Author’s response to reviews

Title: Association between De Ritis ratio (aspartate aminotransferase/alanine aminotransferase) and oncological outcomes in bladder cancer patients after radical cystectomy

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Author’s response to reviews:

November 8, 2018
Hayley Henderson
Editor
BMC Urology
Dear Dr. Henderson,

Please find attached our revised manuscript titled “Association between De Ritis ratio (aspartate aminotransferase/alanine aminotransferase) and oncological outcomes in bladder cancer patients after radical cystectomy” (manuscript ID: BURO-D-17-00065R1), authored by Yun-Sok Ha, et al. Our responses to all of the reviewers’ comments are as follows:

Editor Comments:
Thank you for submitting a revised copy of your manuscript. This manuscript presented the association of the De Ritis ratio (the ratio of serum AST/ALT levels) to the prognosis of Urothelial bladder cancer after radical cystectomy. The intended use was to identify high-risk patients who should receive, for example, neoadjuvant chemotherapy in addition to the radical cystectomy. The finding is novel, the study approach is reasonable, however, some issues remained to be addressed in the data analysis and presentation.

REQUESTED REVISIONS:

Major Issues

1. In addition to the ratios, the original AST and ALT levels should also be included in all univariate and multivariate analyses. Otherwise, whether the clinical response was due to the ratio or to either one of the variables was unclear.

Response: In the univariate and multivariate Cox analyses, individual AST and ALT levels were not associated with metastasis, cancer related death and overall death. The table below shows the results of the multivariate Cox analysis. Reduced ALT level was marginally associated with cancer related death and overall death (HR, 0.932; 95% CI, 0.867–1.001; P= 0.054 and HR, 0.938; 95% CI, 0.879–1.001; P= 0.052, respectively). In this regard, it seemed that only AST/ALT ratio had a clinical implication on bladder cancer patients after radical cystectomy.

<table>
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<th>Parameters</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
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<tr>
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<td>Multivariate Cox proportional analysis of overall death</td>
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<tr>
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<tr>
<td>ALT</td>
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</tr>
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</table>

2. Since the major focus (AST, ALT) is intimately related to liver fibrosis, and the prevalence of viral hepatitis is high in Korea, the HBV/HCV carrier status shall be analyzed.

Response: We have described the exclusion criteria including patients with hepatitis. We also excluded the patients who were HBV/HCV carriers. We have clarified this in the Methods section. Please see lines 10–11, page 8.

3. page 9, it was mentioned that ROC with the Youden index was used for determining the cutting point of AST/ALT ratio. It was unclear which two groups of patients (metastasis vs. non-metastasis?) were classified by the AST/ALT values in the ROC analysis. Also, the number of patients in the two clinical groups should also be presented. The area under the ROC should be presented. The ROC plot should be...
presented in the Figure.
Response: Thank you for your valuable comments. We have already described metastasis as a status variable as follows; “the receiver-operating characteristic curve of the De Ritis ratio for metastasis was used.” Please see line 3-4, page 9. During the follow-up periods, 44 patients showed metastasis, while 74 patients did not experience metastasis. We have added the number of patients to the revised manuscript (line 4, page 9). The area under the curve of the De Ritis ratio ROC was 0.606. We have added the ROC curve plot to the revised manuscript as the revised Fig. 1.

4. AST/ALT high and low are associated to the age (Table 1), thus age should be carefully addressed in the multivariate analysis. It was unclear in Table 3 whether the age in the multivariate analysis was a continuous variable or a binary variable (>70 and <70 years old)?
Response: In Table 3, age was a binary variable. We have corrected the table to aid clarification. Please see the revised Table 3.

The authors ascribed the potential implication of AST/ALT as the energy utilization by anaerobic glycolysis. However, other potential mechanisms should also be explored, for example, by examining the HBv/HCV carrier status or liver fibrosis of the patients.
Response: As we mentioned above, HBV/HCV carriers were excluded, as did patients with liver cirrhosis. Please see the Patients and Methods section, line 10-11, page 8.

5. In the background section of your Abstract, can you please also put your study into context. Why is this research relevant and/or important - and then go on to list your objectives.
Response: Thank you for your valuable comments. We have added the following sentences to the Background section of the abstract: “New biological prognostic predictors have been studied; however, some factors have limited clinical application due to tissue-specific expression and high cost. There is the need for a promising predictive factor that is simple to detect and that is closely linked to oncological outcomes in patients with urothelial bladder cancer (BC) who have undergone radical cystectomy (RC).”

6. Please remove the text from the Acknowledgements section as the funding information has been presented in the Funding section
Response: As instructed, we have deleted the said text.

Minor issues:
Table 1: standard deviation of the BMI should be shown
Response: We have added the standard deviation of BMI to the revised Table 1.

page 10 line 48-52, The values (75.5% vs. 53.6%; 79.6% vs. 62.3%;77.6% vs. 59.4%) were poorly presented. According to the context, the former value (for example 75.5%, 79.6%) was related to high AST/ALT level but actually it was related to low AST/ALT level.
Response: We made a mistake in declaring the results; the results were reversed, and have been corrected. Please see lines 14-16, page 10.

page 6, line 54 grammar error: "These rates are based off of evidence of treatment [5, 6]."
Response: The sentence was wrongly phrased and has been replaced as follows: These results provided evidence for neoadjuvant chemotherapy. Please see lines 17, page 6 in the revised manuscript.

In conclusion, we would like to thank the reviewers for carefully reviewing our manuscript. The
recommended revisions have significantly improved the quality of the manuscript.

Thank you for considering this manuscript for publication in BMC Urology.

Sincerely,

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