

## Original Article

# A new nomogram for the individualized prediction of children's mortality risk in pediatric intensive care unit

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**Abstract:** Objective: We developed a new nomogram for the prediction of mortality risk in children in pediatric intensive care units (PICU). Methods: We conducted a retrospective analysis using the PICU Public Database, a study that included a total of 10,538 children, to develop a new risk model for mortality in children in the intensive care units (ICU). The prediction model was analyzed using multivariate logistic regression with predictors including age and physiological indicators, and the prediction model was presented as a nomogram. The performance of the nomogram was evaluated based on its discriminative power and was internally validated. Results: Predictors contained in the individualized prediction nomogram included the neutrophils, platelets, albumin, lactate, oxygen saturation ( $P < 0.1$ ). The area under the receiver operating characteristic (ROC) curve for this prediction model is 0.7638 (95% CI: 0.7415-0.7861), which has effective discriminatory power. The area under the ROC curve of the prediction model in the validation dataset is 0.7404 (95% CI: 0.7016-0.7793), which is still effectively discriminative. Conclusion: The mortality risk prediction model constructed in this study can be easily used for individualized prediction of mortality risk in children in pediatric intensive care units.

**Keywords:** Pediatric ICU, mortality, nomogram, prediction

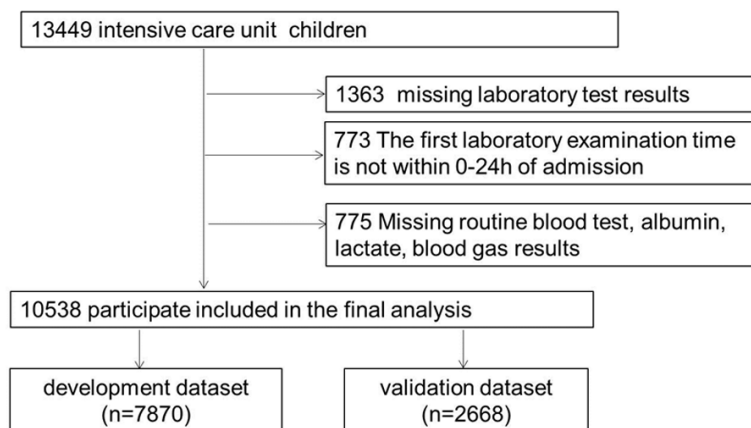
## Introduction

Risk stratification is essential for the timely medical intervention of critically ill children. Predictive models that can be used to dynamically assess the risk of death in ICU children are important to accurately identify the risk of death in critically ill children. The probability value of the predictive model identifies potential risks in a timely manner and helps guide treatment decisions and resource allocation to provide optimal management of PICU patients with available resources. Assessment of disease status and prediction of mortality risk is a complex project due to the complexity of the disease. Therefore, there is no consensus on the criteria for this risk of childhood death assessment, and there are currently 3 widely used scoring criteria. Such as pediatric risk of mortality (PRISM) [1], pediatric index of mortality (PIM) [2], and pediatric critical illness score (PCIS) [3]. PRISM III takes 24 h to complete and cannot be used to guide admission to the ICU [4], and the PRISM3 mortality prediction for-

mula is commercially patented. PIM3 was developed in 2013 with data from children in Australia, the United Kingdom, Ireland and New Zealand. The formula and coefficients for PIM3 predicted mortality are specified in the article and are freely available. PCIS was developed in 1995 by the Chinese Medical Association and is currently the most widely used method in China to assess the severity of the disease course of children in the ICU, but the score is not suitable for neonates and critically ill states with chronic disease [3].

We hope to create a simple, economical, and objective death risk prediction model to detect high-risk patients in time after admission. We developed a multifactorial prediction model to predict the risk of death in ICU children based on physiological characteristics. This nomogram was more convenient in clinic in China because the predictors were easy to obtain and the prediction steps were simple to operate. In this research, we used multivariable logistic regression analysis to screen 5 predictors for

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**Figure 1.** Flowchart of participants.

nomogram. Our study presented a new simplified nomogram of pediatric mortality risk (neutrophils, platelets, albumin, lactate and oxygen saturation) that can be easily used for individualized prediction of critically ill children at the time of admission.

