Received: 3 June 2021 | Revised: 26 June 2021 | Accepted: 5 July 2021

DOI: 10.1002/jcla.23909

RESEARCH ARTICLE

WILEY

Diagnostic value of red blood cell distribution width, platelet distribution width, and red blood cell distribution width to platelet ratio in children with hemophagocytic lymphohistiocytosis

Ya Xi[1] | Yongying Bai[2]

[1]Department of Central Laboratory, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center of Medicine, National Clinical Research Center for Child Health, Hangzhou, China

[2]Department of Clinical Laboratory, Branch of National Clinical Research Center for Obstetrics and Gynecology, Women's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Correspondence
Ya Xi, Department of Central Laboratory, the Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center of Medicine, National Clinical Research Center for Child Health, 3333 Binsheng Road, Hangzhou, Zhejiang 310051, China.
Email: 6515220@zju.edu.cn

Abstract

Background: To investigate whether red blood cell distribution width (RDW), platelet distribution width (PDW), and red blood cell distribution width to platelet ratio (RPR) can serve as biomarkers to distinguish hemophagocytic lymphohistiocytosis (HLH) from sepsis in children.

Methods: This is a retrospective study, involving 71 HLH patients, 105 sepsis patients, and 88 normal controls from January 2018 to December 2019. RDW, PDW, and RPR values were obtained from peripheral blood samples before standard treatment. The clinical differential diagnostic values of RDW, PDW, and RPR were analyzed by receiver operating characteristic (ROC) curve. In addition, peripheral blood samples after treatment from HLH patients were also collected for the same analyses.

Results: RDW, PDW, and RPR levels of the HLH patients were significantly higher than those of sepsis and normal controls ($p < 0.001$). In ROC curve analysis of the RDW, PDW, and RPR for diagnosis of HLH, the area under the curve (AUC) could reach to 0.7799 (95% CI = 0.7113–0.8486), 0.7835 (95% CI = 0.7093–0.8577), and 0.9268 (95% CI = 0.8886–0.9649), respectively. When using the criteria of RDW >13.75, PDW >13.30, and RPR >0.08, the sensitivity was 76.06%, 67.61%, and 84.51%, while the specificity was 68.57%, 85.71%, and 87.62%, respectively. After treatment of HLH patients, PDW and RPR were significantly reduced ($p < 0.001$).

Conclusions: This study shows that RDW, PDW, and RPR, which can be easily and cheaply detected, are novel indicators for differential diagnosis of HLH. PDW and RPR are useful indices for monitoring the effects of treatment on HLH.

KEYWORDS
hemophagocytic lymphohistiocytosis, platelet distribution width, red blood cell distribution width, red blood cell distribution width to platelet ratio, sepsis

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe rare syndrome characterized by pathologic immune activation and hyperinflammation with harmful effects on multiple organs.[1,2] The clinical presentations of HLH may include fever, cytopenias, splenomegaly, and hyperferritinemia, none of which is specific for this rare though life-threatening condition.[3–5] HLH patients can quickly develop hepatitis, liver failure, coagulation disorders, central nervous system involvement, multiple organ failure, and other manifestations, leading to a high mortality rate.[6] Prior to the initiation of HLH directed therapy, the long-term survival rate of HLH was about 95%.[7] Although the histiocytic society has established a set of clinical and laboratory criteria for HLH-94 and HLH-2004 clinical trials to help formalize the diagnosis of HLH syndrome, most of the diagnostic items of the syndrome are nonspecific, so the delay of diagnosis and misdiagnosis often remains a significant concern.[8,9] Moreover, HLH shares similarities with other inflammatory states, for example, sepsis, and the high inflammatory response present in both states of HLH and sepsis provides overlapping clinical features, including fever and worsening performance status. Worse still, the differential diagnosis of HLH and sepsis is critically important because the life-saving aggressive immunosuppressive treatment, required in the effective HLH therapy, is absent in sepsis guidelines. Therefore, early recognition and initiation of therapy are therefore of utmost importance. Thus, we enrolled HLH and sepsis patients in this study to identify new diagnostic biomarkers to distinguish HLH from sepsis.

