The role of red blood cell distribution width (RDW) in the diagnosis of pediatric sepsis

Lingjun Xu[1,2], Lingfeng Yuan[3], Keqiang Chi[2], Dan Zhong[2], Liang Huang[4]

[1]Nanchang University, Nanchang; [2]Department of Emergency, Jiangxi Provincial Children's Hospital, Nanchang; [3]Department of Function, Jiangxi Provincial Children's Hospital, Nanchang; [4]Department of Emergency, The First Affiliated Hospital of Nanchang University, Nanchang, China.

ABSTRACT

Background. Early diagnosis of pediatric sepsis is difficult, so it is necessary to find a reliable auxiliary diagnostic method. The purpose of the study was to assess the role of RDW in the diagnosis of pediatric sepsis.

Methods. We did a case control study reviewing pediatric inpatients (≥28 days, <18 years old) who were diagnosed with sepsis between April 2020 and November 2022. According to the sepsis-3 and Pediatric Sequential Organ Failure Assessment (pSOFA) scoring standards, 66 septic inpatients of the pediatric intensive care unit (PICU) were included in the sepsis group and 66 non-septic inpatients of the PICU were included by using the random sampling method during the same period as the control group.

Results. RDW values in the sepsis group were higher than those in the control group (P<0.001). The cut-off value, sensitivity, specificity and area under curve of RDW for sepsis were 39.15, 0.955, 0.758 and 0.943,respectively.

Conclusions. Our study confirms that RDW may have a good value on the early diagnosis of pediatric sepsis.

Key words: red blood cell distribution width (RDW), diagnosis, pediatric, sepsis.

Sepsis is a syndrome of organ dysfunction, is caused by the body's dysfunctional response to infection, and is a common sickness in intensive care units with a high death rate.[1] Globally, about 1.2 million children get the disease every year, and the fatality rate varies due to different medical and sanitary conditions in different countries.[2] Early diagnosis of sepsis is difficult due to factors such as limited admission time and overlapping clinical symptoms of different diseases.[3,4] The new diagnostic criteria for sepsis is Sepsis-3[5], but its Sequential Organ Failure Assessment (SOFA) score is for adults and is not suitable for children. In this case, pSOFA was proposed to cater to the new diagnostic criteria for pediatric sepsis. The pSOFA scores were performed and verified using age-adjusted variables and the results indicated that the use

of pSOFA was feasible in children and showed good results.[6]

It is still a difficult problem to obtain a single biomarker with reliable high specificity and sensitivity to rapidly identify sepsis.[7,8] At present, the theory of an uncontrolled inflammatory response is considered to be an important basis for the onset of sepsis. Red blood cell distribution width (RDW), represents the heterogeneity of the volume of red blood cells in peripheral blood. Previous studies revealed that the changes of RDW is closely associated with inflammatory response.[9] The inflammatory response induce the tumor necrosis factor and interleukin-6 receptor expression, the release of inflammatory mediators affects the iron metabolism and hematopoietic function of bone marrow, and the proinflammatory factors could cause a large rise of immature erythrocytes, thus causing the increase of RDW.[10,11] Purtle et al. found that RDW can be used for a inflammatory marker.

The possible mechanism is that inflammation affects the maturation of erythrocytes, causes myelosuppression, reduces the generating of erythropoietin, decreases iron bioavailability, lead to erythropoietin resistance and apoptosis of the red blood cells, and allows immature erythrocytes release into the bloodstream. The result is an increase in RDW.[12]

Sepsis could obviously cause changes in ion channels and glycoproteins on the erythrocyte membrane, resulting in changes in erythrocyte morphology and thus the RDW level is increased.[13] One of the primary pathological mechanisms of sepsis is oxidative stress, which could decrease rate of survivors of erythrocytes and lead to the release of immature and big erythrocytes into the blood, directly causing an increase in RDW.[14] Sepsis can induce hemolysis and shorten the life span of erythrocytes, which may cause a rise of RDW. The system of renin-angiotensin is significantly activated in sepsis patients, angiotensin II can upregulate the level of erythropoietin, and directly acting on RBC precursors, which may cause an increase in RDW.[15] According to these reasons given above, it could be inferred that the level of RDW in septic patients may be higher than in non-septic patients. Thus, we made the scientific hypothesis that RDW may have efficacy in diagnosing sepsis. But, most studies indicate that RDW is a valuable metric for assessing the prognosis of sepsis. These investigations reveal a correlation between elevated RDW levels and increased fatality rates.[16-19]

At present, few studies have investigated the diagnostic value of RDW in sepsis. The objective of this study was to assess the diagnostic value of RDW in pediatric sepsis.

