Author's response to reviews

Title: Is Elevated Red Cell Distribution Width a Prognostic Predictor in Adult Patients with Community Acquired Pneumonia?

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Author's response to reviews: see over
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To
Prof. Philippa Harris, Executive Editor
BMC Infectious Diseases

Re: Is Elevated Red Cell Distribution Width a Prognostic Predictor in Adult Patients with Community Acquired Pneumonia?

Dear Prof. Harris,

Thank you for the review of our manuscript # MS: 2213895061046209 entitled "Is Elevated Red Cell Distribution Width a Prognostic Predictor in Adult Patients with Community Acquired Pneumonia?" by Eyal Braun, Jad Kheir, Tanya Mashiach, Mohammad Naffaa and Zaher S. Azzam.

In keeping with the suggestions provided to us, we reviewed our data and edited our manuscript to address the concerns of the reviewers. We believe that we have addressed most of the reviewers' concerns and hope that this revised manuscript is now acceptable for publication in BMC Infectious Diseases.

Please let us know if additional information is necessary.

Thank you for considering our work.

Sincerely Yours

Zaher S. Azzam M.D.
Reviewer #1: Patrick Lillie (Comments to the Author (Required)):
We appreciate the reviewer's careful revising of the manuscript and the suggestions. We are providing a point-by-point reply.

Minor Essential Revisions:

Comment # 1 The definition of Community Acquired Pneumonia should be specified in greater detail - are the authors including everyone who had a diagnosis of CAP included in their notes (which may or may not be correct) or are they radiologically confirmed new infiltrates on chest x-ray?

Response: In following up with the reviewer's constructive comment, to clarify which patients were included in the cohort, we added the following paragraph to the methods section; "we included patients who had radiologically confirmed new infiltrates". As we stated in the methods section; “we excluded patients who were transferred from another hospital, hospitalized for any cause other than CAP during the 30 days prior to admission, or partially treated patients with antibiotics before admission”.

Discretionary revisions
Comment # 1: It would be interesting to have some discussion around the mechanism/reason behind the association of mortality and RCDW. Also it would be interesting to see if the addition of RDW to current assessment scores such as CURB-65 improves the performance of the score.

Response: We appreciate the reviewer’s comment; we have added in the discussion section (page 14, paragraph 1) possible explanations about mechanism underlying the association between high levels of RDW and adverse outcome in patients hospitalized with pneumonia.

We agree with reviewer about the importance of investigating the association between CURB-65 and RDW; however, we apologize not being able to pursue this suggested point as it is beyond the scope of the manuscript. Notably, the "confusion" item in CURB-65 could not be retrieved retrospectively from the records of the hospital; however, we added the following sentence to discussion section (page 14, paragraph 2); "Conceivably, RDW should be evaluated for incorporation in the commonly used risk assessment scores".

Comment # 2: The manuscript is very long and it may well be more readable if some of the tables / results were incorporated into supplementary information. For example, The paragraphs and associated figures on Charlson score and mortality, the Relationship between RDW and different blood count indices and RDW and BUN Could all be summarized in supplementary information or condensed.
Response: We appreciate the reviewer’s comment; however, we prefer to keep the structure of the original manuscript.
Reviewer 2: Kate Adams (Comments to the Author (Required)):

We appreciate the reviewer's careful revising of the manuscript and the suggestions. We are providing a point-by-point reply.

Discretionary revisions:

Comment # 1 I think both the background section and the discussion would benefit from some exploration in to why a raised RDW may be associated with complicated Admissions and or mortality. Some of the previously published studies have made some suggestions and it would certainly be worth referencing these or better still building on them. A plausible reason as to why increased RDW may be associated with an increase in mortality would strengthen the argument for doing this study in the first place and add weight to the conclusions.

Response: We thank the reviewer for this constructive suggestion. We have added the following sentence to the background: “The exact mechanisms causing elevated RDW in these diverse conditions are unknown, however, it is assumed to be related to inflammatory processes that might interfere with the process of erythropoiesis” (page 4, paragraph 3) and we have added in the discussion section (page 14, paragraph 1) possible explanations about mechanism underlying the association between high levels of RDW and adverse outcome in patients hospitalized with pneumonia.

Comment # 2 It would also be useful in either the background or the methods section to have a bit more about database. There is reference to it being the Prometheus Rambam health care centre integrated computer system. Is this a primary or secondary or tertiary care centre? What is the catchment area for the patients? Are these patients within the private or public health system? This is all important information that can’t be gleaned from the demographic information provided and is important in relation to how this study may translate to other populations.

