	Q3	Q4	P-value
N	6719	6661	6836	6745	
Age, mean $\pm$ SD, year	65.20 $\pm$ 15.16	64.97 $\pm$ 15.87	63.66 $\pm$ 16.59	62.93 $\pm$ 16.75	< 0.001
BMI(kg/m2)	27.31 $\pm$ 8.74	27.92 $\pm$ 8.67	27.62 $\pm$ 8.69	26.89 $\pm$ 8.54	< 0.001
Albumin	2.84 $\pm$ 0.72	3.09 $\pm$ 0.69	3.14 $\pm$ 0.72	3.00 $\pm$ 0.77	< 0.001
APACHE-II score	78.55 $\pm$ 32.03	69.95 $\pm$ 29.35	69.39 $\pm$ 28.84	70.21 $\pm$ 28.58	< 0.001
Sex (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%)	

Mean $\pm$ 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

log2 platelet count	Q1	Q2	Q3	Q4	P-value
Yes	1025 (15.26%)	1180 (17.72%)	1138 (16.65%)	1042 (15.45%)	< 0.001
COPD					
No	5756 (85.67%)	5424 (81.43%)	5616 (82.15%)	5664 (83.97%)	< 0.001
Yes	963 (14.33%)	1237 (18.57%)	1220 (17.85%)	1081 (16.03%)	
Mechanical breathing					0.013
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%)	< 0.001
Diabetes					
No	5726 (85.22%)	5594 (83.98%)	5700 (83.38%)	5725 (84.88%)	< 0.001
Yes	993 (14.78%)	1067 (16.02%)	1136 (16.62%)	1020 (15.12%)	
Sepsis					0.940
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%)	0.012
Oxygen-therapy					
No	4406 (65.58%)	4364 (65.52%)	4477 (65.49%)	4448 (65.95%)	0.012
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%)	

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

log2 platelet count	Q1	Q2	Q3	Q4	P-value
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					

We performed the analyses 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). Statistically significant in $p < 0.05$ (both sides).

Results

Baseline characteristics of participants

The participants of baseline characteristics is shown in Table 1. The mean age was 64.23 ± 16.14 years, 52.99% were male. All-cause mortality in hospital and in ICU is 21.48% and 14.24%, respectively. Compared with patients in Q2-Q4, patients in Q1 were elder, mostly male, and had a higher APACHE IV score with a higher proportion of mechanical ventilation and a lower proportion of congestive heart failure, COPD, diabetes and the use of anticoagulant drugs.

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

We listed the effect sizes and 95% confidence interval (95% CI) in Table 2. Model 1 (unadjusted model) indicated that all-cause mortality in hospital (RR: 0.73, 95% CI: 0.70–0.75) and in ICU (RR: 0.71, 95% CI: 0.69–0.74) were negatively associated with log2 platelet count. These results were verified by sensitivity analysis. Similar results can be detected in adjusted model 2 (socio-demographic variables such as age, sex, race/ethnicity), i.e., a negative association between log2 platelet count and all-cause mortality both in hospital (RR: 0.72, 95% CI: 0.70–0.75) and in ICU (RR: 0.71, 95% CI: 0.68–0.74) were also existed. In model 3 (fully-adjusted model), log2 platelet count was still shown to be negatively correlated with all-cause mortality in hospital (RR: 0.87, 95%CI: 0.84–0.91) and in ICU (RR: 0.87, 95% CI: 0.83–0.92) when all covariates presented in Table 1 were adjusted.

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)
Mortality in Hospital			
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
Mortality in ICU			
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 for.			
Fully-adjusted model: all covariates presented in Table 1 are adjusted for.			

The results about the nonlinearity of log2 platelet count and all-cause mortality both in ICU and in hospital were shown in Fig. 2, Fig. 3, and Table 3, respectively. By recursive algorithm, we got the inflection points for log2 platelet count (6.83 and 6.86), the credible intervals of the inflection points are 6.29–7.18 and 6.48–7.2 respectively. To facilitate clinical application, we have carried out an inverse log2 logarithmic conversion. Therefore, the inflection points are $114 \times 10^9/L$ and $116 \times 10^9/L$, with the confidence intervals of $78 \times 10^9/L$ – $145 \times 10^9/L$ and $89 \times 10^9/L$ – $147 \times 10^9/L$ respectively.