Material and Methods

Study design

This clinical research was a single center case control study using available electronic medical record data. The hospital ethics committee approved the study with the code JXSETYY-YXKY-20220279 on December 8, 2022. It included inpatients of ≥28 days and <18 years of age who presented to the hospital and were diagnosed with sepsis in the pediatric intensive care unit (PICU) between April 2020 and November 2022 and non-septic inpatients of the PICU who were hospitalized at our hospital during the same period. We divided the study population into a sepsis group and a control group and designed a data collection form, reviewed electronic medical records, and registered the clinical data for the included population.

Study population

Our method for determining the sample size is as follows: We obtained the area under the curve (AUC) (0.658) in the pre-experiment and used the software of PASS (Version 15.0.5, NCSS, LLC) to estimate the sample size. After entering the interface of Tests for One ROC Curve of this software, we had to fill in the following parameter values: "Two-Side Test, Power=0.9, Alpha=0.05, AUC0=0.5, AUC1=0.658" and then calculated the total sample size as 132, with 66 cases and 66 controls. In view of the high clinical mortality rate of pediatric sepsis, highlighting the seriousness of pediatric sepsis, this study adopted the criteria of Sepsis-3 to define pediatric sepsis. According to the criteria of Sepsis-3[5] and pSOFA[6], 66 patients were enrolled in the sepsis group, and 66 non-septic patients were enrolled in the control group by using a random sampling method during the same period. SOFA scores for children were based on the pSOFA developed by Matics et al.[6], and pSOFA were retrospectively calculated based on patients' medical records where possible. We divided all the enrolled patients into two parts: sepsis (patients were diagnosed according to criteria of Sepsis-3: infection plus pSOFA ≥2); controls (patients did not meet the diagnostic criteria of Sepsis-3). Two researchers carried out this process independently by conducting a retrospective review of the electronic medical record. Before data analysis, RDW values were unknown to the researchers during the selection of sepsis and control groups, another researcher

made a final decision on inconsistencies. Infection was defined by clinical symptoms, radiographic and laboratory findings.

Inclusion and exclusion criteria

The inpatients ≥28 days and <18 years of age who were admitted to the PICU of the hospital and were diagnosed with pediatric sepsis based on the criteria of Sepsis-3, and the inpatients of the PICU who did not meet the diagnostic criteria of Sepsis-3 by using the random sampling method during the identical time were enrolled in our research. Both groups included patients who had or had not used antibiotics prior to admission. The exclusion criteria of this study were (i) ≥18 years old; (ii) failure to confirm the parameter of RDW; (iii) incomplete data; (iv) leukemia, lymphoma and other severe hematological diseases.

Data collection

Demographic characteristics and clinical information of all the enrolled patients were collected retrospectively basing on reviewing the electronical hospital medical records. Researchers were unaware of RDW levels in the collection of patients' information. In addition, the RDW values we collected for this study were RDW-SD (the actual width of the red cell volume distribution curve measured at the 20% height of the curve in femtoliters [fL]), and the timing of our collection was the time of the initial admission to the PICU.

