Review Article

IS ELEVATED RED BLOOD CELL DISTRIBUTION WIDTH VALUE A PROGNOSTIC MARKER IN SEPSIS PATIENTS?

ABSTRACT:

Sepsis and its complications are a common cause of infectious disease and death in worldwide. But the infection can be challenges to confirm and there is gold standard methods to confirm it. Red blood cell distribution width (RDW) value frequently measured at every complete blood count. In sepsis the RDW morphology changes are believed to be mainly related to prognosis . RDW has also been studied as an independent variable in different predictive score. We systematically review the articles can RDW be used as prognostic marker in patient with sepsis.

Keywords : Sepsis, RDW

Comment [VR1]: Grammatical error in sentence, so meaning not clear

Comment [VR2]: Is it RBC morphology or RDW morphology?

INTRODUCTION:

Sepsis is a dysregulated host response to infection resulting in potential life-threatening organ dysfunction. Diagnosis of the infections, there is no existing gold standard method. Delays in the empirical treatment of sepsis and bacteremia increase mortality, length of hospitalization, and cost. Increase in (RDW), a simple and routine investigation, can be used as a prognostic marker in sepsis patients.

RED BLOOD CELL DISTRIBUTION WIDTH :

The red blood cell distribution width is an indicator of changes in RBC size or RBC volume. Most automated instruments will quantitatively evaluate the red blood cell volume

changes indicated by the RDW, which resembles to the microscopic examination of the degree of heterogeneous effects. The RDW derived from the pulse height analysis can be stated as the standard deviation of fl (SD), or as a percentage of the coefficient of variation (CV) of the red blood cell volume measurement.

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS EXPLAINING RDW CHANGES IN SEPTIC PATIENTS :

Rheological changes of red blood cells can change the RDW of patients with sepsis. (1) The mechanism of shape (spherical), volume, and deformability changes is still not fully understood,(1) but several mechanisms have been proposed in patients with sepsis: the redistribution of phosphatidylserine on the lobules of the outer membrane of red blood cells,(2)(3) altered acidic membrane content of salivary red blood cells,(4)(5) with 3 protein phosphorylation,(6) redox imbalance,(7–9) calcium,(10) 2,3-diphosphoglycerate(11) and adenosine triphosphate(12) homeostasis changes and nitric oxide pathway modulation.(13,14) In addition, the inflammatory response indirectly regulates hematopoietic function through abnormal iron metabolism, increased hemolysis, and reduced red blood cell lifespan, which in turn leads to increased release of immature forms into the blood. (7)

RDW AND PROGNOSIS IN SEPTIC PATIENTS :

Many studies on RDW and prognosis are for all icu admitted patients,(15,16) with sepsis. Only a less studies have concentrated on how RDW predicts the mortality of patients with sepsis. (17–20) Some authors have studied in-hospital mortality,(17,21) while the goals of other studies are short-term(18,22)and long-term prognosis. (23) A retrospective study(17) included 279 septic shock patients and described "RDW is a powerful predictor of hospital mortality." The subjects were divided into five equal parts (19.4%) according to the RDW value on the first day of septic shock. RDW is significantly related to mortality within the

Comment [VR3]: All letters in CAPS. Also to expand if first time using

Comment [VR4]: Few instead of less

RDW range, odds ratio [OR] = 4.6 (95% confidence interval [CI], 1.0-23.4; p = 0.06), OR = 8.0 (95% CI, 1.5-41.6; p 19.4%, respectively.

The mortality during these time intervals was studied relative to subjects with RDW <13.5%. The RDW value at the time of ICU admission and its relationship with mortality in the intensive care unit was also studied in patients with community-acquired intra-abdominal sepsis. (24) Among these patients, RDW has a good distinguishing ability in predicting ICU mortality, and the area under the curve (AUC) estimated by receiver operating characteristic (ROC) analysis is 0.867 (95% CI, 0.791–0.942). In addition, some authors focused on elderly patients with sepsis and septic shock.(21,25) Both studies found a significant correlation between the increase in RDW and ICU mortality in elderly patients(21) and the 30-day mortality. (26) The average age of the study by Wang et al. (21) is 81.5±8.3, and the average age by Kim et al.(25) is 78 years. The potential problems of these studies are first related to the type-retrospective, but the second most important is the study population.

Comment [VR5]: What does author want to convey here

Comment [VR6]: Which both studies?