Systemic inflammation is associated with changes in quantity and composition of circulating blood cells. Recent studies have reported that the number and ratio of complete blood cell (CBC) subset in inflammatory diseases. Red blood cell distribution width (RDW), an indicator of the size variability of circulating red blood cells, has been associated with various inflammatory conditions, such as chronic kidney disease,[10] irritable bowel disease,[11] thyroiditis,[12] rheumatoid arthritis,[13] malignancy,[14] and diabetes mellitus.[15] All of these conditions are characterized with inflammatory burden. Platelet distribution width (PDW) is a marker of platelet unequal red blood cells, which describes the size distribution of platelets produced by megakaryocytes and increases with platelet activation.[16] PDW has been associated with coronary heart disease,[17] liver steatosis,[18] irritable bowel syndrome,[19] and diabetic nephropathy.[20] All of these diseases are related with increased inflammation, too. The role of RDW to platelet count ratio (RPR), as a novel inflammatory predictor, has been established in hepatosteatosis[18] and in type 2 diabetes mellitus.[15] Interestingly, to our knowledge, there is almost no research on the clinic value of RDW, PDW, and RPR in HLH patients. Here, we report our finding of increased RDW, PDW, and RPR in HLH patients and discuss the implications of this finding.

2 | MATERIALS AND METHODS

2.1 | Study participants

We conducted this retrospective study in the Children's Hospital of Zhejiang University School of Medicine. The study was approved by the ethics committee of the Children's Hospital of Zhejiang University School of Medicine. All the guardians of the participants gave a written consent and agreed their information to be used for research purposes. A total of 71 newly diagnosed HLH cases were recruited between January 2018 and December 2019 in this study. Children were classified into HLH if they meet at least five of the eight criteria of the International Histiocyte Society (2004-HLH criteria) published in 2007[21]: (a) persistent fever; (b) splenomegaly; (c) cytopenia of at least two lineages—hemoglobin <90 g/L, platelets $<100 \times 10^9$/L, and neutrophils $<1.0 \times 10^9$/L; (d) hypertriglyceridemia (≥3.0 mmol/L) and/or hypofibrinogenemia (fibrinogen ≤1.5 g/L); (e) hemophagocytosis in the bone marrow, spleen, or lymph nodes; (f) low or absent NK-cell activity; (g) hyperferritinemia (serum ferritin ≥500 μg/L); (h) high levels of soluble interleukin-2 receptor (≥2400 U/ml). The soluble interleukin-2 receptor detection was unavailable during the period of this study. The diagnosis of sepsis was based on the presence of acute systemic inflammation symptoms and positive isolation of microorganism(s) cultured from a normally sterile site, including blood, peritoneal fluid, cerebrospinal fluid or tissue. In addition, 88 healthy individuals with no history of major diseases as well as with normal physical examination were recruited. The exclusion criteria of all the participants were as follows: cirrhosis, nonalcoholic fatty liver disease, obesity, lymphoma/leukemia, severe chronic disease, tumor, cardiovascular disease, human immunodeficiency virus infection, and steroid treatment.

2.2 | Examination methods

At admission, the peripheral blood samples were collected from all the participants for the first time. After treatment, peripheral blood samples from HLH patients would also be collected. Complete blood counts were analyzed by hematology analyzer bc-5310 (Mindray, China). RDW and PDW levels were gathered from patients' complete blood count, and RPR was calculated as the ratio of RDW and platelet counts. All operations were carried out in strict accordance with the standard operating procedures of the instrument, and the quality control meets the requirements.

2.3 | Statistical analysis

The statistical analyses were carried out with SPSS 19.0 software. Descriptive statistics were performed, including frequency distributions for categorical data and median (interquartile range) for

continuous variables. The nonparametric Mann-Whitney *U* test was used to analyze RDW, PDW, and RPR abundances in two groups. Receiver operating characteristic (ROC) curve was applied to analyze the differential diagnosis values of RDW, PDW, and RPR. Youden index (sensitivity + specificity−100%) was used to identify the optimal cutoff threshold value. The graphs were generated by using Graph Pad Prism 5.0 and MedCal version 19.7.2. A p value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of participants