Statistical analysis

SPSS statistical software V.22.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. The numerical data were expressed in mean plus or minus standard deviation ($\bar{\chi} \pm s$), while the categorical data were expressed in absolute values and relative percentages. The differences between the two groups of the measurement data were tested by t-test. The differences between the two groups of the counting data were tested by chi-square test. P<0.05 was considered statistically significant. Receiver

operator characteristic (ROC) analysis was used to evaluate the diagnostic efficacy of RDW in sepsis and 95% confidence interval (CI) and AUC were reported. MedCalc (Version 15.2.2, MedCalc Software, Ostend, Belgium) evaluated whether the difference in AUC between RDW, procalcitonin (PCT) and C-reactive protein (CRP) were statistically significant (with Bonferroni's correction). The Youden method was used to estimated the best cut-off value of RDW in the prediction of sepsis, the best cut-off value is chosen under the maximum Jorden index (sensitivity+specificity-1). The sensitivity, specificity, accuracy and Yuden index of RDW for predicting sepsis at the best cut-off value were calculated. Evaluate the predictors of sepsis were basing on univariate and multivariate logistic regression.

Results

The study included 132 pediatric patients. Demographic, clinical, including age-specific vital signs[20], temperature, receiving a transfusion, anemia, purpura, lung disease, intestinal disease, CNS disease, antibiotic use before admission, positive blood culture, admission to the emergency department (ED), various clinical data of the enrolled patients are displayed in Table I. Age (P=0.063) and gender (P=0.363) among the two groups had no statistical differences, tachycardia (P<0.001), temperature (P=0.027), positive blood culture (P=0.006), neutrophil ratio (NE%) (P<0.001) and platelets (PLT) (P=0.001) had statistical differences (Table I) .

RDW, CRP and PCT were significantly higher in the sepsis group compared to the control group (P<0.001 for all) (Table I, Fig. 1A-C).

In ROC curve analysis for predicting sepsis, the AUC of RDW (0.943; 95% CI 0.908-0.978) was greater than that of CRP (0.749; 95% CI 0.667-0.831) and PCT (0.751; 95% CI 0.669-0.834) (Fig. 2). The differences between RDW and PCT (DeLong, P<0.0001) and RDW and CRP (DeLong, P<0.0001) were both statistically

Table I. Demographic, clinical and laboratory data of the sepsis and control groups.

	Sepsis (n=66)	Controls (n=66)	p-Value
Demographic			
Age, days, χ±s	971.56±1459.95	1436.26±1385.57	0.063
Male sex, n (%)	40 (60.6)	45 (68.2)	0. 363
Clinical data, n (%)			
Age-specific vital signs			
Tachycardia	58 (87.9)	33 (50.0)	**<0.001**
Polypnea	47 (71.2)	40 (60.6)	0.199
Hypotension	8 (12.1)	3 (4.5)	0.115
Temperature <36 or >38 °c	28 (42.4)	16 (24.2)	**0.027**
Receiving transfusion	2 (3.0)	1 (1.5)	0.559
Anemia	26 (39.4)	24 (36.4)	0.720
Purpura	5 (7.6)	1 (1.5)	0.071
Lung disease	31 (47.0)	21 (31.8)	0.075
İntestinal disease	15 (22.7)	18 (27.3)	0.546
CNS disease	13 (19.7)	15 (22.7)	0.670
Antibiotic use before admission	47 (71.2)	39 (59.1)	0.177
Positive blood culture	9 (8.2)	0 (0)	**0.006**
Admission in ED	62 (93.9)	65 (98.5)	0.171
Hematological tests, χ±s			
WBC,×10^9/L	11.96±10.06	14.71±7.33	**0.074**
NE%	60.16±20.46	72.63±17.57	**<0.001**
RBC,×10^{12}/L	4.13±0.87	4.31±0.81	0.230
HGB, g/L	104.83±23.26	111.94±18.61	0.055
MCV, fL	82.90±7.99	80.79±5.07	0.072
RDW, fL	47.30±9.04	37.34±2.42	**<0.001**
PLT, 10^9/L	228.12±173.65	313.17±117.70	**0.001**
PDW, fL	12.63±3.20	11.74±2.36	0.073
Biochemical tests, χ±s			
CRP, mg/L	70.80±79. 63	17.79±30.37	**<0.001**
PCT, ng/mL	31.98±37.13	5.69±15.91	**<0.001**

