Author's response to reviews

Title: The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis

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Author's response to reviews: see over
Response to reviewer and editor

We greatly thank you so much for considering our paper revision. We tried to clarify and have corrected it as your valuable points.

Response to reviewer Mehmet Coban

Reviewer's report I

Title: The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis

Version: 1  Date: 15 July 2015

Reviewer: mehmet coban

Reviewer's report:

I have read the current manuscript with great interest. This is a well written and conceived paper and the question posed by the authors is well defined. The methods are appropriate and well described. The figures appear to be genuine and I think there is not any evidence of manipulation. The discussion and conclusions are well balanced and adequately supported by the data. The title and abstract accurately convey what has been found.

Minor Essential Revisions:

I found only one printing error in the paper. "chornic", the last word of line 254, should be corrected as "chronic".

We greatly thanked you and have corrected it.

Page 14: Until now, there is little about the diagnostic power of NLR for infection in liver cirrhosis even though there are some reports about the role of NLR in infection among patients with acute exacerbation of chronic obstructive pulmonary disease and in emergency department [36, 37].
Response to reviewer David G Watt

Title: The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis

Version: 1 Date:31 July 2015

Reviewer: David G Watt

Reviewer's report:

The authors report the use of CRP and NLR to diagnose infections and predict outcomes in cirrhotic patients admitted to hospital. They include 184 patients and conclude that CRP was a significant indicator of infection and elevated NLR a poor predictor of 1 month survival.

Major Revision:

The question is defined well although it is well known that CRP is useful in helping predict those who will develop infection, methods appropriate, data sound, figures genuine there are a few major revisions that need to be addressed:

1. In the results section of abstract and manuscript the authors state the odds ratio for CRP and the presence of SIRS to be 1.017 yet a highly significant p value. I can't quite understand this, can they check the statistical methods?

   → We thanked your comment. We made an error in the abstract and have corrected it in the abstract and table 2.

   Abstract page3; For diagnose of the infection, baseline CRP concentration was a significant factor compared to the presence of SIRS (odds ratio 1.202, P = 0.003).

2. The conclusions of the abstract state NLR is a poor predictor of 1 month survival in one sentence then in the next one state CRP and NLR are good predictors of outcomes? These 2 statements contradict each other.
→ We agree with your point and have corrected it. We mean that CRP and NLR are useful and powerful predictors for the unfavorable outcomes.

Abstract page 3: CRP was a significant indicator of infection in hospitalized cirrhotic patients and a NLR was a useful predictor of 1-month survival, particularly in Child–Pugh class C patients. This study suggests that the inflammatory markers such as CRP and NLR can help identify cirrhotic patients at risk of unfavorable outcomes.

Page 15: In conclusion, CRP and NLR are helpful diagnostic markers of infection in hospitalized cirrhotic patients. In Child–Pugh class C patients, an elevated NLR predicted a poor 1-month survival. Therefore, hospitalized cirrhotic patients with an elevated CRP concentration and NLR should be monitored carefully for the presence of infection. In addition to the classical MELD score, NLR may be a useful predictor of the short-term mortality easily in hospitalized cirrhotic patients.

3. They mention in the methods that cirrhosis was diagnosed on biopsy or on "obvious clinical, biochemical and imaging features". They should specifically mention what these were.

→ We added the definition of LC diagnosis.

Page 6: The diagnosis of cirrhosis was based on liver biopsy or clinically when the patients had at least two of the following three criteria: an inhomogeneous hepatic surface with splenomegaly or portal hypertension on radiological findings; platelet count <100,000/mm3 or variceal changes on endoscopy [22].

4. The study states that all the hospitalized patients were treated with empiric broad spectrum antibiotics at admission. Surely this is a confounder to the study? Could patients with mild SIRS have been treated and therefore their results did not trigger a rise in CRP? I don’t understand how the study can be aiming to look at whether CRP and NLR can improve diagnostic accuracy of infection when everyone gets
antibiotics anyway, does it matter what the CRP levels were then? They are being treated at any rate, I really struggled with this concept

→ We agree that it can be confusing to the readers. We administered the antibiotics after the initial physical examination for the diagnosis of SIRS and laboratory test including NLR and CRP. We tried to clarify it in method.

