

## Role of Red Cell Distribution Width in Prognosis of Patients of All Age Groups with Sepsis- A Narrative Review

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### ABSTRACT

**Introduction:** Sepsis is life threatening emergency situation that is frequently encountered in every emergency department. Knowing the prognosis of such patient is crucial which is difficult in the busy emergency rooms. There are lots of prognostic tools in practice and red cell distribution width is newer tool that is under test to predict prognosis of patients with sepsis. In recent day different scientific papers are published over red cell distribution width (RDW) in association with sepsis. This article tried to review such articles and give the holistic view of RDW in association with sepsis.

**Method:** Articles were searched in Pubmed, Google scholar, The Cochrane Library, Scopus and Hinari. 26 articles were found and thorough revision of articles was done.

**Result:** Most of the articles point towards overwhelming efficacy of RDW in sepsis across all age group. It can also be used in septic patients with anemia and who received blood transfusions recently. Only few papers are published involving pediatric population and patients with anemia and recent blood transfusion history.

**Conclusion:** RDW is efficacious tool than currently practiced tools to predict prognosis of patient with sepsis across all ages. There are only few studies in pediatric population and patients with anemia and history of recent blood transfusion, so caution is advised while applying RDW among pediatric population and in patients with anemia and recent blood transfusion.

**Keywords:** RDW, review article, prognosis of sepsis, sepsis

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## INTRODUCTION

Definition and diagnostic criteria for sepsis is changing day by day so is the prognostic tool. Sepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate greater than 2 mmol/L in the absence of hypovolemia.<sup>1</sup> Patients with infection can be identified to have sepsis if they have at least two of following clinical criteria that together constitute a new bedside clinical score termed quick SOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation or systolic blood pressure of 100mmHg or less.<sup>2,3</sup>

Commonly used prognostic indicators include Acute Physiological and chronic health evaluation II (APACHE II), sequential organ failure Assessment (SOFA), Mortality in Emergency Department Score (MEDS), New York Sepsis severity score. In recent years Red cell distribution Width (RDW) is being investigated for its prognostic value in septic patients. Red cell distribution width (RDW) is an index of variation of erythrocyte volume (i.e. anisocytosis). It is conventionally included in a standard complete blood count (CBC) and is automatically calculated by dividing the standard deviation (SD) of erythrocyte volume from the mean corpuscular volume (MCV). RDW has been used to help classify anemia as it reflects the degree of variation in erythrocyte size. The value of this parameter increases parallel with anisocytosis. It is conventionally increased in patients with anemia attributable to iron deficiency, deficit of folic acid/vitamin B12, patients with autoimmune disorders, myelodysplastic syndrome, hemolytic anemia, liver impairment and sickle cell disease.<sup>3</sup>

The normal range of RDW is 11.5% to 14.5% with no clinical scenarios that produce RDW <11.5%. Any process that results in the release of reticulocytes into the circulation will result in an increase in RDW. When patients are infected, microbes release various toxins/lipopolysaccharides which activate inflammatory cascade via various interleukins, cytokines.<sup>4</sup> Cytokines are responsible for the clinically observable effects of the bacteremia in the host.<sup>1</sup> These cytokines induce direct red cell blood cell damage by erythrophagocytosis or apoptosis, interfere with iron homeostasis, inhibit erythropoiesis by myelosuppression and down regulate erythropoietin-receptor expression.<sup>4</sup> These mechanism is thought to lead to anisocytosis

and increased RDW.<sup>6</sup> RDW has been utilized in diverse diseases other than traditionally for interpretation of anemia. In chronic diseases, elevated RDW was associated with increased mortality among healthy middle-aged and older adults from the general population and patients with cardiovascular disease, stroke, heart failure, and chronic dialysis.<sup>6-14</sup> In acute conditions, RDW can also be used as a mortality predictor among patients with acute pancreatitis, acute dyspnea during an emergency department visit, out-of-hospital cardiac arrest, and critical illnesses in ICU setting.<sup>7,8,12,15,16</sup> For septic patients, RDW was also found to be an independent indicator of mortality in patients with gram-negative bacteremia, community-acquired pneumonia, severe sepsis, and septic shock.<sup>17,18</sup>

RDW is new tool to predict mortality among septic patients and is being tried to combine with other laboratory parameters to develop new clinical scores too. There are many studies done in adult population and few articles among elderly population and pediatric population. This review article is done see the usefulness of RDW to predict mortality among septic patients of all age groups.

