Author's response to reviews

Title: FULL BLOOD COUNT VALUES AS A PREDICTOR OF POOR OUTCOME OF PNEUMONIA AMONG HIV-INFECTED PATIENTS.

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Author’s response to reviews:

Dear Editor:

Find enclosed a manuscript that we consider can be interest for your journal. The manuscript title (changed as suggested by reviewer 2) is FULL BLOOD COUNT VALUES AS A PREDICTOR OF POOR OUTCOME OF PNEUMONIA AMONG HIV-INFECTED PATIENTS by Silvia Camón, et al. submitted for a consideration of a publication in the journal BMC infectious diseases, after having made the changes that reviewers indicated. The answers to the reviewers are highlighted and explained below.
Community-acquired pneumonia is an important cause of mortality in HIV infected patients. The recognition of early predictors of poor outcome would allow us to give the urgent and global need for safe, effective and affordable HIV and pneumonia with markers whose results are obtained quickly.

I declare on behalf of all authors, that there are no financial, personal or professional interests that could be construed to have influenced the manuscript.

Thank you for your time and consideration.

Sincerely,
Rafael Perello MD,PhD
Barcelona

Reviewer 1

Abstract

Respiratory clinical infection=chest infection?: respiratory clinical infection not always mean chest infection. Respiratory clinical infection means: symptoms as dyspnea, cough, mucosity, and Chest infection always implies pulmonary condensation in the X-Ray. They are the IDSA criteria. Page 3, line 13-14.

Pneumococcal pneumonia remains the most common cause of CAP among the 160 HIV-positives: suggest Streptococcus pneumoniae was the most frequently identified etiologic agent: We have suggested this issue in the abstract.as the reviewer indicates. Page 2, line 16-17.

Conclusion: Red blood cell distribution and lymphocytes were the most useful predictors that can identify poor prognosis in HIV-infected patients with CAP, but any of them can predict mortality. I would suggest a positive conclusion such as Red blood cell distribution and lymphocytes were the most useful predictors of disease severity identifying HIV infected patients with CAP who required ICU admission: We agree with the reviewer, and we have included this new sentence in the conclusion abstract as the reviewer indicates. Page 2, line 24-25.
Introduction.

Community-acquired pneumonia (CAP) is the most common cause of HIV infection in an Emergency Department. I believe you mean CAP is the most common infection affecting HIV patients presenting to the ED and one of the major causes of death due to infectious etiology, both in HIV infected as well as in the general population: now we have included the sentence in the manuscript as the reviewer indicates. Page 3, line 2-3.

I suggest you use the terminology HIV infected throughout the text. We agree and changes have been made in the manuscript as the reviewer indicates. Page 2, line 4.

The existence of biomarkers; substitute existence by identification or recognition of biomarkers. Having allowed us to predict the severity of the HIV patient with CAP, may allow us to predict? We think to predict severity of CAP, that if we could find a biomarker that showed poor outcome, it could be applied in order to do a better management of this pathology. Page 3, line 7.

Most of the biomarker studies are performed in the general population whereas in the HIV-infected population, the studies with biomarkers are generally not immediately available, such as interleukins (10), which require the data of CD4 values (11), nor inpatients with opportunistic infections (12). I think this paragraph should be re-written. I believe that all routine tests are requested for HIV patients, such as FBC and CRP levels. ESR is often not requested in the acute setting, Procalcitonin is expensive and not yet available for most countries. Even less so interleukins. Although CD4 counts are usually not requested in the acute setting, very often HIV infected patients have a recent CD4 count available, which helps the clinician make the most appropriate diagnostic considerations and guides initial empirical treatment: the studies made previously in HIV infected patients and biomarkers, make reference to poor prognosis in opportunistic infections (today we hardly see these pathologies because most patients are on TAR), but not specifically in pneumonia. By the other hand, we agree that not all hospitals can detect procalcitonin, because it is more expensive (in our hospital it is not available at the ED), including CRP. Sometimes patients don’t remember his CD4 count, although we can know an approximation if we have the lymphos count (Napoli et al J Emerg Med. 2013). We could try to save resources using simple blood test if the results of our study will be correct. Page 3, line 13-20.

Therefore, our group evaluated the prognosis of HIV-infected patients diagnosed with CAP based on blood count values, since their results are obtained quickly and can be useful in the management of this pathology. This is not something new. Please report to older studies where Hb levels and lymphopenia (based on percentage Lymphocyte counts on FBC) were used as predictors of CD4 counts below 200. Hb levels below 10 are predictive of CD4<200. This dates
back to the late 80's or early 90's. We have reported the study of Duong T, Plus One 2012 but this study is not specifically related to CAP. Majority of this papers make reference to the poor outcome of HIV evolution, not about CAP. Page 3, line 19-20.