## Methods

### Subjects

Our study was based on a pediatric intensive care (PIC) public database. 10,538 ICU children were included in this retrospective analysis. By random grouping, the training set contained 7870 children and the validation set contained 2668 children. PIC is a single-center pediatric public database containing vital sign measurements, medications, laboratory measurements, fluid balance, diagnosis codes, length of stay, and survival data for children in the intensive care units of the Children's Hospital of Zhejiang University School of Medicine, China, from 2010 to 2018 [5]. The laboratory test results we analyzed were the first results within 24 hours of admission. The median of the first examination of admission was 2.30 hours (Q1-Q3: 1.50-4.20).

The PIC database is a public database, the program does not affect clinical care, and all protected health information has been deidentified, so the requirement for individual patient consent was waived [5]. We requested access through the PIC website and the program documented on PhysioNet, and signed a data use agreement.

### Statistical analysis

Continuous variables are presented according to the mean (SD). Multiple logistic regression analysis was used to construct the mortality risk prediction model and presented in nomograms. The Akaike information criterion was used as a stopping rule and forward-backward stepwise selection was used for feature selection [6]. The area under the ROC curve was used to quantify the discriminative power of the prediction model.

The "rms" package was used for the nomogram. Statistical analysis was performed using R version 3.5.1. All statistical tests were two-sided, and  $p$ -values  $<0.05$  were considered significant.

## Results

### Clinical characteristics

The mean age at ICU admission for 10538 children was 8.35 months (Q1-Q3: 1.12-40.06), 6318 were boys and 4713 were girls, and 5.7% (601 patients) died. The participant flow chart is shown in **Figure 1**, and the baseline characteristics of the training and validation sets are shown in **Table 1**.

### Feature selection

Factors that differed in univariate analysis ( $P<0.1$ ) were included in a multifactorial logistic regression analysis. Based on data from the training set of 7870 children, texture characteristics were reduced to five potential predictors of mortality, including neutrophils, platelets, albumin, lactate, and oxygen saturation (**Table 2**).

### Development of an individualized prediction model

A total of 5 predictors were included in the prediction model. Platelets, albumin and oxygen saturation are protective factors for mortality, while neutrophils and lactate are risk factors for mortality (**Table 2**). The mortality risk predic-

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**Table 1.** Characteristics of participant in the development and validation set

Characteristic	Development dataset (n=7870)			Validation dataset (n=2668)		
	Survivors (n=7436)	Deaths (n=434)	<i>p</i>	Survivors (n=2501)	Deaths (n=167)	<i>p</i>
Age (months)	30.25 ± 43.28	25.13 ± 41.92	<0.001	27.65 ± 41.87	20.90 ± 38.66	0.005
Neutrophils (×10 <sup>9</sup> /L)	5.87 ± 5.39	7.78 ± 6.45	<0.001	5.85 ± 5.47	7.60 ± 6.39	<0.001
Platelet (×10 <sup>9</sup> /L)	306.38 ± 131.27	239.31 ± 143.31	<0.001	304.93 ± 127.63	249.26 ± 147.29	<0.001
Albumin (g/L)	39.27 ± 6.93	33.76 ± 8.14	<0.001	39.07 ± 6.91	33.86 ± 8.01	<0.001
Lactate (mmol/L)	2.45 ± 2.14	4.86 ± 4.89	<0.001	2.49 ± 2.21	4.68 ± 4.48	<0.001
Oxygen Saturation (SO <sub>2</sub> ) (%)	92.87 ± 12.57	85.69 ± 19.59	<0.001	93.02 ± 12.31	86.83 ± 18.72	<0.001

Note: *P* value is derived from the univariable association analyses between each of the variables and mortality.

**Table 2.** Risk factors of mortality

Intercept and variable	$\beta$	Odds ratio	95% CI of OR	<i>p</i>
Intercept	1.0941			
Neutrophils (×10 <sup>9</sup> /L)	0.0145	1.0146	0.9999-1.0296	0.0517
Platelet (×10 <sup>9</sup> /L)	-0.0022	0.9978	0.997-0.9986	<0.001
Albumin (g/L)	-0.0596	0.9421	0.9291-0.9554	<0.001
Lactate (mmol/L)	0.1305	1.1394	1.1097-1.1699	<0.001
Oxygen Saturation (SO <sub>2</sub> ) (%)	-0.0187	0.9815	0.9758-0.9872	<0.001
Area under ROC curve				
Development dataset		0.7638	(0.7415-0.7861)	
Validation dataset		0.7404	(0.7016-0.7793)	

tion model was constructed based on multi-factor logistic regression and finally presented as a Nomogram (**Figure 2**).

