Parameters in complete blood cell count and coagulation function test predict in pediatric critical illness—A retrospective study

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Research Article

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Abstract

Background. The complete blood cell count is associated with the prognosis of critically ill children. Pediatric critical illness score (PCIS) is often used to evaluate the criticality of pediatric critical illness. We aimed to determine most parameters in the complete blood cell count (CBC) and coagulation function test of patients who were admitted to PICU in our hospital and compare those parameters of critically ill and non-critically ill children grouped by PCIS and whether CBC can identify and assess the severity of illness in critically ill children.

Methods. We performed a retrospective study of pediatric intensive care population who took both blood routine examination and coagulation function test within 24 hours of admission in PICU of The First Affiliated Hospital of Bengbu Medical College, from April 2015 to December 2019. Data collected include patient demographics and clinical data. Statistical analysis including Mann-Whitney U Test, binary logistic regression and so on.

Results. The parameters in the complete blood cell count and coagulation function test showed a significant difference between critical illness and non-critical illness in this study. Multivariate logistic regression analysis showed that RDWSD and PT prolongation are associated with PCIs ($p < 0.001$, $p = 0.006$, respectively). We created a nomogram for pediatric critical illness by using these risk factors. The area under of ROC curve (AUC) of pediatric critical illness for the combination of RDWSD and PT prolongation was 0.664(95%confidence interval 0.609-0.720). The nomogram had a bootstrapped-concordance index of 0.58.

Conclusion. RDWSD and PT prolongation are reliable indicators for predicting pediatric critical illness.

Introduction

The primary mission of pediatric intensive care units (PICU) is to improve the survival of critically ill children. The pediatric critical illness score has been published in 1995, including ten physiological parameters^[1]. Because of its simplicity, and convenience, it is widely used in China. The Pediatrics Group of the Emergency Branch of the Chinese Medical Association and the Emergency Medicine Group of the Pediatrics Association of the Chinese Medical Association organized 12 hospitals to jointly test the score in 1998. The results show that PCIS can accurately determine the severity of the disease. The lower the score, the more organ failure and the higher the fatality rate. This score has become the most widely used tool in pediatrics in China to assess the severity of the disease^[2].

The complete blood count(CBC) is a convenient and inexpensive evaluation to calculate the cellular components. It is one of the most frequently used laboratory tests in medicine^[3]. It reflects the inherent physiological imbalance of the patient's disease state. Several clinical prediction models, such as acute physiology and chronic health evaluation (APACHE), pediatric critical illness score (PCIS), systemic

inflammatory response syndrome (SIRS) scores, and pediatric risk of mortality III have incorporated CBC to enhance its predictive performance [4]. But some parameters in the CBC may be overlooked.

Recently, some parameters in CBC were considered to be reliable indicators in terms of the severity and prognosis of certain diseases. One of these parameters is red cell distribution (RDW), which had been associated with sepsis [5], cardiovascular and cerebrovascular diseases [6], and lung cancer [7].

At the same time, recent studies have shown that coagulation disorders often appear in critically ill patients. In severe infections, severe trauma, burns, surgery, and malignant tumors, a large number of tissue factors expressed by activated macrophages, vascular endothelial cells, and cancer cells [8] are released into the blood to activate the exogenous coagulation system and make prothrombin converted to thrombin [9]. Finally, fibrinogen is converted into fibrin, which collects blood cells and other components in the blood to form a blood clot [10]. This view shows that coagulation function-related parameters are related to critical illness.

In this retrospect analysis, we aimed to decide most parameters in CBC and in coagulation function tests of patients who were admitted to PICU in our hospital and compare those parameters of critically ill and non-critically ill children grouped by PCIS.

Materials And Methods

Patient selection

This retrospective study included pediatric patients admitted to the PICU of The First Affiliated Hospital of Bengbu Medical College, from April 2015 to December 2019 who took both blood routine examination and coagulation function test within 24 hours of admission. Patients below 28 days or above 18 years of age, Patients whose blood routine examination or coagulation function test exceeds the detection range of the instrument cannot be statistically analyzed, Patients with diseases that cause coagulation to disorder such as rodenticide poisoning, and patients with information incomplete were excluded from this study. Patients who have at least five of the following ten physiological indicators (Heart rate, blood pressure (systolic blood pressure), respiratory rate, oxygen partial pressure, blood pH, blood sodium, blood potassium, creatinine or urea nitrogen, hemoglobin level, gastrointestinal system performance) to complete the PCIS score were included in this study.