Methods

P. jirovencii is misspelt: it has been correct in the manuscript as reviewer indicates. Page 4, line 6.

In definitions, how long after hospitalization was CAP diagnosed? the time to diagnose a CAP depends on the clinician experience and the time to get a chest radiography. In general, around two hours. Page 4, line 14-15.

In order to obtain a microbiological diagnosis, a nasopharyngeal swab to detect respiratory viruses was used (Viral Culturette, Direct, Becton-Dickinson Microbiology Systems, MD, EEUU), urinary antigens to identify Streptococcus pneumoniae (BinaxNOW S. pneumoniae Urinary Antigen Test) and Legionella pneumophila (BinaxNOW Legionella Urinary Antigen Test) in concentrated urine in advance, and two blood cultures (Bactec 9240; Becton Dickinson. PLEASE GIVE COUNTRY FABRICATION NAMES FOR THE SEVERAL MENTIONED TESTS. EEUU is USA? Yes, and we have included in the manuscript the country fabrication of the tests. as reviewer indicates. Page 5, line 6-7.

Scores should not come under Laboratory Studies. The Fine score is not routinely used for assessment of CAP severity. CURB 65 and Pneumonia Severity Index are. Please explain : These scores have not been standardized to be used for immunosuppressed population. Page 5, line 12-14.

Is the APACHE II score validated for HIV infected patients? Yes, Afesa et al used APACHE II score in previous studies(it is referred in the text). Page 5, line 12-14.

Results

Blood culture, Gram stain and culture, urinary antigen were positive in 34, 32 and 52 patients for S. pneumoniae, respectively. This is important information. Please write separately and give percentages. We have reported the percentages of each of them in the results section as reviewer indicates. Page 6, line 10-11.

Separate positive Gram stain of sputum from sputum culture mortality group: We have reported the percentages of blood culture, gram stain and sputum culture, urinary antigen in the results section as reviewer indicates Page 6, line 11-12.
Group of patients who died sounds better poor evolution_ you mean unfavorable outcome? Yes, and we agree with the reviewer we have included now this sentence in the manuscript. as reviewer indicates Page 6, line 16.

Discussion

We hypothesized that the different values of full blood count can predict pneumonia outcome in HIV-infected patients, but we obtained the opposite results for the primary end-point. Please rewrite. I do not see how you obtained "opposite results". This sentence means the multivariate analysis showed not poor outcome in terms of mortality therefore contradicts our hypothesis (full blood counts values can predict 30 days mortality). We have also defined the primary and secondary end points, for the manuscript is better understood. Page 7, line 12, Page 5, line 17-20.

Regarding your discussion on platelets: My view is that plenty of literature is available on how low platelets are a marker of severe bacterial infections and intravascular coagulation in sepsis. This is more relevant to the patients with pneumonia in this study than this discussion on disease progression of HIV and platelets : We have explained the role of platelets in several infections, and referred it in the text as reviewer indicates. Page 7, line 23-24.

But despite the important role they play in the entire infectious process, in our study, neither the PLT value nor the PDW value showed a predictive value of poor prognosis. You have shown that patients who died had significantly lower values of PLT (112.7±57.6 vs. 196.55±102.6; p <0.009) on univariate analysis. I think this is an important result : Yes. We agree with you, about the results of univariate analysis, but the multivariate analysis doesn’t shown it, that is we can suggest that platelets could be a biomarker of mortality but we cannot say categorically. Page 6, line 26-27. and Page 7, line 25-27.

As for the WBC value, our study utilized both the frequency of EOS and total LYM and compared count of EOS with previous studies. These results were in accordance with the same ones performed by our group previously(20), which show that they are not a factor of poor prognosis. You have shown that the group of patients who died had lower EOS percentages (0.044±0.039 vs. 0.108±0.138; p <0.033) on univariate analysis : Yes, we agree with you about the results of univariate analysis but the multivariate analysis did not show it. Page 6, line 25-30, page 7, line 1-2, and page 7, line 29-31

Bordon et al showed that total CD4, CV and ART variables were not a predictor of poor prognosis in HIV infected patients with CAP. Several studies disagree with this. Please make a better literature review and expand your discussion : We have make a better literature review and the discussion has been expanded in the manuscript as reviewer indicates Page 8, line 6-8
I do not think thalassemia is relevant to the present discussion. We have removed thalassemia references in the manuscript, as reviewer indicates.

