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Association between platelets and in-hospital mortality in critically ill patients with tumours: a retrospective cohort study

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ABSTRACT

Objectives Platelet count is an independent predictor of mortality in patients with cancer. It remains unknown whether the platelet count is related to in-hospital mortality in severely ill patients with tumours.

Design A retrospective study based on a dataset from a multicentre cohort.

Setting This was a secondary analysis of data from one Electronic Intensive Care Unit Collaborative Research Database survey cycle (2014–2015).

Participants The data pertaining to severely ill patients with tumours were collected from 208 hospitals located across the USA. This study initially a total of 200 859 participants. After the population was limited to patients with combined tumours and platelet deficiencies, the remaining 2628 people were included in the final data analysis.

Primary and secondary outcome measures The main measure was the platelet count, and the main outcome was in-hospital mortality.

Results After adjustment for the covariates, the platelet count had a curvilinear relationship with in-hospital mortality (p<0.001). The first inflection point was 18.4 (per 10 change). On the left side of the first inflection point (platelet count ≤184 'x10ˆ9/L), an increase of 10 in the platelet count was negatively associated with in-hospital mortality (OR 0.92, 95% CI 0.89 to 0.95, p<0.001). The second inflection point was 44.5 (per 10 change). Additional increases of 10 in the platelet count thereafter were positively associated with hospital mortality (OR 1.13, 95% CI 1.00 to 1.28, p=0.0454). The baseline platelet count was in the range of 184 'x10ˆ9/L–445 'x10ˆ9/L(p=0.0525), and the hospital mortality was lower than the baseline platelet count in other ranges.

Conclusions The relationship between platelet count and in-hospital mortality in critically ill patients with tumours was curvilinear. The lowest in-hospital mortality was associated with platelet count between 184 'x10ˆ9/Land 445 'x10ˆ9/L. This indicates that both high and low platelet count should receive attention in clinical practice.

BACKGROUND

Platelets are cytoplasmic fragments produced by megakaryocytes. In addition to

Strengths and limitations of this study

► This is the first study to describe a curvilinear relationship between the platelet count and in-hospital mortality in critically ill patients with tumours.

► The platelet count, which is easy to obtain, was used as an indicator for the prediction of prognosis in critically ill patients with tumours.

► The large sample size from Electronic Intensive Care Unit Collaborative Research Database strengthened the statistical power and credibility.

► A retrospective cohort study design may lead to certain types of bias (eg, information bias, confounding bias).

► Data were collected from 2014 to 2015, and it was impossible to observe changes over the course of a longer time frame.

participating in the process of haemostasis and maintaining the integrity of the vascular endothelium,[1] they also participate in the occurrence and development of tumours.[2] An increase in the number of platelets is closely related to the occurrence and metastasis of tumours,[3] and a decrease in the number of platelets can increase the risk of bleeding and death.[4]

Abnormal platelets are one of the most common problems in various intensive care units (ICUs) and are thought to play an important role in the deterioration of the prognosis of ICU patients.[5] Studies have found that thrombocytopaenia is associated with an increased risk of haematological malignancies[6] and an increase in mortality in critically ill patients.[7]

However, in patients with severe tumours, whether platelets are related to in-hospital mortality is still unknown. There is a lack of relevant studies on the cut-off value for platelets with regard to safety in patients with

severe tumours, and given the limitations in methodology, it is impossible to draw a reliable conclusion regarding the relationship between the two factors. Therefore, we conducted a retrospective cohort study to explore the relationship between platelets and in-hospital mortality in patients with severe tumours and to obtain the platelet threshold that indicates a decreased risk of mortality, which can serve as a reference in future clinical work.