CNS: central nervous system, CRP: C-reactive protein, ED: Emergency Department, NE%: neutrophil ratio, RBC: red blood cell, HGB:hemoglobin, MCV: mean corpuscular volume, PCT: procalcitonin, PDW: platelet distribution width, PLT: platelets, RDW:red blood cell distribution width, WBC: white blood count.
T-test was used to test the differences between the two groups for quantitative variables, Fisher's exact test was used to test the differences between the two groups for categorical variables, and P<0.05 was considered statistically significant.
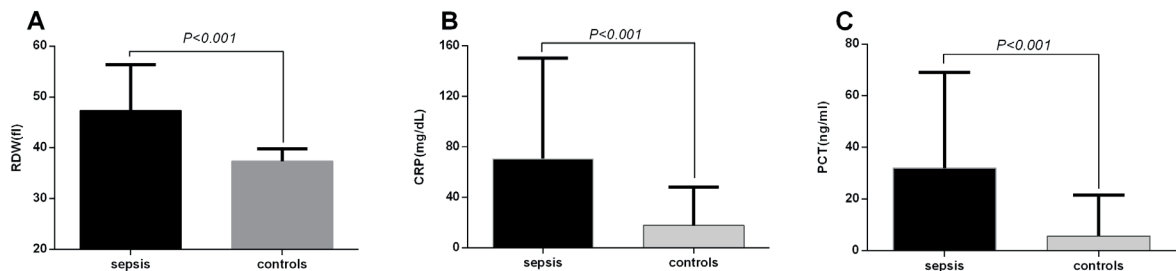

Fig. 1. Comparison of RDW, CRP and PCT levels between the two study groups. (A) Differences in RDW between the two groups. (B) Differences in CRP between the two groups. (C) Differences in PCT between the two groups.

CRP: C-reactive protein, PCT: procalcitonin, RDW: red blood cell distribution width.

significant with Bonferroni's correction, while the CRP: C-reactive protein, PCT: procalcitonin, RDW: red blood cell distribution width, ROC: receiver operating characteristic. difference between PCT and CRP was not significant (DeLong, P=0.9807). The optimal cut-off value of RDW in sepsis diagnosis was 39.15 basing on the Youden index. Sensitivity, specificity, accuracy and Youden index under the cut-off value were 0.955, 0.758, 0.856 and 0.713, respectively. At univariate logistic regression analysis, p-Value of tachycardia (P=0.003), temperature (P=0.045), NE% (P=0.001), RDW (P<0.001), PLT (P=0.002), CRP (P<0.001), and PCT (P<0.001) were less than 0.05, which were thought to be related to sepsis. The correlation factors of P<0.05 coming from the univariate logistic regression analysis were enrolled in the multivariate logistic regression analysis. But, only NE% (P=0.017), RDW (P=0.001) and CRP (P=0.011) were the independent predictors for pediatric sepsis at the multivariate logistic regression analysis (Table II).

Discussion

In this case control study, we assessed the accuracy of using RDW in diagnosing pediatric patients with sepsis. The primary results are
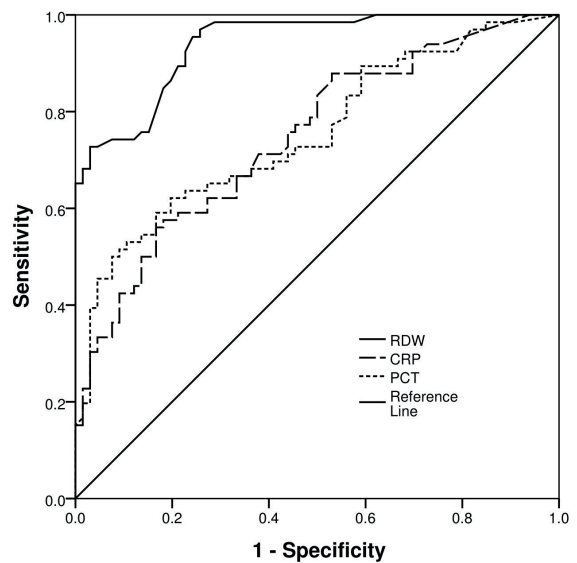

Fig. 2. ROC curve analysis for comparison of RDW, CRP and PCT levels in sepsis prediction.