Response: We appreciate the valuable remarks of the reviewer. Rambam Health Care Campus is a tertiary public government hospital with 1000 admission beds. It offers different services to the large and diverse population of Haifa, the surrounding towns and villages of the northern part of Israel that include over one and a half million citizens. This remark was added the methods section (Page 5, paragraph 1).

Comment # 3: It would also be worth putting a few words of explanation as to what the Charlson score is as not all readers will be familiar with this.

Response: In compliance with the reviewer suggestion, we added the following explanation about the score; “The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions, (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk
of dying associated with each one. Scores are summed to provide a total score to predict mortality (reference 1 in the authors' response).

**Comment #4:** It struck me as a little odd that a cut off of p<0.1 was chosen as the cut off level of significance in the univariate analysis to select variables for the multivariate analyses. This seems quite a low threshold given that p values of <0.1 are not generally regarded as being significant. It may be that there was good reason why this was chosen but if so I think this should be outlined.

**Response:** We appreciate the valuable remarks of the reviewer; the cutoff of P<0.1 is what commonly used to select univariate parameters to be include in multivariate calculations; please refer to reference 2 in the authors' response.

**Minor essential revisions:**

**Comment #1:** In the background the last line of first paragraph would read better if it was phrased as ....in an attempt to determine who is at risk of an adverse outcome...

**Comment #2:** In the methods section at the end of the fourth paragraph please add if these were the vital signs recorded on admission. At the moment the sentence just States the vital signs of the patients were noted.

**Comment #3:** In the results section in the first line under the title Univariate analysis of complicated hospitalisations and 90 day mortality, the figures 956 patients (28.1%) are quoted as being shown in table 1a. However, these figures don’t actually appear in table 1a – the box where they should be is blank.

**Comment #4:** In the section headed Multivariate analysis of complicated hospitalisations in the third sentence there needs to be a space between BUN >30mg/dl and the and which follows.

**Comment #5:** In the third paragraph of the discussion the spelling of hypernatraemia needs to be corrected. In the sixth paragraph it should read In concordance rather than In concordant. I would suggest that the last sentence of the same paragraph is changed to read ....both a short and long term association with RDW rather than showed both short and long term effects of RDW as I don’t think there is evidence to say this is a direct effect of an elevated RDW.

**Response:** We reviewed the manuscript and corrected the typographical errors.

**References:**

Reviewer # 3 (Comments to the Author (Required)):
We appreciate the reviewer's careful revising of the manuscript and the suggestions.
We are providing a point-by-point reply.

Major comments:

Comment # 1: The clinical relevance of the composite endpoint (hospitalization longer than ten days, admission to intensive care unit and in-hospital mortality) is unclear to me. I do not feel these 3 variables being of equivalent importance.
Response: We thank the reviewer for this note, as accepted though not always, the use of composite end points is usually justified by the assumption that the effect on each of the components will be similar and that patients will attach similar importance to each component. Our data disclosed consistently that each endpoint was associated with elevated RDW; therefore the above mentioned composite endpoint is also associated with high confidence to RDW. However, following the reviewer's note, we added statistical data concerning each of the components of the composite endpoints in the "Results" section. This data shows that elevated RDW is associated with worse prognosis with each of the outcomes (length of stay, in-hospital mortality and ICU admission).

Comment # 2: What is “partial antibiotic treatment before admission”? I wonder if it is reasonable to exclude patients who received prior recent antibiotic therapy since inadequate treatment is known to influence outcome.
Response: We appreciate the reviewer’s comment; every antibiotic treatment that was administered before hospital arrival was defined as partial antibiotic treatment before admission. Since, antibiotics may interfere with disease course and in order to ensure as much as homogenous groups as possible in this retrospective cohort, we decided to exclude this group of patients.

Comment # 2: Mechanistic evaluation is lacking. Thus I’m not convinced that the association between RDW and outcome is not Studied criteria that were included in the analysis were highly selected, particularly for biological parameters. What about blood gas analysis, lactate level, or inflammatory biomarkers, which are known to be also associated with outcome in several infectious diseases?
Response: We appreciate the valuable remarks of the reviewer; it is reasonable to assume that RDW is a good integrative marker of complex malnutrition-inflammation syndrome in patients with CAP and interesting to explore this relationship. In our future planning we intend to prospectively address the issue of inflammatory stress (CRP, procalcitonin and interleukin-6), RDW; we added this remark to the discussion. Notably, this cohort was retrospective and there was no available data concerning blood gases and lactate levels for every patient.
Minor Comments
Several abbreviations are not explicated in the abstract. All along the Results, IQ values should be added to medians.
Response: We reviewed the manuscript and corrected typographical errors and explicated abbreviations.
Reviewer # 4 (Comments to the Author (Required)):
We appreciate the reviewer's careful revising of the manuscript and the suggestions. We are providing a point-by-point reply.