METHODS
Data source
This study used data collected from the Electronic Intensive Care Unit (eICU) Collaborative Research Database (eICU-CRD), which covered 200 859 ICU admissions in 208 US hospitals between 2014 and 2015. To mitigate potential concerns about privacy, the identifying information of the participants was encoded as nontraceable codes in this study. Data were collected from the hospital electronic medical records system, including physical and medical records, medication records, laboratory records and imaging data. After finishing the web-based training courses and the Protecting Human Research Participants examination (No. 36208651), we obtained permission to extract data from eICU-CRD. We extracted and analysed the data from this public database.[8] The data from the official eICU website (https://eicu-crd.mit.edu/) were analysed.

Study design
This was a secondary analysis based on a dataset from a multicentre cohort. We set the platelet count as the target independent variable and recorded it as a continuous variable. The outcome variable was in-hospital mortality and was recorded as a binary variable (1=death, 0=survival).

Study population
We performed a secondary data analysis based on data from 1 year of the eICU survey cycles, namely, 2014–2015. After a series of screening steps, we finally selected 2628 out of 200 859 participants for the final data analysis. We screened participants according to the exclusion criteria listed below: (1) people aged <18 years (n=475); (2) subjects without tumour data (n=1 98 057); (3) patients who were readmitted (n=42 397) and (4) patients with missing platelet counts (n=174). This research was not part of a clinical trial, and therefore, did not need to be registered.

Clinical variables and outcomes
In this study, the independent variable was the platelet count ('x10^9/L). The target dependent variable was in-hospital mortality.

Among the covariates, the continuous variables consisted of age (years), body mass index (BMI) (kg/m^2), prothrombin time-international normalised ratio (PT-INR) (ratio), partial thromboplastin time (PTT) (sec), PT (sec), haemoglobin level (g/L) and red cell count (x10^12/L).

The categorical variables included sex (male, female), race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other), tumour type (haematologic malignancies, thoracic tumours, skin tumours, muscle tumours, skeletal tumours, gastrointestinal (GI) tumours, head and neck tumours, central nervous system (CNS) tumours, unknown primary tumours, genitourinary (GU) tumours), co-occurring acute respiratory failure (ARF) or acute coronary syndrome (ACS), coagulopathy or stroke, use of anticoagulation or antiplatelet drugs, use of mechanical ventilation and use of glucocorticoid. In general, the covariates included demographic data, tumour type, laboratory data, comorbidities and interventions.

Patient and public involvement
Patients were not involved in this study.

Statistical analysis
We accounted for marked variance and used ANOVA and χ^2 tests.

Continuous variables are expressed as the means±SD.

Categorical variables are expressed as frequencies or percentages. To investigate whether platelets were correlated with in-hospital mortality in the selected participants, our statistical analysis consisted of three main steps.

Step 1: Univariate and multivariate binary logistic regression models were constructed. We constructed three distinct models: an unadjusted model (no covariates were used for adjustment), a minimally adjusted model (only sociodemographic variables were used for adjustment) and a fully adjusted model (the covariates presented in table 1 were used for adjustment).

Step 2: As the possibility of a non-linear relationship between platelet count and mortality cannot be ruled out, we used smooth curve fitting (penalised spline method) to address the non-linearity. When non-linearity was detected, we first calculated the inflection point using a recursive algorithm and then constructed a three-piecewise linear regression model on both sides of the inflection point. We determined the best fitting model (linear regression model vs three-piecewise linear regression model) based on the p values for the log likelihood ratio test. In this step, we used the ggplot2 package, nlme package and mgcv package in R.

Step 3: To ensure the robustness of the data analysis, we performed a sensitivity analysis. The purpose was to verify the results obtained using the platelet count as a continuous variable. The 'P for trend' used in this study was based on the purpose of sensitivity analysis. The exposure variable platelet count was a continuous variable in the research. Therefore, to determine whether there was a potential non-linear relationship, we converted the platelet count into a categorical variable by tertile and performed a trend test to observe whether the p value