The enrolled 71 HLH patients included 29 boys (40.85%) and 42 girls (59.15%), and 105 sepsis patients included 50 boys (47.62%) and 55 girls (52.38%), while 88 healthy individuals included 49 boys (55.68%) and 39 girls (44.32%). The data of clinical characteristics of HLH were analyzed and shown in Figure 1. Nearly all the patients demonstrated fever and splenomegaly were present in more than 90% of the patients (fever: 70/71, 98.59% ;splenomegaly: 68/71, 95.77%). Other clinical and laboratory tests included anemia (44/71, 61.97%), neutropenia (38/71, 53.52%), thrombocytopenia (33/71, 46.48%), hypofibrinogenemia (44/71, 61.97%), hypertriglyceridemia (28/71, 39.44%), hyperferritinemia (49/71, 69.01%), impaired NK-cell activity (47/71, 66.20%), and hemophagocytosis (20/24, 83.33%).

3.2 | Comparison of RDW, PDW, and RPR between HLH, sepsis, and normal groups

We compared the levels of RDW, PDW, and RPR of the participants between HLH, sepsis, and normal controls. The median (interquartile range) values of RDW, PDW, and RPR in HLH patients were 14.90 (13.80, 16.40), 14.90 (11.70, 17.00) and 0.139 (0.074, 0.245), and 13.10 (12.20, 14.60), 10.40 (9.50, 12.20) and 0.033 (0.027, 0.042) in sepsis patients, while 12.40 (12.00, 12.80), 10.60 (9.50, 11.90) and 0.041 (0.035, 0.046) in normal controls. Results presented in Figure 2 clearly showed that compared with the sepsis and normal controls, HLH individuals had significantly higher levels of RDW, PDW, and RPR ($p < 0.001$). In addition, the levels of RDW were significantly increased while decreased of RPR in children with sepsis compared with normal controls (RDW: $p < 0.001$; RPR: $p < 0.01$), but there was no significant differences between the sepsis and normal controls with regard to PDW ($p > 0.05$).

3.3 | ROC analysis for differential diagnosis of HLH and sepsis

To determine whether the level of RDW, PDW, and RPR had differential diagnostic value, the ROC curve was applied to analyze sensitivity and specificity and the Youden index was used to select the optimal cutoff. The AUC for RDW (95% CI = 0.7113–0.8486, $p < 0.001$), PDW (95% CI = 0.7093–0.8577, $p < 0.001$), and RPR (95% CI = 0.8886–0.9649, $p < 0.001$), which suggested sufficient accuracy and specificity, presented in Figure 3. With an optimal cutoff of RDW (13.75), PDW (13.30), and RPR (0.08) according to the Youden index, the sensitivity and specificity were the maximal. RDW had 76.06% sensitivity, 68.57% specificity, 62.07% positive predictive value (PPV), 80.90% negative predictive value (NPV), and 71.59% diagnostic efficiency. In addition, PDW had 67.61% sensitivity, 85.71% specificity, 76.19% PPV, 79.65% NPV, and 78.41% diagnostic efficiency. Moreover, RPR presented the best differential diagnostic value of three hematological parameters. The data showed that the sensitivity, specificity, PPV, NPV, and diagnostic efficiency of RPR could reach 84.51%, 87.62%, 82.19%, 89.32%, and 86.36%, respectively. Results of ROC curve analysis and selected cutoff points for RDW, PDW, and RPR were presented in Table 1.

3.4 | RDW, PDW, and RPR levels in patients with HLH after treatment

We compared the differences of RDW, PDW, and RPR before and after treatment in HLH patients. The median (interquartile range) values of RDW, PDW, and RPR were 14.90 (13.80, 16.40), 14.90 (11.70, 17.00), and 0.139 (0.074, 0.245) before treatment, respectively, while 15.05 (12.80, 16.80), 10.80 (9.38, 15.78), and 0.056