CRP: C-reactive protein, PCT: procalcitonin, RDW: red blood cell distribution width, ROC: receiver operating characteristic.

summarized in the following aspects: (i) RDW values were higher in the sepsis group than that in the control group; (ii) It revealed that RDW was a strong independent predictor for pediatric sepsis with the univariate and multivariate logistic regression analysis; (iii) It revealed that the best RDW value for detection of pediatric sepsis was 39.15 with the ROC curve analysis,

Table II. Univariate and multivariate logistic regression for sepsis.

Predictor	univariate logistic regression		multivariate logistic regression	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age	1.000 (1.000-1.000)	0.067		
Tachycardia	3.878 (1.583-9.500)	**0.003**	2.552 (0.249-26.152)	0.430
Temperature	3.429 (1.113-10.570)	**0.045**	0.723 (0.130-4. 033)	0.712
Purpura	5.328 (0.605-46.910)	0.132		
WBC	0.963 (0.924-1.005)	0.081		
NE%	0.966 (0.946 -0.985)	**0.001**	0.938 (0.889-0.989)	**0.017**
RDW	2.538 (1.711-3.764)	**<0.001**	2.733 (1.543-4.842)	**0.001**
PLT	0.996 (0.993-0.999)	**0.002**	0.995 (0.989-1.001)	0.122
PDW	1.120 (0.989-1.269)	0.075		
CRP	1.020 (1.010-1.030)	**<0.001**	1.027 (1.006-1.048)	**0.011**
PCT	1.042 (1.020-1.065)	**<0.001**	1.013 (0.984-1.042)	0.399

CI: confidence interval, CRP: C-reactive protein, NE%: neutrophil ratio, OR: odds ratio, PDW: platelet distribution width, PLT: platelets, RDW: red blood cell distribution width, WBC: white blood cell count.
P<0.05 was considered statistically significant.

the AUC of CRP and PCT were both smaller than that of RDW, and RDW had a good diagnostic accuracy for pediatric sepsis. Overall, our study confirms that RDW may have a good value on early diagnosis of pediatric sepsis. In this study, multivariate analysis suggested that RDW and CRP were independent influencing factors for sepsis. However, PCT was not statistically significant in the multivariate analysis. This is inconsistent with previous research. The possible reason is that PCT could be rised in severe non-septic patients too.[21-23] Therefore, it has certain influences on the research results.

RDW represents the variability of size in circulating red blood cells with the quantitative form. There is accumulating evidence indicating that RDW values are greatly increased in the infection and sepsis patients.[24-26] However, non-infectious factors may also increase the RDW value. One study showed that the RDW of patients could also be obviously increased by the transfusion of erythrocytes and the RDW value mainly reflected the difference between the mean corpuscular volume of patients and the volume of individual erythrocytes, which would be increased by the transfusion of erythrocytes.[27] Fogagnolo et al.[28] found that whether a patient was transfused or not was an important factor determining the RDW value, which may greatly affect the cut-off value of RDW in predicting disease. When they analyzed the clinical variables associated with high RDW, low hemoglobin level was also closely related to high RDW. The increased RDW value may not only reflect the decreased erythrocyte deformability, but may also be secondary to pre-existing chronic anemia or increased reticulocyte production.[29] In our study, the statistical differences in receiving blood transfusions and anemia among the two groups were not significant, so we avoided these factors affecting the diagnostic effectiveness of RDW.

Although most studies suggest that increased RDW may be associated with higher mortality and RDW can be used in evaluating the prognosis of sepsis[16-19], there may also