Table 1 Characteristics and outcomes of participants

Platelet count Median (min-max) ('x10^9/L)	First tertile (n=869) 97.0 (1.0–157.0)	Second tertile (n=874) 199.0 (158.0–243.0)	Third tertile (n=885) 320.0 (244.0–699.0)	P value
Demographics				
Age (years, mean±SD)	66.8±13.9	66.9±13.9	64.6±13.6	<0.001
Sex, n (%)				<0.001
Male	532 (61.2)	472 (54.0)	415 (46.9)	
Female	337 (38.8)	402 (46.0)	470 (53.1)	
BMI (kg/m^2, mean±SD)	23.7±9.8	24.5±10.0	23.4±10.3	0.068
Ethnicity, n (%)				0.073
African-American	92 (10.8)	76 (8.8)	84 (9.6)	
Asian	4 (0.5)	13 (1.5)	4 (0.5)	
Caucasian	603 (70.4)	646 (74.6)	637 (72.6)	
Hispanic	120 (14.0)	98 (11.3)	126 (14.4)	
Native American	9 (1.1)	7 (0.8)	4 (0.5)	
Other/Unknown	28 (3.3)	26 (3.0)	22 (2.5)	
Tumour type, n (%)				0.580
Haematologic malignancy	111 (12.8)	108 (12.4)	102 (11.5)	
Chest tumours	240 (27.6)	232 (26.5)	264 (29.8)	
Skin, muscle and skeletal tumours	29 (3.3)	20 (2.3)	25 (2.8)	
GI tumours	227 (26.1)	231 (26.4)	224 (25.3)	
Head and neck tumours	96 (11.0)	75 (8.6)	86 (9.7)	
CNS tumours	45 (5.2)	55 (6.3)	47 (5.3)	
Unknown primary	10 (1.6)	11 (1.3)	9 (1.0)	
GU tumours	111 (12.8)	142 (16.6)	128 (14.5)	
Laboratory data				
Red cell count (x10^12/L, mean±SD)	3.3±0.9	3.8±0.8	3.8±0.8	<0.001
Haemoglobin (g/L, mean±SD)	10.0±2.5	11.4±2.4	11.1±2.4	<0.001
PT-INR (ratio, mean±SD)	1.6±1.4	1.4±1.0	1.5±1.3	0.017
PT (sec, mean±SD)	18.0±13.3	15.8±9.0	16.8±13.5	0.007
PTT (sec, mean±SD)	36.2±13.5	33.0±11.5	32.7±11.9	<0.001
Comorbidities, n (%)				
ACS				0.107
No	833 (95.9)	819 (93.7)	843 (95.3)	
Yes	36 (4.1)	55 (6.3)	42 (4.8)	
ARF				0.481
No	661 (76.1)	685 (78.4)	689 (77.9)	
Yes	208 (23.9)	189 (21.6)	196 (22.2)	
Stroke				0.004
No	830 (95.5)	839 (96.0)	869 (98.2)	
Yes	39 (4.5)	35 (4.0)	16 (1.8)	
Coagulopathy				<0.001
No	806 (92.8)	853 (97.6)	868 (98.1)	
Yes	63 (7.3)	21 (2.4)	17 (1.9)	
Intervention, n (%)				
Anticoagulant drugs				0.119
No	848 (97.6)	840 (96.1)	863 (97.5)	
Yes	21 (2.4)	34 (3.9)	22 (2.5)	

Continued

Table 1 Continued				
Platelet count **Median (min-max) ('x10⁹/L)**	**First tertile (n=869)** **97.0 (1.0–157.0)**	**Second tertile (n=874)** **199.0 (158.0–243.0)**	**Third tertile (n=885)** **320.0 (244.0–699.0)**	**P value**
Mechanical ventilation				0.366
No	695 (80.0)	721 (82.5)	725 (82.0)	
Yes	174 (20.0)	153 (17.5)	160 (18.1)	
Antiplatelet drugs				0.247
No	798 (91.8)	789 (90.3)	818 (92.4)	
Yes	71 (8.2)	85 (9.7)	67 (7.6)	
Glucocorticoids (%)				0.003
No	709 (81.6%)	765 (87.5)	751 (84.9)	
Yes	160 (18.4%)	109 (12.5)	134 (15.1)	
In-hospital mortality, n (%)				<0.001
No	672 (77.6%)	767 (88.3)	744 (84.7)	
Yes	194 (22.4%)	102 (11.7)	134 (15.3)	

Analysis of variance (for continuous variables) and X^2 tests (for categorical variables) were performed to identify differences among tertiles.