Clinical and laboratory data

Data on patients' age, sex, duration of hospitalization, admission diagnosis, and discharge status were collected. Both blood routine examination and coagulation function test are determined by Japanese Sysmex-XN900 and Sysmex-CS5100. The following admission data were also collected: leukocyte (WBC), erythrocyte (RBC), hemoglobin (HB), Hematocrit (HCT), mean red blood cell volume (MCV), mean hemoglobin (MCH), mean hemoglobin concentration (MCHC), red blood cell distribution width-CV value (RDWCV), red blood cell distribution width-SD value (RDWSD), Neutrophils (N), lymphocytes (L),

monocytes (MONO), Platelet (PLT), Mean platelet volume (MPV), plateletcrit (PCT), Platelet distribution width (PDW), platelet-large cell ratio (P-LCR), Prothrombin time (PT), international standardized ratio (INR), prothrombin activity (PA), thrombin (TT), activated partial thrombin time (APTT), fibrinogen (FIB), and D-dimer (DD). PT prolongation is calculated by PT subtract control.

Definitions

We used the worst indicators within 24 hours of the patients' admission for PCIS score, with scores >90% of the total score as non-critical, and $\leq 90\%$ of the total score as critical [1].

Statistical analyses

Based on the PCIS score, each patient was subdivided into two groups: non-critical and critical. SPSS Statistics 25 software was used for statistical analysis. R software with RMS packages was used for the nomogram compute. Continuous variables were presented as median and interquartile due to significant skewness. In the comparison of variables distributed homogeneously, the t-test was used for continuous variables. For variables not showing homogeneous distribution, the Mann-Whitney U-test was used. $P < 0.05$ was accepted as statistically significance. Univariate logistic regression analysis was performed to identify risk factors for critical illness. All P values were two-sides and risk factors with P values < 0.05 in univariate analysis were included in a multivariate analysis. Multivariate logistic regression analysis was performed to identify independent risk factors, and a stepwise method was used to identify the useful combination of factors that could most precisely predict critical illness. Using the R language, a nomogram based on multivariable logistic analysis was established to predict the critical of pediatric illness. The predictive performance of this model was then evaluated using the concordance index (C-index). The receiver operating characteristic (ROC) curves were used to evaluate and compare the abilities for predicting pediatric critical illness.

Results

Patient characteristics

In this retrospective study, 99 children did not complete the examination within 24 hours of admission, 12 children's blood routine examination or coagulation function test exceed the detection range of the instrument, 18 children with diseases that cause coagulation disturb, 11 children failed to completed PCIS scoring due to lack of physiological parameters and 41 children with information incomplete were excluded. A total of 485 children meeting the inclusion criteria were enrolled in the study. The demographic characteristics of the study are shown in Table 1. In this study, 375(77.32%) children were enrolled in the critical group and 110(22.68%) children were enrolled in the non-critical group. There were no statistical differences between the critical group and the non-critical group in gender ($p = 0.164$). Age was lower in the critical group (1.58 vs. 3.07 years, $p = 0.001$).

As shown in Table 2 and Fig. 1, there were no significant differences for WBC, RBC, HB, HCT, MCV, MCH, N, L, MONO, PLT, MPV, PCT, PDW, P-LCR, APTT and FIB, but significant differences for HB ($p=0.022$), MCHC($p=0.001$), RDWCV($p<0.001$), RDWSD($p<0.001$), PT prolongation($p=0.013$), INR($p=0.015$), PA($p=0.026$) and DD($p<0.001$). HB, MCHC, and PA were significantly higher in the non-critical group compared to those who got critically ill. And RDWCV, RDWSD, PT prolongation, INR, and DD were significantly lower in the non-critical group compared to those who got critically ill.

Nomogram for critical illness

We investigated the association between parameters in complete blood cell count and coagulation function test and pediatrics critical illness scores in pediatric critical illness in univariate analysis. RBC, HB, MCHC, RDWCV, RDWSD, PT prolongation, INR, and PA were significantly associated with a critical ill (Table 3). The study performed a multivariate logistic regression analysis with these associated factors using a stepwise method. We identified RDWSD and PT prolongation as independent risk factors and that a combination of these factors predicted critical illness in pediatrics (Table 3). We then built a nomogram for pediatric critical illness by using these factors (Fig. 2). We also analyzed the abilities of RDWSD and PT prolongation in predicting pediatric critical illness. The area under the curve (AUC) was 0.664 (95% confidence interval 0.609-0.720 Fig. 3). And the nomogram had a bootstrapped-concordance index of 0.58.

Table1.Demographic Characteristics of Groups			
	Critical n=375	Non-critical n=110	P value
Age, y	1.58(0.38, 5.92)	3.07(1.38, 5.88)	0.001
Gender			0.164
Boys	219(58.4%)	56(50.9%)	
Girls	156(41.6%)	54(49.1%)	
Data are presented in Mean (P25, P75).			