## METHOD

Original articles were searched in Google Scholar, Pubmed, The Cochrane Library and Scopus using key word RDW, Sepsis, RDW in Sepsis. Articles available online in above search engines were searched in a month duration (from 1st November 2019 to 1<sup>st</sup> December 2019). All available articles mentioning prognostic value of RDW in sepsis were included. Review articles, case reports, case series were excluded. Total of 26 articles were reviewed among which 5 included pediatric population, 3 included geriatric population. Using Hinari 17 full articles were reviewed. Results and methodology summary were analyzed. Detail data sets were not analyzed as it was narrative review rather than systemic review/meta-analysis. So nine abstracts were also analyzed during this review.

## RESULT

Increase in RDW value above normal (>14.5%) is proportionally associated with increase in mortality among septic patients. In retrospective study done among 500 term neonates with early onset or late onset neonatal sepsis, red cell distribution width was significantly higher in non-survivors compared with survivors ( $P < 0.0001$ ), Table 1. Red cell distribution width had an area under the receiver operating characteristic curve of 0.75 for

**Table 1. Summary of reviewed articles**

S.N	Authors	Title of Study	Type of study	Summary
1	Bazick H and et al	Red Cell Distribution Width and all cause mortality in critically ill patients.	Multicenter observational study, 51,413 patients	RDW is a robust predictor of the risk of all cause patient mortality and bloodstream infection in the critically ill. <sup>8</sup>
2	Fu J et al	Predictive value of red cell distribution width on the prognosis of patients with abdominal sepsis	Observational study, 162 patients	RDW can evaluate the prognosis of patients with abdominal sepsis, and its predictive value is greater than traditional evaluation parameters such as APACHE II score, Lactate and Procalcitonin. <sup>26</sup>
3	Alexis R et al	Red cell distribution width as a marker for severity of illness and mortality in pediatric sepsis	Prospective cohort, 90 patients	More research needed to establish significance of RDW in PICU patients. <sup>22</sup>
4	Mahmood N and et al	Broadening of the red blood cell distribution width is associated with increased severity of illness in patients with sepsis	Retrospective study, 349 patients	RDW may have value in differentiating between more severe and less severe cases of sepsis. <sup>29</sup>
5	Ellahony D and et al	A Study of Red Cell Distribution Width in Neonatal Sepsis	Retrospective study, 500 full term neonates	RDW is a useful prognostic marker in neonatal sepsis. Larger sample size needed to further confirm. <sup>19</sup>
6	Martin SL and et al	Red cell distribution width and its association with mortality in neonatal sepsis	Prospective observational study, 251 case and controls each	High RDW is associated with neonatal sepsis and is an independent outcome predictor for mortality associated with neonatal sepsis. <sup>20</sup>
7	Sadaka F and et al	Red Cell Distribution Width and Outcome in Patients With Septic Shock	Retrospective cohort, 279 patients	Red cell distribution width on day 1 of septic shock is a robust predictor of mortality. The RDW is far better than either APACHE II or SOFA, and the sum of RDW and APACHE II was a stronger predictor of mortality. <sup>30</sup>
8	Ozdogan H and et al	The predictive value of red cell distribution width levels on mortality in intensive care patients with community-acquired intra-abdominal sepsis	Retrospective analysis, 51 survivor and 52 non survivors	increased RDW is associated with mortality in ICU patients with community acquired intra-abdominal sepsis. <sup>33</sup>
9	Ju X and et al	Dynamic Change of Red Cell Distribution Width Levels in Prediction of Hospital Mortality in Chinese Elderly Patients with Septic Shock	Observational study, 45 patients (>65 years)	Continuous increase in RDW level, rather than the level of RDW itself, was more useful in predicting hospital death in elderly patients with septic shock when RDW was >15%. <sup>25</sup>
10	Kim S and et al	Red cell distribution width and early mortality in elderly patients with severe sepsis and septic shock.	Retrospective study, 417 patients (>65 years)	Initial RDW values were significantly associated with 30-day mortality in older patients hospitalized with severe sepsis and septic shock. <sup>23</sup>
11	Lorente L and et al	Red Blood Cell Distribution Width during the First Week Is Associated with Severity and Mortality in Septic Patients	Prospective observational multicenter study, 297 patients	Non-surviving septic patients showed persistently higher RDW during the first week of ICU stay than survivors. RDW during the first week could be used as biomarker of outcome in septic patients. <sup>32</sup>
12	Jo YH and et al	Red cell distribution width is a prognostic factor in severe sepsis and septic shock	Retrospective study, 566 patients	Red cell distribution width is associated with 28-day mortality in patients with severe sepsis and septic shock. <sup>17</sup>
13	Chen CK and et al	The utility of red cell distribution width to predict mortality for septic patients visiting the emergency department	Retrospective cohort study, 11899 patients	RDW is an independent predictor of mortality among septic patients. Simply using RDW quartiles, clinicians could stratify patients according to risk of mortality and treat them accordingly. <sup>14</sup>