Comment # 1: The last sentence of the Introduction on page 3 should specify that the study aimed to identify prognostic factors among patients with community acquired Pneumonia (similar to what is written in the background of the abstract on page 2).
Response: In following up with the reviewer's constructive comment, we have rephrased the aim to clarify this point.

Comment # 2: “Complicated hospitalization” is an interesting composite outcome, but it is heterogeneous as it incorporates length of hospitalization, admission to ICU, and in-hospital mortality. Considering that in-hospital mortality was examined as distinct outcome, why not evaluate whether RDW is associated with length of hospitalization and ICU admission as separate outcomes?
Response: We thank the reviewer for this important note, as accepted though not always, the use of composite end points is usually justified by the assumption that the effect on each of the components will be similar and that patients will attach similar importance to each component. Our data disclosed consistently that each endpoint was associated with elevated RDW; therefore the above mentioned composite endpoint is also associated with high confidence to RDW. Actually, we have examined the association between RDW and 90-day mortality and reported this data on the main text.

Comment # 3: The statistical analysis section on page 5 was difficult to follow. The first paragraph does not clearly state the outcome that would be analyzed. Also, it is stated that multinomial logistic regression was used, but I did not find the results for a model with an outcome the 3 or more categories/levels. The Results & Tables indicate that only dichotomous outcomes were examined.
Response: We thank the reviewer for these notes: we added a sentence to the first paragraph to explain the outcome that would be analyzed. We meant that “multivariate” and not “multinominal” logistic regression would be used. We corrected it in the main text.
We kindly refer the reviewer to Table 2 that shows to our understanding the results of multivariate analysis of complicated hospitalization that discloses 6 categories.

Comment # 4: In Table 2, it is unclear why categories of RDW & WNC were combined. It seems that RDW would have an independent association with “complicated hospitalization”. Also, the text on page 7 indicates the model AUC was 0.76, but Figure 1 states the AUC=0.83. Do these models have different covariates inthem? I find that Figures 1 & 2 do not add much value to the current report.
Response: Abnormal WBC values, leukocytosis and leukopenia, are parameters of inflammation, in order to show that RDW is a bad prognostic factor independent of leukocytes values; moreover, this stratification showed that a combination of abnormal WBC and elevated RDW was associated with worst prognosis. We added two new tables, 5A & 5B to summarize these data and also depicted this information in the main text. We apologize for the mistake in the model AUC; however, following the reviewer suggestion, we decided to delete these figures from the manuscript.

Comment # 5: In addition to the work showing the strong relationship of RDW with adverse outcomes in patients with significant cardiovascular disease, there was a recent meta-analysis by Patel KV, Semba R, Ferrucci Letal (JGerontolMedSci2010) demonstrating that RDW is a strong predictor of mortality in many different patient subpopulations and medical conditions beyond CVD, including obesity, cancer, diabetes, chronic kidney disease as well as among smokers. The current study extends this previous paper by demonstrating that elevated RDW is a prognostic risk factor among younger patients hospitalized with CAP.
Response: We thank the reviewer's constructive comment. We have added the suggested reference and expanded more about the association between RDW and other diseases in the discussion section.

Comment # 6: Rather than entering variables that were significantly associated with "complicated hospitalization" in univariate analyses, it would be very interesting to determine whether RDW is a significant predictor of "complicated hospitalization" (length of stay, mortality, & ICU admission) independent of standard prognostic scores, such as the Pneumonia Patient Outcomes Research Team (PORT) score, and whether RDW adds discriminatory power beyond this score. This would help focus and simplify the analysis by keeping the same set covariates across models & outcomes (e.g., Model 1: Outcome A=PORT Score; Model 2: Outcome A=PORT Score + RDW). That is, 2 models for each outcome (use linear regression for length of stay and binary logistic regression for in-hospital mortality and ICU admission as separate outcomes). Figures 3 & 4 could be maintained for the composite outcome of complicated hospitalization.
Response: We thank the reviewer for these comments: following the suggested remarks, we added statistical data in the "Results" section. This data shows that elevated RDW is associated with worse prognosis with each of the outcomes (length of stay, in-hospital mortality and ICU admission). Concerning the PORT score, it would have been interesting to include it in the study; however, objectively, we did not find after reviewing charts of the included all the parameters of the score mainly altered mental status and respiratory rates; notably, most of the other parameters were included in the univariate analysis. We felt that it might be inappropriate to calculate the PORT score when some of the data concerning these two parameters are missing.
Comment # 7: Please report the manufacturer and model name of the automated cell counter that was used to measure RDW (e.g., Coulter, Advia, Sysmex).

Response: We apologize for not including this important point in the methods; we have incorporated the laboratory assays in the methods section.