*Predictive performance of nomogram in the development dataset and independent validation in the validation set*

The area under the ROC curve for the prediction model was 0.7638 (95% confidence interval: 0.7415-0.7861) in the development dataset (**Figure 3**). In the validation dataset, the area under the ROC curve for the prediction model was 0.7404 (95% CI: 0.7016-0.7793) (**Figure 3**).

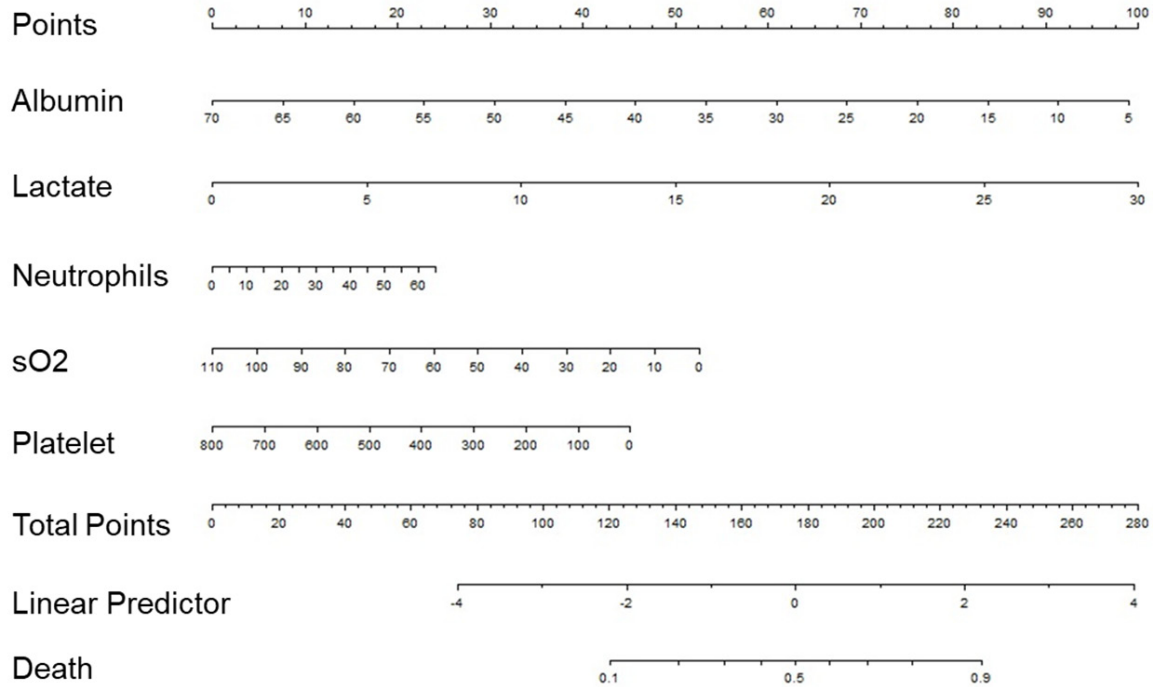
### Discussion

In this study, a predictive model was developed for mortality in the pediatric intensive care unit based on the physiological indicators of the children at the time of admission. We developed a model for predicting the risk of death in ICU children based on 5 physiological indicators (neutrophils, platelets, albumin, lactate and oxygen saturation) with good clinical applicability.