Table 2
Comparison of Complete Blood Count Parameters Across Groups

	Critical n=375	Non-critical n=110	Mann-Whitney U	P-value
WBC	12.47(8.24,19.00)	11.73(8.83,14.12)	18655.500	0.128
RBC	4.22(3.66,4.57)	4.28(4.01,4.64)	18153.500	0.056
HB	114.00(100.00,124.00)	117.00(108.00,125.25)	17671.000	0.022
HCT	0.34(0.31,0.37)	0.35(0.32,0.37)	18814.500	0.161
MCV	81.8(77.90,86.20)	80.60(78.08,84.13)	18333.500	0.076
MCH	27.50(26.00,29.00)	27.45(26.38,28.60)	20395.000	0.859
MCHC	333.00(324.00,345.00)	339.00(331.75,346.00)	16175.500	0.001
RDWCV	13.70(13.10,14.70)	13.20(12.70,14.10)	15342.000	<0.001
RDWSD	40.70(38.40,44.30)	39.25(37.28,41.03)	15083.000	<0.001
N	8.19(4.34,13.68)	7.09(4.81,10.96)	18577.000	0.113
L	2.63(1.48,4.39)	2.45(1.43,4.23)	19963.000	0.609
MONO	0.76(0.44,1.36)	0.74(0.48,1.13)	19893.500	0.571
PLT	309.00(236.00,408.00)	309.00(230.00,393.25)	20023.500	0.642
MPV	7.30(6.80,9.00)	7.10(6.70,9.13)	25521.500	0.349
PCT	0.30(0.23,0.40)	0.30(0.23,0.39)	25722.000	0.435
PDW	11.20(10.10,12.40)	10.90(10.18,11.80)	25055.000	0.195
P-LCR	24.00(19.50,29.40)	22.75(18.58,26.60)	24389.500	0.070
PT prolongation	0.00(-0.90,1.50)	-0.50(-1.03,0.40)	23532.000	0.013
INR	1.08(1.00,1.22)	1.05(0.99,1.12)	23596.500	0.015
Table 2. (continued)				
	Critical n=375	Non-critical n=110	Mann-Whitney U	P-value
PA	82.00(68.00,93.00)	85.00(76.00,94.00)	88246.500	0.026
TT	15.30(13.90,17.10)	15.15(13.80,16.53)	25843.000	0.492
APTT	32.70(28.70,37.00)	32.85(28.28,36.15)	26216.000	0.691
FIB	3.15(2.36,4.17)	3.09(2.57,3.87)	26075.000	0.612

	Critical n=375	Non-critical n=110	Mann-Whitney U	P-value
DD	0.67(0.33,1.85)	0.34(0.21,0.87)	20886.000	<0.001

Table 3. Most parameters of CBC associated with critical illness

Factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
WBC	1.026	0.999-1.053	0.057			
RBC	0.666	0.480-0.925	0.015			
HB	0.985	0.973-0.997	0.012			
HCT	0.019	0.000-1.278	0.065			
MCV	1.033	0.999-1.068	0.056			
MCH	1.005	0.927-1.089	0.906			
MCHC	0.984	0.972-0.996	0.011			
RDWCV	1.331	1.116-1.587	0.001			
RDWSD	1.102	1.048-1.1159	<0.001	1.100	1.046-1.158	<0.001
N	1.027	0.996-1.059	0.092			
Table 3. Most parameters of CBC associated with critical illness						
Factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
L	1.047	0.976-1.124	0.198			
MONO	1.123	0.914-1.380	0.268			
PLT	1.001	0.999-1.002	0.422			
MPV	1.074	0.928-1.242	0.337			
PCT	2.829	0.531-15.082	0.223			
PDW	1.082	0.967-1.210	0.170			
P-LCR	1.026	0.997-1.056	0.085			
PT-prolongation	1.187	1.055-1.336	0.004	1.199	1.055-1.363	0.006
INR	6.458	1.721-24.234	0.006			
PA	0.989	0.980-1.000	0.040			
Table 3. Most parameters of CBC associated with critical illness						
Factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
TT	1.004	0.964-1.046	0.844			

Factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
APTT	1.014	0.988-1.041	0.301			
FIB	1.079	0.920-1.265	0.351			
DD	1.033	0.991-1.077	0.126			

Discussion

In this study, we created a nomogram for pediatric critical illness, RDWSD and PT prolongation were identified as potential risk factors for pediatric critical illness.