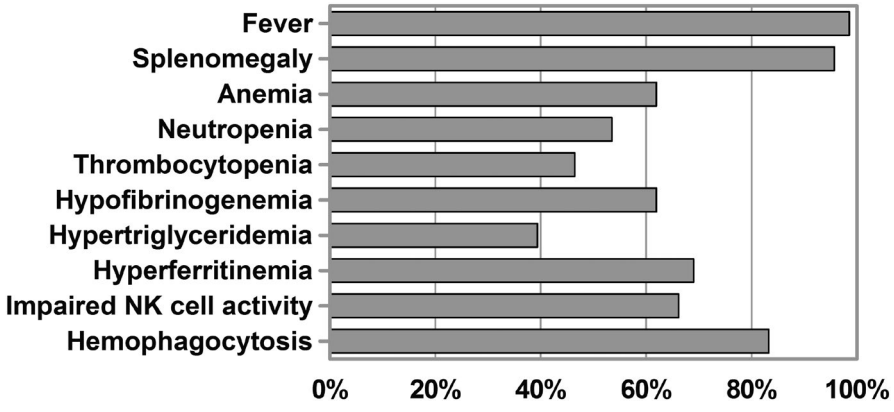

FIGURE 1 Clinical and laboratory parameters of 71 patients with HLH. The bar represents the percentage of positive patients according to HLH-2004 criteria. Abbreviation: HLH, hemophagocytic lymphohistiocytosis

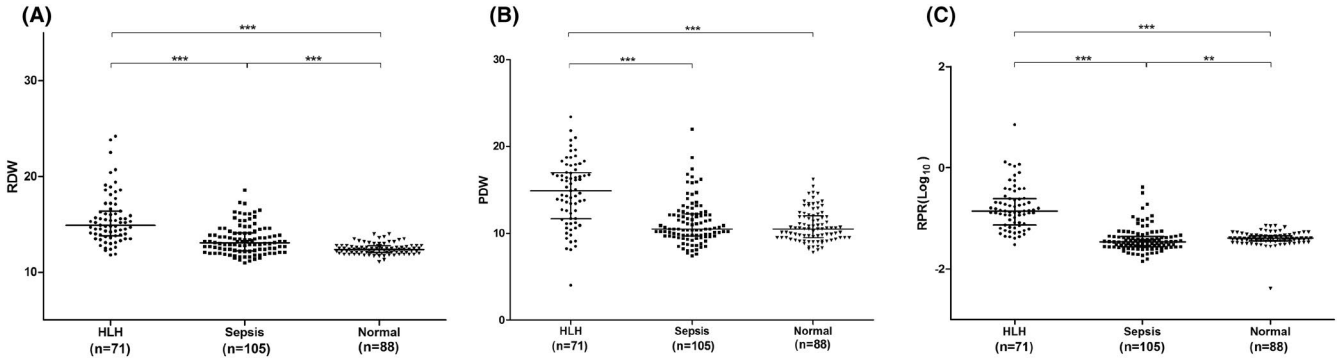

FIGURE 2 Comparison of laboratory parameters—RDW, PDW, and RPR among different groups. A. The expression of RDW in patients with HLH, sepsis, and normal controls. B. The expression of PDW in patients with HLH, sepsis, and normal controls. C. The expression of PPR in patients with HLH, sepsis, and normal controls. Abbreviations: RDW, red blood cell distribution width; PDW, platelet distribution width; RPR, red blood cell distribution width to platelet ratio; HLH, hemophagocytic lymphohistiocytosis. The data of PRP were shown as $\log_{10}$. $^{**}p < 0.01$, $^{***}p < 0.001$