prediction of mortality, which was almost equal to that of CRP and platelet count.<sup>19</sup> Another prospective study done in India among neonates (251 septic and 251 control neonates of >28 weeks of gestation) with sepsis showed significantly higher RDW value amongst the non-survivors than survivors ( $p<.003$ ).<sup>20</sup> Study done by Chen J et al in

58 newborns showed negative correlation of neonate critical illness score (NCIS) with RDW increase while mortality was positively correlated with RDW increase ( $P<0.001$ ).<sup>21</sup> However, study done by Alexis R. and et al among 90 children (Median age 9 years) admitted in PICU with sepsis

or septic shock showed no significant association between RDW and severity of illness or mortality.<sup>22</sup>

Study done among 458 patients with age greater than 65 years with sepsis and or septic shock showed that RDW was an independent predictor of 30-day mortality (hazards ratio, 1.10; 95% confidence interval, 1.04 to 1.17;  $P < 0.001$ ).<sup>23</sup> Other study also concluded that RDW has better efficacy to predict mortality in elderly patients.<sup>24</sup> Continuous increase in RDW level, rather than the level of RDW itself, was more useful in predicting hospital death in elderly patients with septic shock when the level of RDW was  $>15\%$ .<sup>25</sup> A study done among 329 patients admitted to emergency department showed an increase in RDW from baseline during the first 72 hours after hospitalization is significantly associated with adverse clinical outcomes during 90 days follow up.<sup>18</sup> Similarly, another study done in China concluded that RDW can evaluate the prognosis of patients with abdominal sepsis, and its predictive value is greater than traditional evaluation parameters such as APACHE II score, Lactate, and Procalcitonin.<sup>26</sup> Similar other studies also concluded better prognostic value of RDW in patients with sepsis and septic shock.<sup>17,27-32</sup> Increased RDW is associated with mortality in ICU patients with community acquired intra-abdominal sepsis.<sup>33</sup> The area under the receiver operating characteristic curve of RDW to predict mortality was 0.75 (95% confidence interval, 0.72–0.77), which is significantly higher than the areas under the curve of clinical prediction rules (SIRS, MEDS, and CURB65).<sup>34</sup> Combination of RDW with APACHE-II increased the predictive ability of the scoring model in relation to mortality among septic patients (Area under the Curve for APACHE-II being 0.85 and that for combined tool being 0.87).<sup>34-36</sup> During these studies, patients with known history of anemia of any cause and recent blood transfusion were excluded. Limited study has tested RDW in condition with anemia or recent blood transfusion. Study done by Heidi S. Bazick and et al showed no significant effect modification of the RDW- mortality association on the basis of blood transfusion and presence of anemia (Hematocrit 36%).<sup>8</sup> Further analysis may be required to use RDW as prognostic tool in sepsis with anemia of various causes and with history of recent blood transfusion.

Though the prognostic value of RDW in sepsis has been studied in many research papers but still the diagnostic value of RDW in sepsis has not been

studied. One of the study conducted in China showed the combination of the three parameters viz. red cell distribution width, platelet distribution width and Neutrophil-lymphocyte count ratio has similar diagnostic performance as Procalcitonin.<sup>37</sup> RDW might be a rapid and helpful marker for a differential diagnosis between Adult onset Still's Disease from sepsis at an early phase.<sup>38</sup>

## CONCLUSION

RDW can be used to determine the prognosis of sepsis across all age groups. It can also be used in septic patients with anemia and who received blood transfusions recently. Only few papers are published involving pediatric population and patients with anemic and blood transfusion history. So caution is advised while applying RDW among pediatric population and in patients with anemia and recent blood transfusion.

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