ACS, acute coronary syndrome; ARF, acute respiratory failure; BMI, body mass index; CNS, central nervous system; GI tumours, gastrointestinal tumours; GU, genitourinary; PT, prothrombin time; PT-INR, prothrombin time-international normalised ratio; PTT, partial thromboplastin time.

of the trend test was consistent with the p value when the platelet count was a continuous variable.

For missing covariates, we used multiple imputation. Of the 2628 individuals in the analytical sample, we listed the missing data for each variable in online supplemental table 1. Our purpose is to minimise possible deviations and maximise statistical power. Covariates with missing data were excluded from data analysis. We use multiple imputation to generate five sets of imputation data and perform sensitivity analysis with the data before imputation. We found that the data were almost the same preimputation or postimputation, and the six curves had a consistent trend. Please refer to online supplemental table 1 and figure 2 for details.

Data were analysed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Boston, Massachusetts, USA). All statistical tests were two sided, and a p<0.05 was considered statistically significant.

RESULTS
Patient selection
The data pertaining to severely ill patients with tumours were collected from 208 hospitals located across the USA. This study initially a total of 200 859 participants. After the population was limited to patients with combined tumours, 2802 people remained. Among those 2802 people, we further excluded patients with platelet deficiencies, and finally, the remaining 2628 people were included in the final data analysis (see the flow chart in figure 1 for details).

Baseline characteristics of participants
The baseline characteristics of the participants are listed in table 1. Table 1 shows the weighted distributions of sociodemographic characteristics and other covariates in the selected population in the eICU from 2014 to 2015. The average age of the participants was 66.13±13.83 years, and approximately 54% of them were males. There were no significant differences in BMI, ethnicity, tumour type, ACS, ARF, use of anticoagulant drugs, use of antiplatelet
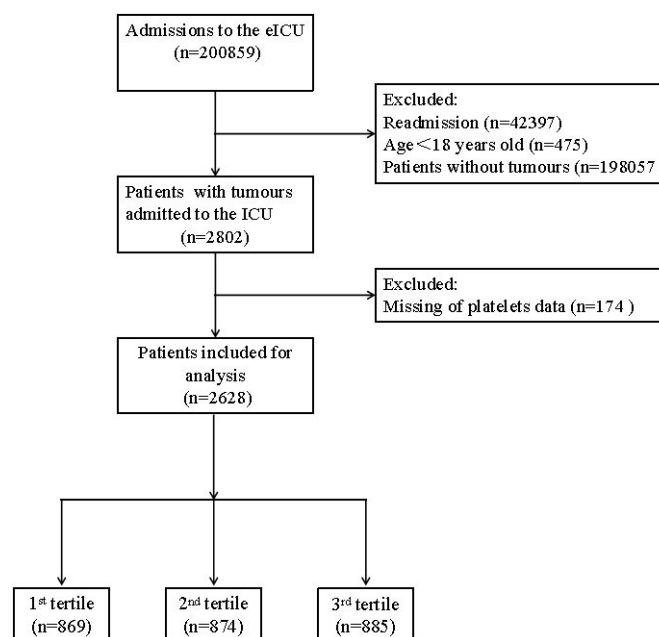

Figure 1 Flow chart of patient selection. eICU, electronic intensive care unit; ICU, intensive care unit.