be different views. Sepsis-related organ dysfunction was associated with changes in microcirculation.[30,31] One study found that the change in microcirculation significantly increased the death rate of sepsis patients, but the increase in RDW had no correlation with the change in microcirculation and the change in red blood cell volume did not affect the prognosis of the patients, so the increase in RDW was not a predictor for poor clinical prognosis of sepsis patients.[32] One study discussed the diagnostic efficacy of RDW in neonatal sepsis[33], but the result did not indicate whether the RDW of sepsis was higher than that of other severe patients without sepsis. Currently, few research have discussed the diagnostic efficacy of RDW in the sepsis of older infants or children. The diagnostic efficacy of RDW in pediatric sepsis patients of different ages was investigated in the research. The results are novel and RDW may be expected to be an effective evaluation tool in pediatric clinics. As we know, early detection of sepsis in children is key to hold back the progression and improve the prognosis of the illness. Complete blood count (CBC) is one of the indicators which widely used in clinical diagnosis of diseases. Our study suggests that RDW has good sensitivity and specificity in the diagnosis of pediatric sepsis under the optimal cut-off value. Assessment of RDW in CBC may be able to accomplish early recognition of patients at danger for pediatric sepsis, so we can reduce the missed diagnosis of pediatric sepsis and achieve the purpose of early treatment and improvement of prognosis. However, the diagnostic value of RDW in early pediatric sepsis needs to be confirmed by further study.

The quick sequential organ failure assessment (qSOFA) supported by the criteria of Sepsis-3 revised in 2016 could be used for non-ICU settings to identify patients who are at danger of sepsis.[5] This index is mainly used to identify the possibility of sepsis in patients outside the ICU at an early stage. The criteria of Sepsis-3 stated that patients with suspected infections were considered at high risk for sepsis if they had a qSOFA score ≥2. There was also a

pediatric standard for age-adapted qSOFA.[34] However, patients with sepsis may also have a qSOFA score <2, because organ dysfunction can manifest in various forms and is not limited to the assessment in qSOFA. One study revealed that qSOFA had low sensitivity in diagnosing sepsis, but whether it's sepsis or not, qSOFA score ≥2 may be able to identify these patients with a high danger of death.[35] It should only be used as an early warning value for sepsis and cannot be used to diagnose sepsis. In clinical practice, qSOFA is a simple way to use initially for early recognition of patients who may be at danger for sepsis, but it has also been shown to be inaccurate for use in the ED.[36,37] First of all, the qSOFA can change at short notice. Secondly, it is well known that triage in the ED is dependent on general practitioners rather than sepsis specialists, so there is a need for a easy way to recognize patients with danger of sepsis. Furthermore, as one of the variables of qSOFA, the Glasgow coma scale score cannot be assessed for patients in some clinical situations.[38] Therefore, according to these previous description, RDW may be more valuable than qSOFA in diagnosing sepsis.

This study has a few limitations. Firstly, our study selected a small number of pediatric patients and was a single center retrospective reserch. The randomly selected control group also had a certain sampling error, which could not completely represent the characteristics of all non-septic pediatric patients. Furthermore, in this study, the medical records of children diagnosed with sepsis in our hospital were reviewed, and the sepsis patients were selected basing on the diagnostic criteria of Sepsis-3. This would ensure that all the enrolled sepsis patients met certain diagnostic standard, but some cases that met the diagnostic standard of Sepsis-3 were not actually diagnosed with sepsis might be missed.

In conclusion, due to a lack of accurate screening tools, the diagnosis and therapy for pediatric sepsis are often delayed in pediatric clinics. RDW represents a fast, reliable, low-cost, and readily available indicator for pediatric sepsis. In the study, RDW was proved to be of good value in the diagnosis of pediatric sepsis and the cut-off value was 39.15 under the best sensitivity and specificity. The value of RDW in the early diagnosis of pediatric sepsis needs further study.

Ethical approval

Informed consent was not required because we did this retrospective study without any intervention in the children. In addition, all patients' data were anonymous. The study was approved by the Ethics Committee of the Jiangxi Provincial Children's Hospital with the code of SKJP220227512 at 2022.03.21, and was performed in accordance with the current revision of the Helsinki Declaration.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: LX, LH; data collection: LX, LY, KC, DZ; analysis and interpretation of results: LX, LH; draft manuscript preparation: LX, LY. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med 2021; 49: e1063-e1143. https://doi.org/10.1097/CCM.0000000000005337

2. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med 2018; 6: 223-230. https://doi.org/10.1016/S2213-2600(18)30063-8

3. Derlet RW, Richards JR. Overcrowding in the nation's emergency departments: complex causes and disturbing effects. Ann Emerg Med 2000; 35: 63-68. https://doi.org/10.1016/s0196-0644(00)70105-3