Regardless of sepsis and septic shock, are older people more likely to have RDW changes. As mentioned above, many diseases and conditions may change RDW, and elderly patients should be considered, because elderly patients often do not have one disease, but many diseases, and most of them may be in advanced stages. Therefore, this concept of fragility should be added to any changes in RDW. (20) It is hoped that after considering all these risk factors in a multivariate analysis, changes in RDW in elderly patients with sepsis will be significantly correlated with mortality, while RDW will still be associated with ICU mortality. After multivariate adjustment, Wang et al.(21) found that RDW was significantly related to ICU mortality (hazard ratio [HR] = 1.18; 95% CI, 1.03-1.35; p = 0.019). Jo et al.(22) retrospectively studied 566 patients with severe sepsis and septic shock (as defined by the old definition of sepsis). The RDW value is divided into three quantiles (<14%, 14.1% to 15.7%,> 15.8%), and the mortality rate is studied range by range. The authors found that

RDW was elevated in non-survivors and was significantly associated with 28-day mortality. COX regression analysis showed that RDW is an independent determinant of 28-day mortality: RDW> 15.8% (HR = 2.57; 95% CI, 1.53-4.34; p 15.5%. The 28-day and 90-day patients are 44.9% Kim et al.(27) Studied the mortality rate, collected the RDW value on admission, and measured its dynamics in the next 72 hours (ΔRDW72hr-adm), patients with an elevated baseline RDW value and patients with an elevated RDW> 0.2% the first 72 hours (ΔRDW72hr-adm> 0.2%) presents the highest risk of mortality at 28 and 90 days. Finally, Han et al. (23) only studied the long-term prognosis. This retrospective observational study used a huge critical care database (Intensive Care Medical Information Center), which included a total of 4264 patients with sepsis, and studied the relationship between their 4-year mortality rate and the baseline RDW value. In the multivariate COX analysis, RDW was individually related with all-cause mortality and had a moderate discriminating ability. ROC analysis estimated its AUC to be 0.64 (95% CI, 0.63-0.66).

Comment [VR7]: What does the author want to convey here is not clear. Please clarify

In a recent study done by Foy et al.(28) studied on a total of 1641 patients showed elevated RDW(>14.5 %) value show increases mortality in-hospital who suffered from SARS-COV-2 infections.

CONCLUSION:

By this review, it is understood that RDW value which is a part of an automated CBC which is a done routinely, which is cheap, easily available parameter on admission can be used as a prognostic marker in patients in sepsis. Furthermore studies are needed to confirm these data.

REFERENCES :

1. Bateman R, Sharpe M, Singer M, Ellis C. The Effect of Sepsis on the Erythrocyte. IJMS. 2017 Sep 8;18(9):1932.

2. Dinkla S, van Eijk LT, Fuchs B, Schiller J, Joosten I, Brock R, et al. Inflammation-associated changes in lipid composition and the organization of the erythrocyte membrane. BBA Clin. 2016 Apr 3;5:186–92.

3. Qadri SM, Bissinger R, Solh Z, Oldenborg P-A. Eryptosis in health and disease: A paradigm shift towards understanding the (patho)physiological implications of programmed cell death of erythrocytes. Blood Rev. 2017 Nov;31(6):349–61.

4. Piagnerelli M, Boudjeltia KZ, Brohee D, Piro P, Carlier E, Vincent J-L, et al. Alterations of red blood cell shape and sialic acid membrane content in septic patients. Crit Care Med. 2003 Aug;31(8):2156–62.

5. Piagnerelli M, Boudjeltia KZ, Brohee D, Vincent J-L, Vanhaeverbeek M. Modifications of red blood cell shape and glycoproteins membrane content in septic patients. Adv Exp Med Biol. 2003;510:109–14.

6. R. Condon M, Feketova E, Machiedo GW, Deitch EA, Spolarics Z. Augmented Erythrocyte Band-3 Phosphorylation in Septic Mice. Biochim Biophys Acta. 2007 May;1772(5):580–6.

7. Ghaffari S. Oxidative Stress in the Regulation of Normal and Neoplastic Hematopoiesis. Antioxid Redox Signal. 2008 Nov;10(11):1923–40.

8. Yerer MB, Yapislar H, Aydogan S, Yalcin O, Baskurt O. Lipid peroxidation and deformability of red blood cells in experimental sepsis in rats: The protective effects of melatonin. Clinical Hemorheology and Microcirculation. 2004 Jan 1;30(2):77–82.

9. Oliveira YPA de, Pontes-de-Carvalho LC, Couto RD, Noronha-Dutra AA. Oxidative stress in sepsis. Possible production of free radicals through an erythrocyte-mediated positive feedback mechanism. Braz J Infect Dis. 2017 Feb;21(1):19–26.

10. Ruef P, Ehrhard M, Frommhold D, Koch L, Fritzsching B, Poeschl J. Lipid A decreases human erythrocytes deformability by increasing intracellular Ca(2+): effects of verapamil, staurosporine and the rho-kinase inhibitor Y-27632. Clin Hemorheol Microcirc. 2011;49(1–4):315–22.

