

This paper reviews the research on RDW as a potential biomarker for some GI disorders. In general, this is an extremely well-written information, full of information that is carefully and critically analyzed. It is probably in the top 10% of papers I have reviewed.

- We are thankful to the referee for the globally favourable comments on our manuscript. We'll do our best to improve it according to the referee's suggestions.

Comments: P 5, 2nd paragraph – please explain more fully about how and why volume of a RBC cell decreases as it ages.

- ANSWER: This has been clearly demonstrated in some papers. For example, Lippi et al showed that (new sentence added to the manuscript) *"RDW increases with ageing, and this is clearly attributable to the gradual increased prevalence of comorbidities, which may actually contribute to derange erythrocyte biology and lead to release of a population of RBCs with heterogeneous size [reference: Lippi G, Salvagno GL, Guidi GC. Red blood cell distribution width is significantly associated with aging and gender. Clin Chem Lab Med 2014;52:e197-9]."*

Also, explain more clearly why RDW increases in severe disease – is this because cells age and are replaced more slowly, or because smaller immature RBC's are produced

- ANSWER: Good point, thanks. Both conditions are involved. New sentence added to the manuscript *"RDW may increase in many disease due to the impaired turnover of RBCs, which may both lead to increased permanence of aged cells in the circulation or release of immature and larger cells from the bone marrow due to increased turnover"*.

P 24 – the following sentence does not make sense: "A RDW value of 14.8% was predicted mortality in 77% cases [61]."

- ANSWER: Good point, thanks. Sentence reedited as follows: *"A RDW value of 14.8% was found to predict mortality in 77% cases [61]."*

There is a need for a careful proofing of the paper. There are many minor typos, such as in the first sentence of the conclusion: "RDW may be a useful prognostic factor"

- ANSWER: The paper has been further revised for correcting typos. As for the sentence, this has been reedited as follows: *"RDW may be useful a prognostic factor"*.

I noticed that LabCorp has a reference range for RDW from 12.3 to 15.4 (for adult women). Please comment on reference ranges, as it appears that many people in the general population have RDW values above the typical cut-offs for increased risk of disease

- ANSWER: This is again a good point. We have hence included the following sentence: *"The cut-offs of RDW may vary according to the technique used for its measurement. This may explain why some subjects may display higher or lower values when RDW is measured with different"*

*analyzers. Moreover, some people in the general population may display values higher than the reference range due to the presence of undiagnosed conditions, which may ultimately lead to increase anisocytosis”.*

In the conclusion, please comment on what seems to be a common cut-off for an RDW above which there is increased risk.

- ANSWER: As stated before, *“A single cut-off for RDW cannot be identified so far, since the various analyzers use different techniques. Therefore, the application of a universal cut-off is unfeasible until a major degree of standardization can be reached [Last reference of the paper: [Lippi G, Pavesi F, Bardi M, Pipitone S. Lack of harmonization of red blood cell distribution width \(RDW\). Evaluation of four hematological analyzers. Clin Biochem 2014;47:1100-3\]](#)”.* This sentence has been included in the manuscript.

Also, please comment that increased RDW seems to be an indicator for severe GI disease, but possibly not for milder GI disease such as IBS.

- ANSWER: Good point, thanks. We have added the following sentence *“An increased RDW value seems to be a marker for severe GI disease, but possibly not for milder GI disease such as IBS. This is probably due to the fact that milder disorders have a much lower impact on erythrocyte biology, so that RBC still display a normal turnover”.*

Comment for future work I wonder if looking at the full distribution graph would be more informative than just RDW, which is a single number. In other words, I suspect that a more sensitive test could be created by looking for example at the fraction of cells that are unusually small, etc. Just a suggestion for future work.

- ANSWER: Good point, thanks. We have added the following sentence *“In modern haematological analyzers, the RDW is conventionally calculated from the histogram of erythrocyte volumes. It is hence predictable that further studies aimed to more deeply investigate the full distribution graph (i.e., identifying extraordinarily large or small cells) may provide more meaningful information than the simple numerical value of RDW”.*