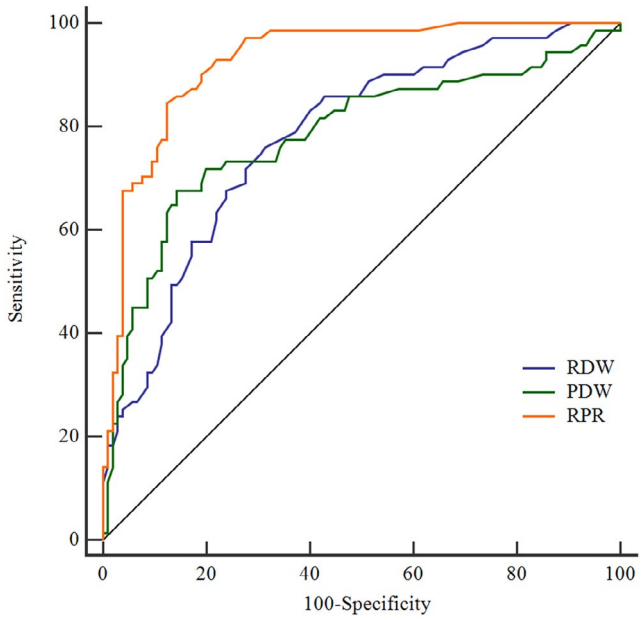

FIGURE 3 ROC analyses for determining the optimal cutoff value of RDW, PDW, and RPR to differentiate HLH from sepsis. The AUC for RDW for distinguishing HLH patients from sepsis patients is 0.7799 (95% CI = 0.7113–0.8486, $p < 0.001$); the AUC for PDW for distinguishing HLH patients from sepsis patients is 0.7835 (95% CI = 0.7093–0.8577, $p < 0.001$); the AUC for RPR for distinguishing HLH patients from sepsis patients is 0.9268 (95% CI = 0.8886–0.9649, $p < 0.001$). Abbreviations: ROC, receiver operating characteristic; RDW, red blood cell distribution width; PDW, platelet distribution width; RPR, red blood cell distribution width to platelet ratio; HLH, hemophagocytic lymphohistiocytosis; AUC, area under the curve

(0.045, 0.089)after treatment, respectively. After clinical treatment, expressions of PDW and RPR were statistically decreased ($p < 0.001$), while the reduction in RDW was not statistically significant ($p > 0.05$). The detailed graphical representation was shown in Figure 4.

TABLE 1 The differential diagnostic value between HLH and sepsis

Variables	RDW	PDW	RPR
AUC	0.7799	0.7835	0.9268
Youden index	0.4463	0.5332	0.7213
Cutoff value	13.75	13.30	0.08
Sensitivity %	76.06	67.61	84.51
Specificity %	68.57	85.71	87.62
PPV %	62.07	76.19	82.19
NPV %	80.90	79.65	89.32
Diagnostic efficiency %	71.59	78.41	86.36

Abbreviations: AUC, area under the curve; HLH, hemophagocytic lymphohistiocytosis; NPV, negative predictive value; PPV, positive predictive value.

4 | DISCUSSION

The differential diagnosis of HLH and sepsis is critically important because the life-saving aggressive immunosuppressive treatment is far different from those of sepsis children. The treatment of HLH requires repeated chemotherapy, while the treatment of sepsis depends on the proper use of antibiotics.[8] Moreover, HLH is a rare disease with poor prognosis and fatal outcome, with mortality rates as high as 95%.[7] Therefore, timely diagnosis is crucial to initiate adequate treatment and thus to improve prognosis. As demonstrated by Jordan et al[22] early therapy reduces mortality to 30%–35%. Given the lack of specific diagnostic tests, we aim to identify rapid and simple biomarkers with high sensitivity and specificity to allow early detection of HLH in HLH patients.

To the best of our knowledge, this is the first study to evaluate the role of RDW, PDW, and RPR in HLH for biomarkers development. The results indicated that RDW, PDW, and RPR in patients with HLH have higher values than those of sepsis and normal individuals. Moreover, the levels of RDW, PDW, and RPR are additional valid

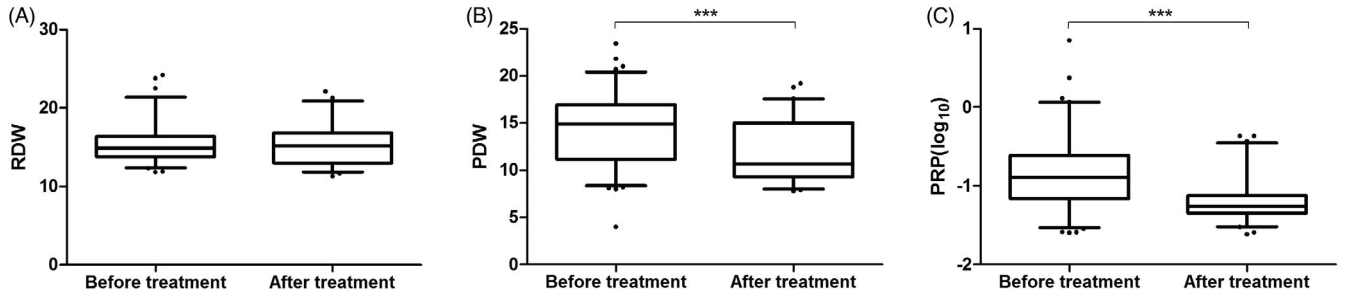

FIGURE 4 Comparisons of RDW, PDW, and RPR in patients with HLH before and after clinical treatment. Abbreviations: RDW, red blood cell distribution width; PDW, platelet distribution width; RPR, red blood cell distribution width to platelet ratio; HLH, hemophagocytic lymphohistiocytosis. The data of PRP were shown as $\log_{10}$. $^{***}p < 0.001$