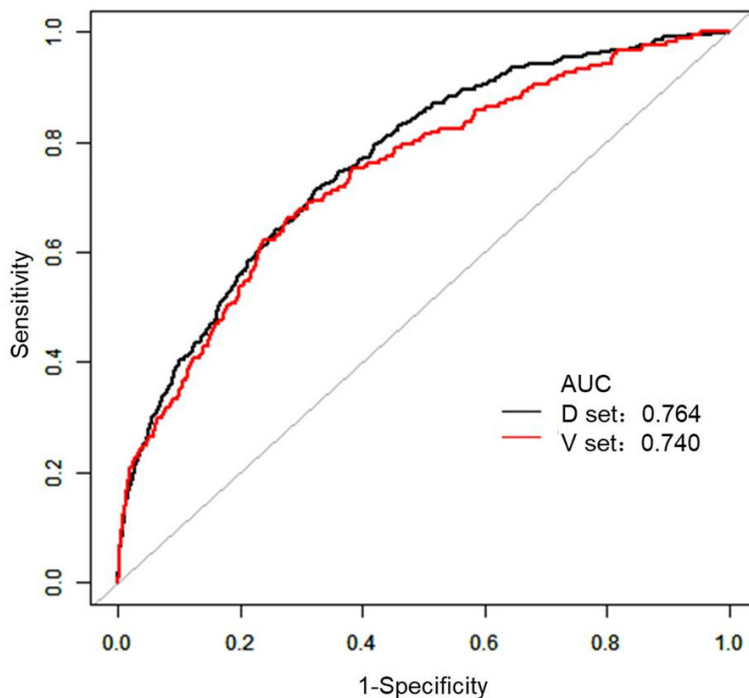
Pollack et al. re-evaluated the physiological parameters and their ranges and diagnostic indicators again in 1996 and developed PRISM III. PRISM III includes 17 physiological parameters, and 26 physiological parameter ranges: 5 for cardiovascular and neurological symptoms (heart rate, body temperature, systolic blood pressure, state of consciousness and pupillary reflex), 5 for acid-base and blood gases (acidosis, acidity, arterial blood partial pressure of carbon dioxide [pa(CO<sub>2</sub>)], blood carbon dioxide level, and arterial blood partial pressure of oxygen [pa(O<sub>2</sub>)]), 4 biochemical tests (glucose, serum potassium, creatinine and urea nitrogen), and 3 hematological tests (platelets, leukocytes, partial thromboplastin time and prothrombin time). Additional items such as surgical conditions and some disease types are included. The population for which PRISM III is indicated includes newborns, infants, children and adolescents, but not adults and preterm infants. The accuracy of its condition assessment and prognosis has been validated in multicenter clinical studies with large samples, and it is the most widely used critical care assessment tool and serves as a reference standard for other scoring methods. Because PRISM III selects the worst value within 24 h or 12 h of ICU admission for calculation, rather than the value at the time of initial ICU admission, early treatment interferes with the assessment results [1].

PIM3 includes 10 indicators: systolic blood pressure, pupillary reflex, partial pressure of oxygen, residual base, mechanical ventilation

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**Figure 2.** Nomogram for predicting mortality of pediatric ICU. To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the risk axes to determine the risk of mortality.



**Figure 3.** ROC of the nomogram.

after 1 h of ICU admission, elective ICU admission, postoperative, and diagnosis of different

risks (low, high, ultra-high). Information for these indicators should be first recorded within 1 h of ICU admission. The PIM3 values calculated from the regression equation cannot be used directly to assess the risk of death and need to be converted to mortality by the formula. Mortality =  $\exp(\text{PIM3 value}) / [1 + \exp(\text{PIM3 value})]$  [2].

As the most widely used method for scoring pediatric critical cases in China, PCIS has 10 physiological indicators, including assessment of pH, PaO<sub>2</sub> (mmHg), hemoglobin, sodium, potassium, creatinine or urea nitrogen, respiratory rate, heart rate, systolic blood pressure, and gastrointestinal system. The simplified scoring system removed PaO<sub>2</sub>, pH, creatinine, or urea nitrogen.

Equal values were scored for each physiological index. The first scoring should be done with-

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in 24 h. Multiple scoring may reflect changes in condition, and for each score, the degree of criticality should be assessed based on the most abnormal measured value [3].

The predictive accuracy of these mortality risk prediction models varied significantly across populations globally. The area under the ROC curve for PRISM III was 0.858 when used in two pediatric intensive care units in Guangzhou, China [7]. In Hunan, China, the area under the curve of PRISM was 0.729, PIM was 0.726, and PIM2 was 0.721 [8]. In an Indian study, the area under the ROC curve was 0.667 for PRISM III scores and 0.728 and 0.726 for PIM2 and PIM3 scores, respectively [9]. In Korea, the area under curve was 0.775, 0.796, and 0.826 for PRISM III, PIM2, and PIM3, respectively [10]. The results of a study in Switzerland showed that the observed mortality rate in the PICU was 2%, whereas the PIM2 predicted a mortality rate of 4.2%, with a difference between predicted and observed values and an AUC-ROC of 0.88 for the entire cohort. PIM2 scores did not accurately predict death in patients with sepsis and those admitted after cardiopulmonary arrest [11]. In our analysis, the area under the curve of the prediction model was 0.7638 (95% CI: 0.7415-0.7861).

Our prediction model is a novel, simple scoring system that was based entirely on physiological markers, which include 5 biomarkers. This method is quick, cheap, and requires little skill.