4. Filbin MR, Arias SA, Camargo CA, Barche A, Pallin DJ. Sepsis visits and antibiotic utilization in U.S. emergency departments*. Crit Care Med 2014; 42: 528-535. https://doi.org/10.1097/CCM.0000000000000037

5. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 801-810. https://doi.org/10.1001/jama.2016.0287

6. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically ill children. JAMA Pediatr 2017; 171: e172352. https://doi.org/10.1001/jamapediatrics.2017.2352

7. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13: 426-435. https://doi.org/10.1016/S1473-3099(12)70323-7

8. Celik IH, Demirel FG, Uras N, et al. What are the cut-off levels for IL-6 and CRP in neonatal sepsis? J Clin Lab Anal 2010; 24: 407-412. https://doi.org/10.1002/jcla.20420

9. Kim DH, Ha EJ, Park SJ, Jhang WK. Evaluation of the usefulness of red blood cell distribution width in critically ill pediatric patients. Medicine (Baltimore) 2020; 99: e22075. https://doi.org/10.1097/MD.0000000000022075

10. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion 2005; 20: 83-90. https://doi.org/10.1191/0267659105pf793oa

11. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009; 158: 659-666. https://doi.org/10.1016/j.ahj.2009.07.024

12. Purtle SW, Moromizato T, McKane CK, Gibbons FK, Christopher KB. The association of red cell distribution width at hospital discharge and out-of-hospital mortality following critical illness*. Crit Care Med 2014; 42: 918-929. https://doi.org/10.1097/CCM.0000000000000118

13. Subramani K, Raju SP, Chu X, et al. Effect of plasma-derived extracellular vesicles on erythrocyte deformability in polymicrobial sepsis. Int Immunopharmacol 2018; 65: 244-247. https://doi.org/10.1016/j.intimp.2018.10.011

14. Yuan T, Cong Y, Meng J, et al. Arachidonic acid causes hidden blood loss-like red blood cell damage through oxidative stress reactions. J Surg Res 2017; 211: 14-20. https://doi.org/10.1016/j.jss.2016.11.060

15. Kato H, Ishida J, Imagawa S, et al. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. FASEB J 2005; 19: 2023-2025. https://doi.org/10.1096/fj.05-3820fje

16. Hu ZD, Lippi G, Montagnana M. Diagnostic and prognostic value of red blood cell distribution width in sepsis: a narrative review. Clin Biochem 2020; 77: 1-6. https://doi.org/10.1016/j.clinbiochem.2020.01.001

17. Zhang L, Yu CH, Guo KP, Huang CZ, Mo LY. Prognostic role of red blood cell distribution width in patients with sepsis: a systematic review and meta-analysis. BMC Immunol 2020; 21: 40. https://doi.org/10.1186/s12865-020-00369-6

18. Moreno-Torres V, Royuela A, Múñez-Rubio E, et al. Red blood cell distribution width as prognostic factor in sepsis: A new use for a classical parameter. J Crit Care 2022; 71: 154069. https://doi.org/10.1016/j.jcrc.2022.154069

19. Cai N, Chen ZQ, Tao M, Fan WT, Liao W. Mean platelet volume and red blood cell distribution width is associated with prognosis in premature neonates with sepsis. Open Med (Wars) 2021; 16: 1175-1181. https://doi.org/10.1515/med-2021-0323

20. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005; 6: 2-8. https://doi.org/10.1097/01.PCC.0000149131.72248.E6

21. Los Arcos M, Rey C, Concha A, Medina A, Prieto B. Acute-phase reactants after paediatric cardiac arrest. Procalcitonin as marker of immediate outcome. BMC Pediatr 2008; 8: 18. https://doi.org/10.1186/1471-2431-8-18

22. Merlet A, Dauchy FA, Dupon M. Hyperprocalcitonemia due to mushroom poisoning. Clin Infect Dis 2012; 54: 307-308. https://doi.org/10.1093/cid/cir845