Table3

Nonlinearity explanation on log2 platelet count and all-cause mortality in hospital and in ICU using two-piecewise linear model

	Mortality in ICU	Mortality in Hospital
	Effect size (95%CI) P value	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 with fully-adjusted model		
#, the inflection point of the platelet count is obtained by log2 inverse logarithmic conversion		
*, the true value of platelets needs $\times 10^9/L$		

Two-piecewise Logistic regression model showed that to the left of the turning point, for every 1 unit increase in log2 platelet count, the risk of hospital mortality decreases by 25% [RR: 0.75, 95% CI: 0.68–0.83] and the risk of ICU mortality decreases by 30% [RR: 0.70, 95% CI: 0.63–0.77]. Conversely, on the right side of the inflection point, the log2 platelet count increase does not further reduce 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 counts and all-cause mortality in hospitals and in ICUs in patients with ARF. Our results showed that after controlling for age, sociodemographic factors, comorbidities, and interventions, platelet count in severe ARF patients was negatively correlated with all-cause mortality in hospital and in ICU in a condition of platelet count less than certain range. However, the nonlinearity test demonstrated that the association between platelet count and mortality presents a saturation effect, that is, within a certain range, the increase of platelet count can reduce the risk of death, but if platelet count is respectively more than $114 \times 10^9/L$ and $116 \times 10^9/L$, the negative relationship between mortality and platelet count would disappear.

Clinical studies have shown that patients with ARF are often accompanied by thrombocytopenia, which is associated with adverse events and increased risk of mortality. Matthew et al. found a strong relationship existed between hematologic failure (manifested by thrombocytopenia) and mortality in populations with ARF treated with mechanical ventilation²⁰. The PROTECT trial enrolling 3721 patients showed that patients with moderate and severe thrombocytopenia more likely had subsequent bleeding and received transfusions, and more importantly, were more vulnerable to die during ICU or hospital stay when compared to patients without thrombocytopenia²¹. Juan et al. reported in a prospective observational study that ARF patients with H1N1 influenza complicated with thrombocytopenia had a lower in-hospital survival rate²². Our results were consistent with those of the above studies. However, linear other than nonlinear correlations between platelet count and mortality were explored in these studies, which, we think, were inconsistent with the real situation in the human body.. On the contrary, in our study, we used a nonlinear model to analyse the relationship between platelet count and all-cause mortality in ARF patients, and the results demonstrated that platelet count was negatively correlated with mortality in hospital and in ICU only when platelet count were less than $114 \times 10^9/L$ and $116 \times 10^9/L$ respectively. Once the patient's platelet count exceeded these ranges, the negative correlation disappeared. From the correlation analysis figure, we detected that the safe range of platelet count were $78 \times 10^9/L$ - $145 \times 10^9/L$ for hospital stay and $89 \times 10^9/L$ - $147 \times 10^9/L$ for ICU stay respectively.

The mechanisms of thrombocytopenia in patients with ARF are associated with several aspects, including 1) suppression of stem cell/progenitor cell function in the hematopoietic system²³⁻²⁶, 2) decreased thrombopoietin (TPO) production, 3) imbalance between platelet consumption and production, 4) dysfunctional bone marrow microenvironment and 5) lung damage^{14, 27, 28}.

Our research has certain advantages. First, the sample size of this research is relatively large. Second, our data from a multicenter ICU, making the results credible for general ICU patients with ARF. Third, we performed sensitivity analysis by converting log2 platelet count into categorical variables by quartiles to improve data robustness. Finally, a two-part linear model was used to observe the saturation effect between log2 platelet count and all-cause mortality in hospitals and ICUs.

However, our study also has some shortcomings. Firstly, the study population is mainly from America, making the possibility of regional or State's bias. Secondly, like other clinical studies, some unmeasured

confounders are not controlled in our data, which inevitably influence the analysis results. Thirdly, this research is a secondary mining of public databases, 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 mortality in hospital and in ICU in critically ill patients with ARF when platelet count is less than $114 \times 10^9/L$ and $116 \times 10^9/L$ respectively. For AFR patients in ICU, the safe ranges of platelet count were $78 \times 10^9/L$ - $145 \times 10^9/L$ and $89 \times 10^9/L$ - $147 \times 10^9/L$.

Declarations

- Ethical Approval and consent to participate

The study has been approved by the Ethics Committee of Affiliated Hospital of Guizhou Medical University .

- Declaration of Conflicting Interests

There were no potential conflicts of interest.

- Funding

No funding.

- Authors' contributions

CX contributed to study concept and design, drafting of the manuscript. ZAQ constructed and cleared data. JJX, MYC, LQ, LW, HTH, LSW and GDX help with data arrangement. FS contributed to the study concept, supervision and organized the final manuscript.

- Data availability statement

The data are available on the eICU- CRD website at <https://eicu-crd.mit.edu>

- Competing interests

There was no competing interests in authors.

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Figures

Figure 1

Flow chart of subject selection. ICU =intensive care unit, ARF= acute respiratory failure

Figure 2

The correlation between log2 basal platelet count and all-cause mortality in Hospital for patients with ARF. The relationship between log2 basal platelet count and all-cause mortality in hospital were nonlinear, in which log2 platelet count was negatively associated with all-cause mortality in hospital when log2 platelet count is less than inflection point, and inflection point was shown 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 mortality in hospital.

Figure 3

The correlation between log2 platelet count and all-cause mortality in ICU in patients with ARF. The relationship between log2 basal platelet count and all-cause mortality in ICU were nonlinear. log2 platelet count was negatively associated with all-cause mortality in ICU when log2 platelet count is less than 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 mortality in ICU.