Table 2 Multivariate analysis using non-adjusted and adjusted logistic regression models

Variable	Crude model (OR, 95% CI)	Minimally adjusted model (OR, 95% CI)	Fully adjusted model (OR, 95% CI)
Platelet count (per change in the platelet count of 10)	0.98 (0.97 to 0.99)	0.98 (0.97 to 0.99)	0.99 (0.98 to 1.00)
1st tertile	Ref	Ref	Ref
2nd tertile	0.46 (0.35 to 0.60)	0.45 (0.35 to 0.59)	0.46 (0.31 to 0.71)
3rd tertile	0.62 (0.49 to 0.80)	0.61 (0.47 to 0.78)	0.66 (0.44 to 0.98)
P for trend	<0.0001	<0.0001	0.0339

Crude model: we did not adjust for other covariates.
Minimally adjusted model: we adjusted for age, ethnicity, sex, BMI.
Fully adjusted model: we adjusted for age, ethnicity, sex, BMI, tumour type, PT-INR, PTT, PT, haemoglobin level, red cell count, ARF, ACS, stroke, coagulopathy, anticoagulant drugs, mechanical ventilation, antiplatelet drugs and glucocorticoids.
ACS, acute coronary syndrome; ARF, acute respiratory failure; BMI, body mass index; PT, prothrombin time; PT-INR, prothrombin time-international normalised ratio; PTT, partial thromboplastin time; Ref, reference.

drugs or use of mechanical ventilation among patients in different tertiles of platelet count (all p>0.05). In total, 194 participants in the first tertile with regard to platelet count died, 102 in the second tertile died, and 134 in the third tertile died. Among the different platelet count tertiles, the participants in the third tertile were younger than those in the first tertile and second tertile. The PT-INR, PTT(s) and bleeding time(s) were prolonged in the first tertile group. The haemoglobin level (g/L) and red cell count (x10^12/L) were lower in the first tertile group. The severely ill patients with cancer were mainly Caucasians, and very few were Asians or Native Americans. The main tumour types were thoracic tumours, GI tumours, skin tumours, muscle tumours, skeletal tumours, unknown primary tumours, head and neck tumours, CNS tumours and GU tumours. The proportions of patients with ARF and mechanical ventilation were higher in the first tertile group. The proportions of patients who had ACS and used anticoagulants were lower in the first tertile group. Interestingly, the mortality rate of patients in the first tertile group was higher than those in the other groups.

Relationship between platelet count and in-hospital mortality

We listed the effect sizes of the association between platelet count(per change in the platelet count of 10) and in-hospital mortality in table 2. Because platelet count fluctuations and changes occur clinically, mostly in 1 to dozens of per 10 changes. Therefore, we used per 10 change to better match the actual clinical situation. Model 1 (crude model) was the unadjusted model. This model indicated that in-hospital mortality (OR 0.98, 95% CI 0.97 to 0.99) was negatively associated with platelet count. These results were verified by sensitivity analysis. In model 2 (minimally adjusted model), after adjusting for sociodemographic variables (age, sex, race/ethnicity, BMI), the association between platelets and in-hospital mortality was still negative (OR 0.98, 95% CI 0.97 to 0.99). Similar results were detected in model 3 (fully adjusted model) (OR 0.99, 95% CI 0.98 to 1.00).