Page 7: At admission, patients routinely underwent a physical examination, laboratory tests, and X-ray of the chest and abdomen. Laboratory tests included blood chemistry and blood cell counts including CRP concentration and ascitic/pleural fluid cell counts. Serum CRP level was measured as high-sensitivity CRP by an immunoturbidimetric assay using the C-Reactive Protein, High Sensitivity reagent (Beckman Coulter, Inc., Fullerton, CA, USA; limit of detection, 0.08 mg/L). The NLR was calculated by dividing the neutrophil count by the lymphocyte count. All the hospitalized patients were administered empiric broad-spectrum antibiotics (ceftriaxone or ciprofloxacin) after initial laboratory test and physical examination, and the regimen was modified or stopped according to the results of the cultures or the infection [7].

5. In discussion the authors mention cirrhosis causes low WBC counts but alcoholic cirrhosis patients can have high WBC even without infection. Therefore how can NLR have a role? The neutrophil count can be high or low without infection on board and therefore in my opinion in cannot be used to diagnose infection as other parameters will alter its result. This would appear to be a major flaw in this study

→ We agree with your comment. In our study, simple WBC counts have several limitations to discriminate infection in cirrhosis patients. However, unlike simple WBC counts, NLR was significantly higher in patients with infection than those without, in whom WBC counts were not different between the two groups (Fig 1A). Specifically, the neutrophil count was higher and the lymphocyte count was lower in cirrhotic patients with infection than those without (Table 1). This suggests that NLR is a more powerful predictor of infection than simple WBC counts. We have adjusted the text and added these to the appropriate secretion of discussion in pages 10 and 13
Page 10: The levels of CRP in patients with infection were significantly higher than those without infection (Fig. 1a). In addition, NLR was significantly higher in patients with infection than those without, in whom WBC counts were not different between the two groups (Fig. 1a). Specifically, the neutrophil count was higher and the lymphocyte count was lower in cirrhotic patients with infection than those without (Table 1).

Page 13: NLR increased in patients with infection and predicted the short-term outcome in hospitalized cirrhotic patients. An increased WBC count might mean the presence of infection, but cirrhotic patients usually have low WBC counts due to hypersplenism and patients with alcoholic cirrhosis show high WBC count even without infection. In the present study, the simple WBC counts were not different between infection and no infection group. However, neutrophil count in the infection group was higher than no infection group and lymphocyte count in the infection group was lower than no infection group. This suggests that NLR is a more powerful predictor of infection than simple WBC counts.

6. **Did the authors look at the role of neutrophils on their own?** Recent reports have suggested that the majority of the prognostic component of the NLR come from the neutrophil count itself.

   → We thanked to your comment. We had checked the WBC, neutrophil and lymphocyte’s predictive power for the infection and one month survival. Neutrophil and lymphocyte had significance between infection and no infection group (please refer the response #5). In logistic regression analysis for the one month survival, WBC counts showed the power in univariate analysis but in multivariate analysis, NLR has significant. As you said, there are recently some reports for the neutrophil’s own prognostic role. We have corrected it in table 2, 3 and added the neutrophil’s role in discussion and new references.

Abstract page 3: **For predicting one-month short-term survival, MELD score, NLR and WBC count were significant factors but in Child-Pugh class C patients, NLR was only an independent factor.**
Page 11: However, for predicting one-month survival after the hospitalization, the baseline NLR as well as MELD score and WBC count was a significant factor (Table 3). Especially, in the patients with Child-Pugh class C, a high NLR was an independent predictor for the one-month survival after admission (Table 3).

Page 13-14: Recently, the neutrophil dysfunction was reported even in the stable cirrhosis patients [34] and predicted outcomes in cirrhosis and alcohol hepatitis [35]. It might be due to the deranged phagocytic activity of opsonized bacteria of neutrophil in advanced cirrhosis. In the present study, neutrophil also showed the significant difference between infection and no infection group.

7. Again I am confused as to the statements in the conclusion. The authors state patients with elevated CRP and NLR should be monitored carefully for presence of infection and considered for prompt antibiotic therapy - but are they not already on antibiotics and therefore being treated regardless?

→ We agree with your point and have corrected it.

Page 13: In conclusion, CRP and NLR are helpful diagnostic markers of infection in hospitalized cirrhotic patients. In Child–Pugh class C patients, an elevated NLR predicted a poor one-month survival. Therefore, hospitalized cirrhotic patients with an elevated CRP concentration and NLR should be monitored carefully for the presence of infection. In addition to the classical MELD score, NLR may be a useful predictor of the short-term mortality in hospitalized cirrhotic patients.