11. Lin X, Rogers S, Timm D, Angelo A, Jaya P, Melanie E et al. Sepsis Induced Red Cell Dysfunction (SiRD): Physiology and Mechanisms. 2017;130(1):3469. - Google Search [Internet]. [cited 2021 Feb 15]. Available from: https://www.google.com/search?q=Lin+X%2C+Rogers+S%2C+Timm+D%2C+Angelo+

A%2C+Jaya+P%2C+Melanie+E+et+al.+Sepsis+Induced+Red+Cell+Dysfunction+(SiRD)%3A+Physiology+and+Mechanisms.+2017%3B130(1)%3A3469.&rlz=1C5CHFA_enIN899IN899&oq=Lin+X%2C+Rogers+S%2C+Timm+D%2C+Angelo+A%2C+Jaya+P%2C+Melanie+E+et+al.+Sepsis+Induced+Red+Cell+Dysfunction+(SiRD)%3A+Physiology+and+Mechanisms.+2017%3B130(1)%3A3469.&aqs=chrome..69i57j69i60.2700j0j7&sourceid=chrome&ie=UTF-8

12. Forsyth AM, Wan J, Owrutsky PD, Abkarian M, Stone HA. Multiscale approach to link red blood cell dynamics, shear viscosity, and ATP release. Proc Natl Acad Sci U S A. 2011 Jul 5;108(27):10986–91.

13. Bateman RM, Sharpe MD, Jagger JE, Ellis CG. Sepsis impairs microvascular autoregulation and delays capillary response within hypoxic capillaries. Crit Care [Internet]. 2015 [cited 2021 Feb 15];19. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4634189/

14. Winkler MS, Kluge S, Holzmann M, Moritz E, Robbe L, Bauer A, et al. Markers of nitric oxide are associated with sepsis severity: an observational study. Critical Care. 2017 Jul 15;21(1):189.

15. Zhang Z, Xu X, Ni H, Deng H. Red cell distribution width is associated with hospital mortality in unselected critically ill patients. J Thorac Dis. 2013 Dec;5(6):730–6.

16. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red Cell Distribution Width and all cause mortality in critically ill patients. Crit Care Med. 2011 Aug;39(8):1913–21.

17. Sadaka F, O'Brien J, Prakash S. Red Cell Distribution Width and Outcome in Patients With Septic Shock. J Intensive Care Med. 2013 Sep 1;28(5):307–13.

18. Lorente L, Martín MM, Abreu-González P, Solé-Violán J, Ferreres J, Labarta L, et al. Red Blood Cell Distribution Width during the First Week Is Associated with Severity and Mortality in Septic Patients. PLOS ONE. 2014 Aug 25;9(8):e105436.

19. Chen K-F, Liu S-H, Li C-H, Wu C-C, Chaou C-H, Tzeng I-S, et al. Development and validation of a parsimonious and pragmatic CHARM score to predict mortality in patients with suspected sepsis. Am J Emerg Med. 2017 Apr;35(4):640–6.

20. Kim YC, Song JE, Kim EJ, Choi H, Jeong WY, Jung IY, et al. A Simple Scoring System Using the Red Blood Cell Distribution Width, Delta Neutrophil Index, and Platelet Count to Predict Mortality in Patients With Severe Sepsis and Septic Shock. J Intensive Care Med. 2019 Feb;34(2):133–9.

21. Wang A-Y, Ma H-P, Kao W-F, Tsai S-H, Chang C-K. Red blood cell distribution width is associated with mortality in elderly patients with sepsis. The American Journal of Emergency Medicine. 2018 Jun;36(6):949–53.

22. Jo YH, Kim K, Lee JH, Kang C, Kim T, Park H-M, et al. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. The American Journal of Emergency Medicine. 2013 Mar;31(3):545–8.

23. Han Y-Q, Zhang L, Yan L, Li P, Ouyang P-H, Lippi G, et al. Red blood cell distribution width predicts long-term outcomes in sepsis patients admitted to the intensive care unit. Clinica Chimica Acta. 2018 Dec;487:112–6.

24. Kaya Ozdogan H. Red Cell Distribution Width is Predictive of Mortality in Intensive Care Patients with community-acquired Intra-abdominal Sepsis. Ulus Travma Acil Cerrahi Derg [Internet]. 2015 [cited 2021 Feb 16]; Available from: https://www.journalagent.com/travma/pdfs/UTD_21_5_352_357.pdf

25. Kim S, Lee K, Kim I, Jung S, Kim M-J. Red cell distribution width and early mortality in elderly patients with severe sepsis and septic shock. Clin Exp Emerg Med. 2015 Sep 30;2(3):155–61.

26. Fraenkel PG. Anemia of Inflammation: A Review. Med Clin North Am. 2017 Mar;101(2):285–96.

27. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care. 2013;17(6):R282.

28. Foy BH, Carlson JCT, Reinertsen E, Padros I. Valls R, Pallares Lopez R, Palanques-Tost E, et al. Association of Red Blood Cell Distribution Width With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection. JAMA Netw Open [Internet]. 2020 Sep 23 [cited 2020 Dec 18];3(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7512057/