The results regarding the non-linearity of the relationship between the platelet count and in-hospital mortality are shown in figure 2 and table 3. The recursive algorithm, after adjustment for demographic data, tumour type, interventions, comorbidities and laboratory data, showed that the platelet count had a curvilinear relationship with in-hospital mortality (p<0.001). The first inflection point was 18.4 (per 10 change). On the left side of the first inflection point (platelet count ≤184 'x10^9/L), an increase of 10 in the platelet count was negatively associated with hospital mortality (OR 0.92, 95% CI 0.89 to 0.95, p<0.001). The second inflection point was 44.5 (per 10 change). Additional increases of 10 in the platelet count after the second inflection point were positively associated with hospital mortality (OR 1.13, 95% CI 1.00 to 1.28, p=0.0454). The baseline platelet count was in the
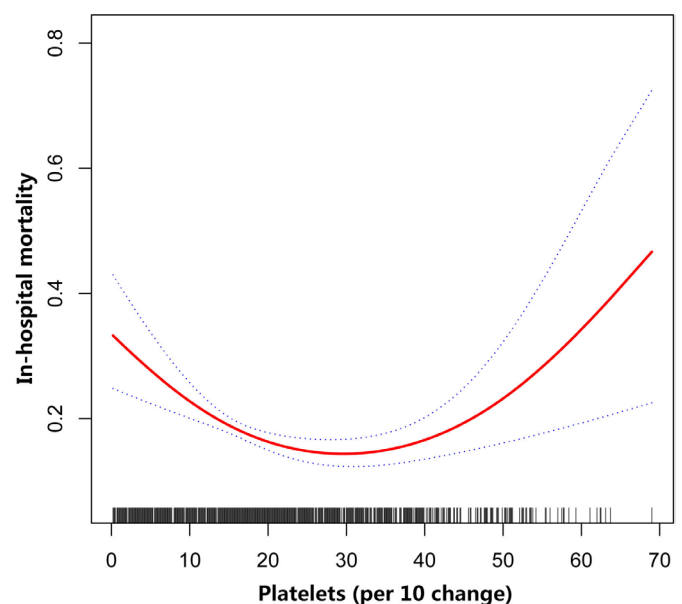

Figure 2 Non-linear relationship between the platelet count (per change in the platelet count of 10) and in-hospital mortality.

Table 3 Non-linear relationship between the platelet count and in-hospital mortality using a three-piecewise linear model

Outcome	Effect size (OR, 95% CI), p value
Model fit using binary logistic regression	0.99 (0.98 to 1.00) 0.1779
Model fit using three-piecewise linear model	
Inflection points of the platelet count (per change in the platelet count of 10)	18.4, 44.5
<18.4	0.92 (0.89 to 0.95) <0.0001
18.4–44.5	1.03 (0.99 to 1.06) 0.0525
>44.5	1.13 (1.00 to 1.28) 0.0454
P for log likelihood ratio test	<0.001

The adjustment strategy was the same as that for the fully adjusted model.

range of 184 'x10^9/L to 445 'x10^9/L(p=0.0525), and the hospital mortality was lower than the baseline platelet count in other ranges.

A logistic regression model showed that on the left side of the first inflection point, for every increase of 10 in the platelet count, the risk of in-hospital mortality was reduced by 8% (OR 0.92, 95% CI 0.89 to 0.95). In contrast, on the right side of the second inflection point, for an increase of 10 in the platelet count, the risk of in-hospital mortality increased by 13% (OR 1.13, 95% CI 1.00 to 1.28). Furthermore, between the first and second inflection points, an increase in platelets did not affect the risk of in-hospital mortality. The platelet count had a curvilinear relationship with in-hospital mortality.

We tested the interaction between platelet count and other variables in the model, and no interaction was found. See our online supplemental table 3 for details.

DISCUSSION

Platelet abnormalities are a common problem in the ICU, and our main purpose was to study the relationship between the platelet count and in-hospital mortality in critically ill patients with tumours. In this study, our results show that after controlling for demographic data, tumour type, laboratory data, comorbidities and interventions, there was a curvilinear relationship between the platelet count and in-hospital mortality in critically ill patients with tumours. The analysis of non-linearity showed that when the platelet count was less than 184 'x10^9/L, an increase in the platelet count was associated with a significantly reduction in the risk of in-hospital mortality. When the platelet count was greater than 445 'x10^9/L, an increase in the platelet count was associated with a significantly increase in the risk of in-hospital mortality. To our knowledge, this is the first study to describe a curvilinear

relationship between the platelet count and in-hospital mortality in critically ill patients with tumours. Using these data, we were able to identify an overall platelet range from 184 'x10^9/L to 445'x10^9/L that was associated with the lowest in-hospital mortality rate in this patient population. This information will be useful for gaining a deeper understanding of the relationship between the platelet count and the prognosis of critically ill patients with tumours, with the aim of reducing adverse outcomes by keeping the baseline platelet count of critically ill patients with tumours within the specified range.