As a non-specific marker of tissue hypoxemia, elevated lactate is not a direct cause of high mortality, but rather a pathophysiological indicator of an aggravated disease process. A study pointed out that admission lactate levels are convenient and effective predictors of prognosis in ICU patients, and initial lactate was closely associated with PRISM-III. Initial lactate levels and PRISM-III scores are strongly correlated, making lactate a promising prognostic indicator to enhance appropriate patient care to reduce the risk of death [12]. However, calculation of the PRISM-III score takes place 12 to 24 hours after admission and therefore does not provide immediate information for clinical risk stratification. A previous study by our research group published serum lactate levels at admission, which remained an independent risk factor for all-cause mortality risk in the

pediatric intensive care unit after adjusting for confounding factors such as liver and kidney dysfunction, inflammation, acid-base disorders, and malnutrition [13].

Platelet and neutrophil counts can be obtained from routine complete blood count tests at low cost and are easily obtained in key practices. In critically ill patients, the initial response to infectious agents is composed mainly of neutrophils. In adults, the vast majority of studies were consistent with the effect of platelets on mortality. Thrombocytopenia is an independent risk factor for mortality risk in ICU trauma patients [14]. In septic shock, thrombocytopenia is associated with mortality [15]. The severity of sepsis is associated with thrombocytopenia, which increases the risk of death in ICU patients [16]. Another study reported thrombocytopenia in sepsis-3 patients with worsening disease and increased 28-day mortality in patients with platelet counts  $<50 \times 10^9/L$  [17].

Serum albumin has been identified as a possible predictor of mortality in a variety of critically ill patient populations, such as sepsis [18], all-cause hospitalization and death [19], and short- and long-term mortality risk in hospitalized patients [20, 21].

Oxygen saturation is an important physiological parameter of the respiratory circulation [22], and clinicians must titrate supplemental oxygen to provide adequate oxygen to tissues while avoiding oxygen-related damage to organs [23]. In patients with acute ischemic stroke treated with endovascular thrombectomy, general anesthesia is associated with higher  $SpO_2$  compared with monitored anesthesia care, and high  $SpO_2$  values are associated with higher mortality [24]. The shock index to pulse oximetry ratio predicts mortality in emergency trauma patients [25].

### *Strengths and weaknesses of this study*

Strengths of this study: First, the predictors we used are the results of conventional tests and are simple and easy to obtain. Second, our newly established model only contains 5 physiological parameters, which are simpler and more convenient than the existing scoring system, and we draw concise nomograms to facilitate application in clinical practice. This predic-

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tive model allows for a rapid and accurate assessment of the risk of death in children in the ICU.

This study has several limitations. First, the quality of retrospective clinical data and recorded data may affect the validity of predictive models. Second, only 1 PICU center was included in this study. Third, the prediction model was not validated externally. Therefore, further multicenter studies are needed in the future to validate the accuracy of the prediction model.

### Conclusion

In conclusion, this study presents a new simplified columnar chart of pediatric mortality risk (neutrophils, platelets, albumin, lactate and oxygen saturation) that can be easily used for individualized prediction of critically ill children at the time of admission.

### Disclosure of conflict of interest

None.

