

ANSWERING REVIEWERS



August 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12242-doc).

Title: Is neutrophil to lymphocyte ratio associated with liver fibrosis in patients with chronic hepatitis B ?

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer (1)

1. In material and Methods, authors should mention from patients history the exact way of the infection as well as the years of infection.

Because of the retrospective nature of our study, we could not determined the exact way of the infection as well as the years of infection.

2. Furthermore it would be great if patients in two groups were subdivided to groups according to the sex and also it would be great the mean age to be referred. Finally, in this section, they should define the score of the Histological Activity Index score as well as the fibrosis according to metavir.

Groups were subdivided into groups according to sex, and mean age of subgroups are mentioned in results section. Moreover, HAI and Metavir scores of subgroups are mentioned.

3. In the section of introduction authors should mention some other abnormal situations that affect the N/L RATIO and to clarify that all these causes have been excluded in the study.

In 'Introduction' section, some other situations which may affect NLR are mentioned and in 'Material and Methods' section, exclusion criteria are mentioned in a detailed manner.

4. In their results they should mention the statistic data including the mean difference, sd and P value

All statistics data is arranged in the light of reviewer's suggestion.

5. Finally, in the discussion text they should improve the scientific term for the INR in a more sufficient and appropriate one (not long is not a scientific term for INR, so please improve your characterism).

In the 'Discussion' part, the term 'INR' is improved in a sufficient manner.

Reviewer (2)

1. Please add in vivo or in vitro experiments to explain why N/L ratio changed in CHB patients?

Previously, it has been shown that, NLR ratio is changed in chronic hepatitis B patients. And also in that studies, the reason was explained why NLR ratio is changed in CHB patients.

(1-Neutrophil-lymphocyte ratio: a novel predictor for short-term prognosis in acute-on-chronic hepatitis B liver failure. 2-Prognostic value of the neutrophil-to-lymphocyte ratio in patients with acute-on-chronic liver failure. 3-Prognostic value of preoperative peripheral neutrophil-to-lymphocyte ratio in patients with HBV-associated hepatocellular carcinoma after radical hepatectomy.)

2. The authors aimed to investigate the association between N/L ratio and the severity of the liver fibrosis in patients with CHB. They would be better to find out whether N/L ratio was associated with CHB first. At least normal control for CHB patients was lacked.

As mentioned above, it has been shown that NLR ratio is changed in chronic hepatitis B patients. Moreover, it was suggested that NLR may be a novel predictor for short term prognosis in CHB. On the other hand, CHB prognosis is closely related with. In the light of these facts, we planned a research to explore the likely relationship between NLR and fibrosis grade in patients with CHB.

3. How to define the score F0, F1, F2, F3 and F4 respectively? Please describe it in detail in Methods section.

F0, F1, F2, F3 and F4 scores were defined according to Metavir Score. The related reference was added to manuscript (1-Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20:15.)

4. Please add subtitles in Results section

Subtitles are added to manuscript.

5. The patients were also divided into HBe antigen negative (92/129, 71.4%) and positive group (37/129, 28.7%). What about the association between N/L ratio and HBe antigen or HBV DNA level?

HBeAg positivity and HBVDNA levels are closely related to response to CHB treatment, clinical course, fibrosis grade and prognosis. Thus, we evaluated the likely association between NLR ratio and HBeAg and/or HBVDNA levels.

6. What are the relationships between N/L ratio and age, HAI, platelet, ALT which associated with fibrosis?

NLR ratio is changing with aging. Also NLR ratio is an inflammatory marker and it can be expectable to change in a relation with HAI score. Platelet levels and ALT levels are affected in patients with advanced fibrosis, in other word patients with cirrhosis. Thus we evaluated these parameters altogether.

7. The histological activity was graded according to Histological Activity Index score and fibrosis was staged according to metavir" (page 6, line 8th). Please add the references.

The references are added.

8. There were also some tense mistakes in this paper, such as "In our study, INR was not long in patients..."(page 9, line 3rd), "Although there many studies that..."(page 9, line 13th). It was suggested to ask for a native English speaker to edit this article.

The manuscript is edited in view of English tense and grammar mistakes.

Reviewer (3)

1. How the basis of these two groups? If the patients could be divided into more groups.

The two groups were determined compatible with previously designed studies. Moreover, now in this revision, we exhibited new subgroups.

2. PC III (III procollagen), IV-C (IV collagen), LN (laminin) and HA (hyaluronidase) can be used for the diagnosis of liver fibrosis. For the diagnosis of liver fibrosis and measure of the degree of inflammatory activity, how about the advantages of N / L ratio than PC III, IV-C, LN and HA ?

Because of being an easy attainable and cost-effective parameter, NLR was chosen for this

study instead of other parameters which were mentioned by reviewers.

3. The results of the “the highest sensitivity (80.0%) and specificity (53.2%) for angiogenesis should be more properly presented

With these findings, it was shown that NLR ratio is decreasing with the advanced fibrosis grades.

4. In addition to liver fibrosis, there are a variety of other organic disease and inflammation can cause the change of N / L ratio. So this conditions should be excluded in order to increase specificity of N/L ratio for detecting CHB and significant fibrosis

The exclusion criterion has been mentioned in a detailed manner in the manuscript.

5. Add more powerful references, just like “Alkhoury N, et al, Liver Int, 2012.

This mentioned reference is already exist in the references part (Reference 27. Alkhoury N, Morris-Stiff G, Campbell C, Lopez R, Tamimi TA, Yerian L, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2012; 32:297–302.)

6. “Reference” needs to be further updated and checked,e.g.Ref. 25,27,29,30,32,33.

Mentioned references have been checked and updated

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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