biomarkers for differentiating HLH from sepsis. In the past decade, the inclusion criteria have become de facto criteria for the definition/diagnosis of HLH. However, due to the complexity of diagnostic criteria and the similarity with other inflammatory diseases, the diagnosis is often delayed, and misdiagnosis, posing an important problem. Moreover, as mentioned above, the existing standard set is subject to major limitations. Since hemophagocytic syndrome may be difficult to differentiate from severe sepsis,[23] Fardet et al[24] proposed HScore to predict the possibility of a single patient suffering from the syndrome, enabling clinicians to make appropriate treatment decisions as soon as possible. The probability of having hemophagocytic syndrome ranged from <1% with an HScore of ≤90 to >99% with an HScore of ≥250. Although HScore shows excellent discrimination and is a very useful tool for predicting HLH, it is mainly used in adult patients and is a complex index, restricting the efficiency for early diagnosis. Ferritin is a standard laboratory marker for the diagnosis of HLH and has been reported as a useful and convenient screening method for suspected HLH cases.[25] However, the criterion of ferritin above 500 μg/L for the diagnosis of HLH was less specific, as shown in the previous study,[26] and only 10 of 330 patients had ferritin levels above 500 μg/L were diagnosed with HLH. In addition, study by Wang et al[27] showed that the specificity of ferritin was 43% when it was above 500 μg/L. Higher level (>3000 or >10,000 μg/L) has been suggested that the specificity of ferritin may increase in children.[22] Furthermore, serum ferritin level is a nonspecific index, which will increase in the following conditions, such as liver injury, kidney injury, and hematological malignancies.[28] Moreover, Otrock et al even proposed that hyperferritinemia occurred in a variety of situations and was not specific to adult or child HLH and common causes of elevated ferritin should be considered before considering the possibility of HLH.[29] Cui et al[23] reported a better model for differential diagnosis was ferritin + sCD163, which provided a sensitivity of 87.0% and a specificity of 71.7% with the AUC of 0.837. Debaugnies et al[30] analyzed ferritin, glycosylated ferritin, CD14, sCD25, CD163, IL-1ß, IL-6, IL-10, IL-12p70, IL-17α, IL-18, IFN-γ, IP-10, and CXCL9 levels to differentiate HLH from sepsis. Among the above biomarkers tested, ferritin, IL-18, and glycosylated ferritin were the most efficient parameters for early diagnosis of HLH. According to the AUC of three biomarkers (glycosylated ferritin: 0.8484; IL-18: 0.9003; ferritin: 0.9394) and with a sensitivity set at 85%, glycosylated ferritin, IL-18, and ferritin were the biomarkers with the highest specificity: 71%, 79%, and 84%, respectively. However, the above-mentioned examinations either need special instruments or are time-consuming and laborious, which greatly limit their clinical value. In our present study, RDW, PDW, and RPR displayed considerable power for differentiating HLH from sepsis, with the AUC of 0.7799, 0.7835, and 0.9268, respectively. Although the sensitivity of RDW and PDW was slightly lower than previously reported biomarkers,[23,26,27,30] such as glycosylated ferritin, IL-18, ferritin, and ferritin + sCD163, the specificity of RDW and PDW was similar to or even higher than that indexes reported above. Fortunately, among the three indicators, RPR showed optimal performance for differentiating HLH from sepsis, and the sensitivity and specificity were both over 80%, especially the NPV and diagnostic efficiency were all higher than 85%. The findings validate the performance of RDW, PDW, and RPR as additional valid biomarkers for differentiating HLH from sepsis. Their low-cost, consequent wide and easy availability, and high sensitivity and specificity in daily clinical practice have made them eminently suitable for the laboratory testing.