23. Staubli SM, Oertli D, Nebiker CA. Laboratory markers predicting severity of acute pancreatitis. Crit Rev Clin Lab Sci 2015; 52: 273-283. https://doi.org/10.3109/10408363.2015.1051659

24. Salgado MT, Cao Z, Nagababu E, Mohanty JG, Rifkind JM. Red blood cell membrane-facilitated release of nitrite-derived nitric oxide bioactivity. Biochemistry 2015; 54: 6712-6723. https://doi.org/10.1021/acs.biochem.5b00643

25. Park HJ, Song J, Park YB, Lee SK, Lee SW. Red blood cell distribution width is useful in discriminating adult onset Still's disease and sepsis within 24 hours after hospitalization. Korean J Intern Med 2018; 33: 1234-1240. https://doi.org/10.3904/kjim.2016.068

26. Park SH, Park CJ, Lee BR, et al. Sepsis affects most routine and cell population data (CPD) obtained using the Sysmex XN-2000 blood cell analyzer: neutrophil-related CPD NE-SFL and NE-WY provide useful information for detecting sepsis. Int J Lab Hematol 2015; 37: 190-198. https://doi.org/10.1111/ijlh.12261

27. Spadaro S, Taccone FS, Fogagnolo A, et al. The effects of blood transfusion on red blood cell distribution width in critically ill patients: a pilot study. Transfusion 2018; 58: 1863-1869. https://doi.org/10.1111/trf.14759

28. Fogagnolo A, Spadaro S, Taccone FS, et al. The prognostic role of red blood cell distribution width in transfused and non-transfused critically ill patients. Minerva Anestesiol 2019; 85: 1159-1167. https://doi.org/10.23736/S0375-9393.19.13522-5

29. Aslan D, Gümrük F, Gürgey A, Altay C. Importance of RDW value in differential diagnosis of hypochrome anemias. Am J Hematol 2002; 69: 31-33. https://doi.org/10.1002/ajh.10011

30. Lam C, Tyml K, Martin C, Sibbald W. Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 1994; 94: 2077-2083. https://doi.org/10.1172/JCI117562

31. Tyml K, Yu J, McCormack DG. Capillary and arteriolar responses to local vasodilators are impaired in a rat model of sepsis. J Appl Physiol (1985) 1998; 84: 837-844. https://doi.org/10.1152/jappl.1998.84.3.837

32. Fontana V, Spadaro S, Bond O, et al. No relationship between red blood cell distribution width and microcirculatory alterations in septic patients. Clin Hemorheol Microcirc 2017; 66: 131-141. https://doi.org/10.3233/CH-160154

33. Liu ZY, Jiang HZ, Wang L, Chen MX, Wang HT, Zhang JX. Diagnostic accuracy of red blood cell distribution width for neonatal sepsis. Minerva Pediatr (Torino) 2022; 74: 202-212. https://doi.org/10.23736/S2724-5276.21.06149-1

34. Schlapbach LJ, Straney L, Bellomo R, MacLaren G, Pilcher D. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. Intensive Care Med 2018; 44: 179-188. https://doi.org/10.1007/s00134-017-5021-8

35. Tian H, Zhou J, Weng L, et al. Accuracy of qSOFA for the diagnosis of sepsis-3: a secondary analysis of a population-based cohort study. J Thorac Dis 2019; 11: 2034-2042. https://doi.org/10.21037/jtd.2019.04.90

36. Jouffroy R, Saade A, Carpentier A, et al. Triage of septic patients using qSOFA criteria at the SAMU regulation: a retrospective analysis. Prehosp Emerg Care 2018; 22: 84-90. https://doi.org/10.1080/10903127.2017.1347733

37. Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AFT, Lipman J. Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection. Chest 2017; 151: 586-596. https://doi.org/10.1016/j.chest.2016.10.057

38. Askim Å, Moser F, Gustad LT, et al. Poor performance of quick-SOFA (qSOFA) score in predicting severe sepsis and mortality - a prospective study of patients admitted with infection to the emergency department. Scand J Trauma Resusc Emerg Med 2017; 25: 56. https://doi.org/10.1186/s13049-017-0399-4