Red blood cells (RBC), also named erythrocytes, are the most ordinary type of blood cell. Erythrocyte is dumbbell-shaped disks without a nucleus, flattened and depressed in the center and a torus-shaped rim on the edge. Erythrocyte volume varies widely across different people. In humans, RBCs have a diameter ranging from 6 to 8 μm and a thickness of 2 μm . Under particular circumstances, RBCs may remarkable increases or decreases in their typical volume. Changes in the permeability of the cell membrane and the content of intracellular molecules (mainly hemoglobin) can cause red blood cells to shrink and expand in size and volume. The degree of heterogeneity of RBC volume, which is traditionally known as anisocytosis, is conventionally quantified using a simple equation, in which the standard deviation (SD) of RBC volumes is divided by the mean corpuscular volume (MCV) of the erythrocytes, and then further multiplied for 100, to express data as a percentage (i.e. $[\text{SD of RBC volumes}]/[\text{MCV}]\times 100$) [11]. This definition is not ancillary, wherein the morphology of the erythrocytes is not always identical in circulating blood and in the blood vessel. In certain aspects, the RDW reflects the degree of anisocytosis, and can hence be considered an efficient marker of perturbation of erythrocyte biology [12]. Some pathological conditions, such as iron, folate, or vitamin B12 deficiencies[13], erythrocyte fragmentation[14], oxidative stress[15], and inflammation[16] may influence RBC volume and size distribution. This may explain why RDW in association with the activity and severity of various disease states and conditions. Data from the international literature showed that in these diseases, such as cardiovascular diseases, lung cancer, acute kidney injury, sepsis and septic shock, acute pancreatitis, and gastric cancer, an elevated RDWSD value was related to an increased risk of mortality, mortality, and severity [4-7,17-21]. Eva et al. conclude that admission RDW was higher in the death group as compared to the survivor group (17 vs 14.6, $p=0.012$) after studying 131 children [22]. Alexis et al. found the same phenomenon in their study that elevated RDW was associated with outcome in pediatric critical illness and provided similar prognostic information as the more complex PIM-2 severity of illness score [23]. Ahmed et al. evaluated over 3000 critically ill children and confirmed that RDW is independently associated with ICU mortality and morbidity [24]. Our study detected the same conclusion that RDW is in association with the severity of pediatric critical illness.

In the parameters of the coagulation function test, Prothrombin time (PT) was one of the first generated in tests of the hemostasis system. It measures the time to form a fibrin clot in platelet-poor plasma stimulated with a high amount of tissue factor (TF) and anionic phospholipid at an optimal concentration of calcium [25]. The study by Hui Long et al. showed that since hypercoagulability is closely related to disease progression and clinical results, coagulation indicators such as DD and PT should be monitored as soon as possible to detect thrombotic complications [26]. Ning Tang et al. analyzed 183 consecutive patients with confirmed novel coronavirus pneumonia in Tongji hospital, concluded that the non-survivors revealed significantly higher DD and fibrin degradation product (FDP) levels, longer PT, and APTT compared to survivors on admission ($p < 0.05$) [27]. Besides, Ki Hong Kim et al. examined the association between PT prolongation during cardiopulmonary resuscitation and outcome after an out-of-hospital cardiac arrest and found a significant association between severe PT prolongation and poor outcomes [28].

Conclusions. when a child is admitted to PICU, elevated RDWSD and prolonged PT may mean the child ill critically.

This study had a limitation. We created a nomogram for pediatric critical illness by using RDWSD and PT prolongation, but the nomogram had a bootstrapped-concordance index of 0.58. We think it may result from too few risk factors we used, in the next research, we will try to analyze more parameters such as RDWSD to PLT ratio, RDWSD to lymphocytes ratio, and RDWSV to PLT ratio to create a nomogram for pediatric critical illness.

Abbreviations

PCIS: Pediatric critical illness score

CBC: The complete blood count

WBC: leukocyte

RBC: erythrocyte

HB: hemoglobin

HCT: Hematocrit

MCV: mean red blood cell volume

MCH: mean hemoglobin

MCHC: mean hemoglobin concentration

RDWCV: red blood cell distribution width-CV value

RDWSD: red blood cell distribution width-SD value

N: Neutrophils

L: lymphocytes

MONO: monocytes

PLT: Platelet

MPV: Mean platelet volume

PCT: plateletcrit

PDW: Platelet distribution width

P-LCR: platelet-large cell ratio

PT: Prothrombin time

INR: international standardized ratio

PA: prothrombin activity

TT: thrombin

APTT: activated partial thrombin time

FIB: fibrinogen

DD: D-dimer

Declarations

Ethics approval and consent to participate

This retrospective study is approved by The First Affiliated Hospital of Bengbu Medical College, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the retrospective nature of the study, informed consent was waived.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Author contributions

Hang Hang and Wu Zhao wrote the main manuscript text and prepared all figures. Qixiu Guo has helped to collect data. All authors reviewed the manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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Figures

Figure 1

Scatter plots of parameters related to CBC and coagulation function in critically and non-critically ill children, the green one means critical, the yellow one means non-critical group.

Figure 2

Nomogram for pediatric critical illness by using RDWSD and PT prolongation The ROC curve (AUC) of pediatric critical illness for RDWSD

Figure 3

Receiver operating characteristic curve for the prediction model Area under the curve was 0.664 (95% confidence interval 0.609-0.720)