HLH is an entity featured by hyperinflammatory response and "cytokine storm." In inflammation, pro-inflammatory cytokines affect the survival of red blood cells in circulation, damage the red blood cell membrane, and cause larger and newer reticulocytes to enter the blood circulation, increasing the red blood cell distribution width (RDW).[31] In addition, numerous inflammatory cytokines contribute to coagulation disorders, reduce platelet count, and overt disseminated intravascular coagulation.[32] Besides, another important factor in inflammation, tissue factor, can cause coagulation disorders and reduce platelet count.[33] Therefore, red blood cell distribution width and platelet ratio (RPR) have been reported as a useful parameter describing the systemic inflammatory response by a large number of studies.[34,35] Further researches showed that RDW, PDW, and RPR were significantly associated with the prognosis of many diseases, such as cancer, sepsis, and cardiovascular disease.[36–39] However, there are few reports about the relationship between HLH and RDW, PDW, and RPR. In order to determine whether the increased amount of RDW, PDW, and RPR had prognosis value for clinical improvement after clinical treatment, the changes between RDW, PDW, and RPR values before and after treatment were analyzed. In our study, we observed the patients who developed HLH

have higher RDW, PDW, and RPR levels before treatment but lower PDW and RPR levels after treatment, thus providing a useful insight into the application of PDW and RPR in the evaluation of therapeutic effect on HLH.

Nevertheless, some limitations of our study must be considered. First, the soluble interleukin-2 receptor detection was unavailable in our hospital. Therefore, a comparative analysis between RDW, PDW, and RPR levels and the laboratory indexes contained in HLH-2004 criteria are lacking in the study. Second, the analysis was performed on a small sample with a short follow-up period and a single center. Third, this study does not include some key factors of pro-inflammatory cytokines and/or inflammatory markers that may have crucial significance for HLH, such as C-reactive protein, procalcitonin, interleukin, and cytokine. Considering the small number of clinical samples in this study and the potential clinical significance of the results, this study is worthy of expanding the sample size.

In conclusion, our study is the first to indicate that cost-effective and easily calculated hematological parameters RDW, PDW, and RPR are novel indicators for differential diagnosis of HLH and sepsis. PDW and RPR could be additional biomarkers for monitoring therapeutic effects of HLH.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

All the authors have no potential conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Ya Xi https://orcid.org/0000-0003-2747-4129

REFERENCES

1. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. *N Engl J Med*. 2020;382(19):1811-1822.
2. Han X-C, Ye Q, Zhang W-Y, et al. Cytokine profiles as novel diagnostic markers of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children. *J Crit Care*. 2017;39:72-77.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516.
4. Knaak C, Schuster FS, Spies C, et al. Hemophagocytic lymphohistiocytosis in critically ill patients. *Shock*. 2020;53(6):701-709.
5. Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: differential diagnosis of HLH and sepsis. *Crit Rev Oncol Hemat*. 2017;114:1-12.
6. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332-1343.
7. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130(25):2728-2738.
8. Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. *Pediatric Critical Care Medicine*. 2009;10(3):387–392. http://dx.doi.org/10.1097/pcc.0b013e3181a1ae08
9. Wang H, Xiong L, Tang W, et al. A systematic review of malignancy-associated hemophagocytic lymphohistiocytosis that needs more attentions. *Oncotarget*. 2017;8(35):59977-59985.
10. Tekce H, Kin Tekce B, Aktas G, Tanrisev M, Sit M. The evaluation of red cell distribution width in chronic hemodialysis patients. *Nephrol Dial Transpl*. 2014;2014:1-6.
11. Aktas G, Alcelik A, Tekce BK, et al. Red cell distribution width and mean platelet volume in patients with irritable bowel syndrome. *Prz Gastroenterol*. 2014;9(3):160-163.
12. Aktas G, Sit M, Dikbas O, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis? *Exp Clin Endocr Diab*. 2014;122(10):572-574.
13. Cakir L, Aktas G, Mercimek OB, et al. Are red cell distribution width and mean platelet volume associated with rheumatoid arthritis? *Biomed Res-India*. 2016;27(2):292-294.
14. Aktas G, Sit M, Karagoz I, et al. Could red cell distribution width be a marker of thyroid cancer? *J Coll Physicians Surg Pak*. 2017;27(9):556-558.
15. Bilgin S, Aktas G, Zahid Kocak M, Atak BM, Kurtkulagi O, Duman TT, Savli H. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. *The Aging Male*. 2020;23(5):923–927. http://dx.doi.org/10.1080/13685538.2019.1632283
16. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. *Biochem Med (Zagreb)*. 2016;26(2):178-193.
17. Sincer I, Mansiroglu AK, Erdal E, et al. Could platelet distribution width predict coronary collateral development in stable coronary artery disease? *North Clin Istanb*. 2020;7(2):112-117.
18. Aktas G, Duman TT, Kurtkulagi Ö, et al. Liver steatosis is associated both with platelet distriution width, neutrophil/lymphocyte and monocyte/lymphocyte ratios. *Prim Health Care*. 2020;10(4):346. https://www.researchgate.net/publication/344224695
19. Aktas G, Duman T, Atak B, et al. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. *J Family Med Prim Care*. 2020;22(2):107-110. https://www.researchgate.net/publication/342787098
20. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol*. 2019;220(4):354.
21. Henter J-I, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131.
22. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
23. Cui Y, Xiong X, Ren Y, Wang F, Wang C, Zhang Y. CD163 as a valuable diagnostic and prognostic biomarker of sepsis-associated hemophagocytic lymphohistiocytosis in critically ill children. *Pediatric Blood & Cancer*. 2019;66(10):e27909. http://dx.doi.org/10.1002/pbc.27909
24. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613-2620.
25. Lin TF, Ferlic-Stark LL, Allen CE, et al. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. *Pediatr Blood Cancer*. 2011;56(1):154-155.
26. Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2008;50(6):1227-1235.