Zhou *et al*[9] conducted a ground-breaking study using eICU data, but they mainly studied neurological intensive care unit(NICU) patients. In their study, they reported that thrombocytopaenia was associated with in-hospital mortality. Lecumberri *et al*[10] found an inverse relationship between the baseline platelet count and mortality in cancer patients with thrombocytopaenia. Our results are partially consistent with the above results; that is, thrombocytopaenia (platelet count <184'x10^9/L) was found to be associated with an increased risk of in-hospital mortality in critically ill patients with tumours. Furthermore, our research also showed that thrombocytosis (platelet count >445'x10^9/L) was associated with an increased risk of in-hospital mortality. Compared with the above studies, our research population was different: we studied critically ill patients with tumours. The conclusions of the above studies could not be extrapolated to this patient population. The above studies only investigated a linear relationship between platelet count and mortality, which is a limited view of the complexity of the processes in the human body. In contrast, in our study, we assessed whether there was a non-linear relationship and found that when the platelet count was within the range from 184'x10^9/L to 445'x10^9/L, the correlation between the platelet count and the risk of mortality was not significant. This shows that the safe range for the platelet count in tumour patients in the ICU is 184 'x10^9/Lto 445 'x10^9/L.

There are many reasons for platelet abnormalities in tumour patients in the ICU, and multifactorial mechanisms often act simultaneously. The main common mechanisms involve (1) bone marrow metastatic cancer,[11] (2) immune thrombocytopaenia,[12] (3) platelet consumption,[13] (4) bone marrow suppression associated with radiotherapy and chemotherapy,[14] and (5) blood coagulation mechanism abnormalities,[15] such as thrombocytosis and platelet hyperaggregation, which can lead to thrombosis. In tumour patients with platelet abnormalities in the ICU, the balance among platelet production, aggregation and consumption has been disrupted. More than one of these mechanisms may act together to cause platelet abnormalities. Studies have shown that platelets play an important role in the process of tumour metastasis. An increase in the number of platelets is closely related to the progression and metastasis of tumours,[3 16] and a decrease in the number of platelets increases the risk of bleeding and mortality.[4 17] Nijsten *et al*[18] found that

the lack of an increase in the platelet count in critically ill patients was associated with an increase in mortality. Therefore, if a range for the platelet count that indicates relative safety for critically ill patients with tumours can be identified, it will help guide the choice of clinical treatments for patients with platelet abnormalities. This study analysed data from critically ill patients with tumours in the ICU and identified this range of safe values. This information is helpful for guiding early clinical interventions in patients who are at risk, thereby prolonging their survival.

One advantage of the large sample size from eICU-CRD strengthened the statistical power and credibility in the secondary data analysis. Second, this is the first study to describe a curvilinear relationship between the platelet count and in-hospital mortality in critically ill patients with tumours. Third, the platelet count, which is easy to obtain, was used as an indicator for the prediction of prognosis. The use of this indicator should be promoted in clinical practice, as it has strong clinical and practical significance.

This study had certain limitations. First, this research was retrospective and therefore subject to the inherent limitations of a retrospective design. Second, although we used multivariate logistic regression to adjust for potential confounding factors, many potential confounding factors were not included in the analysis, leading to biased results. Third, these values vary from laboratory to laboratory due to characteristics in the population, blood testing methods, ethnic blood characteristics, and even data collection time. Data were collected from 2014 to 2015, and it was impossible to observe changes over the course of a longer time frame.

Fourth, the eICU database only evaluates and treats critical illnesses and does not include information on the treatment of primary tumours and platelets.

CONCLUSION

The relationship between the platelet count and in-hospital mortality in critically ill patients with tumours was curvilinear. The lowest rate of in-hospital mortality was associated with platelet counts between 184'x10^9/L and 445'x10^9/L. This indicates that both high and low platelet counts should receive attention in clinical practice.

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