Anemia is one of the most important causes of death in patients without ART. Anemia is not a cause of death, it is a marker of uncontrolled HIV infection, or of most chronic diseases in fact. We have now included this sentence in the manuscript as reviewer indicates. Page 8, line 11.

Its result must be interpreted carefully in cases of thalassemia since false values may occur. RDW was predictor as LYM of ICU admission. Again thalassemia is not an issue for this discussion. No results were presented for thalassemia in your paper. Did Akgun et al have the intention of studying full blood count parameters? If not, I would not include this sentence in the discussion. We are agree with the reviewer that we did not present any result about thalassemia, and in not an issue for this discussion, that is, the sentence of Akgun et al has been removed from the manuscript as reviewer indicates.

References:

Did you read reference 9? Yes we read the abstract. We found it interesting, and a Chinese student translated it for us. Page 10, line 25.

Reference 13 (now 14) is very old. I do not think you used these 1998 guidelines to treat patients. Reference 14 may be old, but it describes the IDSA’s criteria to define pneumonia (in our manuscript, it is not for the management), but it can be changed if reviewers prefer another. Page 11, line 10.

Table 1. Viral load in undetectable blood: please write "Undetectable viral load" and add the definition of undetectable at the bottom of the table: we have now included this sentence at the bottom of the table as reviewer indicates in table 1. Page 15.

Parenteral drug abuse Median systolic blood pressure of 13? Please review. : Reviewed and removed, because there was a mistake in collecting these variables in table 1. Page 15.

Table 2. S.aureus and rhinovirus are misspelt: It has been corrected as reviewer indicates in table 2. Page 16.

Reviewer 2

Title: The title leads the ready to believe that this a paper evaluating the ability of blood counts to predict a diagnosis of pneumonia rather than pneumonia severity. Please change the title to reflect the main outcome under consideration.: the title of the article has been changed as the reviewer indicates. Page 1, line 1.
Introduction: -Pg 3, line 14: a number before "CD4" is missing : we have correct it in the manuscript as the reviewer indicates. Page 3, line 20.

Methods: -Pg 4, line 14: P. jirovencii is misspelled : we have corrected in the manuscript as the reviewer indicates. Page 4, line 6.

Were radiographic criteria included in the diagnosis of CAP?: we have clarified and explained in the manuscript, that radiographic criteria was included. Page 4, line 14.

- Pg 4, line 28: Please list out the CAP diagnostic criteria :the diagnostic criteria of CAP were the IDSA criteria(reference 14 in the manuscript). Page 4, line 13.

- What was the acceptable period of time allowed after presentation to the emergency department for the drawing of the blood specimen used in the study?: the blood test was drawing when the patients entered in the box at ED, in general no longer than 2 hours since patients arrives at the ED. page 4 line 21-22.

Results

Table 1: consider reporting baseline characteristics by whether or not patients were admitted to the ICU. This would give the reader a better idea of the effect of covariates on pneumonia severity :: we have reported in the new Table 1, as reviewer indicates. Page 14.

- Pg6, line 48: Please clarify which variables were used in the multivariable logistic regression model used. : the variables included in the model were PLT,EOS, LYM,PDW and RDW, we have clarified in the manuscript. Page 6, line 22-23.

In addition to the whole blood counts, were other covariates such as CD4 and viral load included?: we have explained in the manuscript, that no other variables were included in the model, that is, CD4 and viral load were not included in the multivariate regression model. Page 6, line 22-23.

- Given the small n of 9 for the primary outcome it would not be appropriate to adjust for more than one or two covariates in the multivariable analysis. Please comment on this limitation : We have now included this sentence in the limitation section as reviewer indicates. Page 8, line 27-29.
- Table 3: As a footnote, please list the variables controlled for in the multivariable logistic regression analysis. Please also explain the units used, and also define abbreviations. Units and abbreviations have been explained in the new Table 3 as reviewer indicates. Page 17

- Table 3: the OR is reflective of how many units of increase in the whole blood count. For instance, is the odds of ICU admission increased by 1.42 for every unit increase in EOS? Yes, is correct. What are the units? The units of the Eos are the % of leukocytes, 10^9/L, it has been referred in the new Table 3 as supplementary material. Page 17

Discussion

- Please address the small number of outcomes as a limitation in the study: we have included in the limitation section as reviewer indicates. Page 8, line 27-29

Conclusions

- Please include in the conclusion that, although no statistically significant associations were observed between blood counts and mortality, numbers were too small to draw firm conclusions: we have included in conclusion section the sentence that reviewer indicates. Page 9, line 4.