27. Wang Z, Wang Y, Wang J, et al. Early diagnostic value of low percentage of glycosylated ferritin in secondary hemophagocytic lymphohistiocytosis. *Int J Hematol*. 2009;90(4):501-505.
28. Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. *Annu Rev Pathol*. 2018;13:27-49.
29. Otrock ZK, Hock KG, Riley SB, et al. Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis. *Ann Hematol*. 2017;96(10):1667-1672.
30. Debaugnies F, Mahadeb B, Nagant C, et al. Biomarkers for early diagnosis of hemophagocytic lymphohistiocytosis in critically ill Patients. *J Clin Immunol*. 2021;41(3):658-665.
31. Karabulut B, Arcagok BC. New diagnostic possibilities for early onset neonatal sepsis: red cell distribution width to platelet ratio. *Fetal Pediatr Pathol*. 2020;39(4):297-306.
32. Nam M, Son BH, Seo JE, et al. Improved diagnostic and prognostic power of combined delta neutrophil index and mean platelet volume in pediatric sepsis. *Ann Clin Lab Sci*. 2018;48(2):223-230.
33. Kakafika A, Papadopoulos V, Mimidis K, et al. Coagulation, platelets, and acute pancreatitis. *Pancreas*. 2007;34(1):15-20.
34. Yuyun D, Zhihua T, Haijun W, et al. Predictive value of the red blood cell distribution width-to-platelet ratio for hepatic fibrosis. *Scand J Gastroentero*. 2019;54(1):81-86.
35. Bilgin B, Sendur MAN, Hizal M, et al. Prognostic effect of red cell distribution width-to-platelet ratio in colorectal cancer according to tumor stage and localization. *J Cancer Res Ther*. 2019;15(1):54-60.
36. Sayed SZ, Mahmoud MM, Moness HM, et al. Admission platelet count and indices as predictors of outcome in children with severe sepsis: a prospective hospital-based study. *BMC Pediatr*. 2020;20(1):387.
37. Han F, Liu Y, Cheng S, et al. Diagnosis and survival values of neutrophil-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) in esophageal cancer. *Clin Chim Acta*. 2019;488:150-158.
38. Yu J, Wang L, Peng YC, et al. Dynamic monitoring of erythrocyte dstribution width (RDW) and platelet distribution width (PDW) in treatment of acute myocardial infarction. *Med Sci Monit*. 2017;23:5899-5906.
39. Huang J, Yin G, Duan L, et al. Prognostic value of blood-based inflammatory biomarkers in secondary hemophagocytic lymphohistiocytosis. *J Clin Immunol*. 2020;40(5):718-728.

How to cite this article: Xi Y, Bai Y. Diagnostic value of red blood cell distribution width, platelet distribution width, and red blood cell distribution width to platelet ratio in children with hemophagocytic lymphohistiocytosis. *J Clin Lab Anal*. 2021;35:e23909. https://doi.org/10.1002/jcla.23909