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### References

- [1] Pollack MM, Patel KM and Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. *Crit Care Med* 1996; 24: 743-752.
- [2] Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J and Slater A; ANZICS Paediatric Study Group and the Paediatric Intensive Care Audit Network. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care\*. *Pediatr Crit Care Med* 2013; 14: 673-81.
- [3] Zhang L, Huang H, Cheng Y, Xu L, Huang X, Pei Y, Tang W and Qin Z. Predictive value of four pediatric scores of critical illness and mortality on evaluating mortality risk in pediatric critical patients. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2018; 30: 51-56.
- [4] Teres D and Lemeshow S. Why severity models should be used with caution. *Crit Care Clin* 1994; 10: 93-110.
- [5] Zeng X, Yu G, Lu Y, Tan L, Wu X, Shi S, Duan H, Shu Q and Li H. PIC, a paediatric-specific intensive care database. *Sci Data* 2020; 7: 14.
- [6] Collins GS, Reitsma JB, Altman DG and Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015; 350: g7594.
- [7] Zhang L, Wu Y, Huang H, Liu C, Cheng Y, Xu L, Tang W and Luo X. Performance of PRISM III, PELOD-2, and P-MODS scores in two pediatric intensive care units in China. *Front Pediatr* 2021; 9: 626165.
- [8] Qiu J, Lu X, Wang K, Zhu Y, Zuo C and Xiao Z. Comparison of the pediatric risk of mortality, pediatric index of mortality, and pediatric index of mortality 2 models in a pediatric intensive care unit in China: a validation study. *Medicine (Baltimore)* 2017; 96: e6431.
- [9] Tyagi P, Tullu MS and Agrawal M. Comparison of pediatric risk of mortality III, pediatric index of mortality 2, and pediatric index of mortality 3 in predicting mortality in a pediatric intensive care unit. *J Pediatr Intensive Care* 2018; 7: 201-206.
- [10] Jung JH, Sol IS, Kim MJ, Kim YH, Kim KW and Sohn MH. Validation of pediatric index of mortality 3 for predicting mortality among patients admitted to a pediatric intensive care unit. *Acute Crit Care* 2018; 33: 170-177.
- [11] Polito A, Giacobino C, Combescure C, Levy-Jamet Y and Rimensberger P; Swiss Society of Intensive Care Medicine. Overall and subgroup specific performance of the pediatric index of mortality 2 score in Switzerland: a national multicenter study. *Eur J Pediatr* 2020; 179: 1515-1521.
- [12] Gorgis N, Asselin JM, Fontana C, Heidersbach RS, Flori HR and Ward SL. Evaluation of the association of early elevated lactate with outcomes in children with severe sepsis or septic shock. *Pediatr Emerg Care* 2019; 35: 661-665.
- [13] Yue C, Zhang C and Ying C. Admission serum lactate is associated with all-cause mortality in the pediatric intensive care unit. *Am J Transl Res* 2022; 14: 4124-4131.
- [14] Ke RT, Rau CS, Hsieh TM, Chou SE, Su WT, Hsu SY, Hsieh CH and Liu HT. Association of platelets and white blood cells subtypes with trauma patients' mortality outcome in the intensive care unit. *Healthcare (Basel)* 2021; 9: 942.
- [15] Menard CE, Kumar A, Houston DS, Turgeon AF, Rimmer E, Houston BL, Doucette S and Zarychanski R. Evolution and impact of thrombocytopenia in septic shock: a retrospective cohort study. *Crit Care Med* 2019; 47: 558-565.
- [16] Puertas M, Zayas-Castro JL and Fabri PJ. Statistical and prognostic analysis of dynamic changes of platelet count in ICU patients. *Physiol Meas* 2015; 36: 939-53.
- [17] Zhou H, Li Z, Liang H and Yan Z. Thrombocytopenia and platelet count recovery in patients

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- with sepsis-3: a retrospective observational study. *Platelets* 2022; 33: 612-620.
- [18] Kendall H, Abreu E and Cheng AL. Serum albumin trend is a predictor of mortality in ICU patients with sepsis. *Biol Res Nurs* 2019; 21: 237-244.
- [19] Shannon CM, Ballew SH, Daya N, Zhou L, Chang AR, Sang Y, Coresh J, Selvin E and Grams ME. Serum albumin and risks of hospitalization and death: findings from the atherosclerosis risk in communities study. *J Am Geriatr Soc* 2021; 69: 2865-2876.
- [20] Akirov A, Gorshtein A, Adler-Cohen C, Steinmetz T, Shochat T and Shimon I. Low serum albumin levels predict short- and long-term mortality risk in patients hospitalised to general surgery wards. *Intern Med J* 2020; 50: 977-984.
- [21] Akirov A, Masri-Iraqi H, Atamna A and Shimon I. Low albumin levels are associated with mortality risk in hospitalized patients. *Am J Med* 2017; 130: 1465.e11-1465.e19.
- [22] Bickenbach J and Marx G. Point-of-care-monitoring: blood gas analysis. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2010; 45: 722-30.
- [23] Foglia EE, Carper B, Gantz M, DeMauro SB, Lakshminrusimha S, Walsh M and Schmidt B; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association between policy changes for oxygen saturation alarm settings and neonatal morbidity and mortality in infants born very preterm. *J Pediatr* 2019; 209: 17-22, e2.
- [24] Farag E, Liang C, Mascha EJ, Toth G, Argalious M, Manlapaz M, Gomes J, Ebrahim Z and Husain MS. Oxygen saturation and postoperative mortality in patients with acute ischemic stroke treated by endovascular thrombectomy. *Anesth Analg* 2022; 134: 369-379.
- [25] Qi J, Ding L, Bao L and Chen D. The ratio of shock index to pulse oxygen saturation predicting mortality of emergency trauma patients. *PLoS One* 2020; 15: e0236094.