Author's response to reviews

Title: Prediction of Methicillin-resistant Staphylococcus aureus in patients with non-nosocomial pneumonia

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Author's response to reviews: see over
Dear Dr. Nathaniel Nazareno

RE: MS. 1343715367968705

Title: Prediction of Methicillin-resistant *Staphylococcus aureus* in patients with non-nosocomial pneumonia

Thank you very much for reviewing our manuscript. We appreciate your advice about the revision and are very pleased to inform you that we are ready to resubmit our revised manuscript taking into account your comments. All significant changes have been written in red colored text. Thank you again for your kind review and we await your feedback and acceptance.

Sincerely yours,

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Reviewer: Bin Cao

Reviewer's report:

Thank you for the opportunity to review the interesting paper for investigating the predictors for MRSA non-hospitalized pneumonia, including CAP and HCAP. I think the paper has important clinical significance for both Korean doctors and doctors in other countries. But some modification should be done to improve the quality of the paper.

Introduction: clear.

Methods
1. It is not clear about the microbiological methods used in this retrospective cohort study. Single Serology test is not enough for identification of Mycoplasma infection.

Reply: According to your comments, we clarified the microbiological methods for Mycoplasma pneumoniae in this study. This is based on the 'Laboratory diagnosis of Mycoplasma pneumoniae infection' by F.Daxboeck [1]. Antibodies against Mycoplasma pneumoniae were detected by microparticle agglutination assay (MAG). High elevated titer (>1:160) or four-fold increase of the titer between 2-4 weeks interval is considered evidence of Mycoplasma infection (page 7, line 131).

2. It is not clear how the scoring system was created, is there any references to support the author's calculation?

Reply: From logistic regression results, we created a predictive scoring system. The factor with the lowest \( \beta \) coefficient was assigned one point. The points assigned to the other factors were based on their coefficients relative to the factor with the lowest coefficient. Points were then summed to obtain the total risk score. We then explored the predictive value of the point score for correctly indicating the presence of MRSA infection via a receiver operating characteristic (ROC) curve. However, we decided to omit scoring system according to your recommendation below.

Results
1. As a reader, I will be very interested in the distribution of pathogens except MRSA in this institution, including streptococci, MSSA, Mycoplasma, legionella, G negative bacilli, et al.

Reply: As the reviewer mentioned, I also agree with that readers will be interested in the distribution of pathogens in this institution. We added new table (Table 2) presenting the distribution of pathogens in the result section (page 9, line 156).

### Table 2. Distribution of isolated pathogens in pneumonia patients

<table>
<thead>
<tr>
<th>Microbes</th>
<th>No. of isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive pathogens</td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>78(8.3)</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>MSSA</td>
<td>51(5.4)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>167(17.7)</td>
</tr>
<tr>
<td><strong>Gram-negative pathogens</strong></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>175(18.5)</td>
</tr>
<tr>
<td><em>Escherichia Coli</em></td>
<td>49(5.2)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>156(16.5)</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>31(3.3)</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>24(2.5)</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>18(1.9)</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
<td>10(1.1)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>24(2.5)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>25(2.6)</td>
</tr>
<tr>
<td><strong>Atypical pathogens</strong></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>146(15.5)</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>2(0.2)</td>
</tr>
</tbody>
</table>

2. There is no significance for recent hospitalization in multivariate analysis. I would like to delete this factor.

Reply: As the reviewer pointed out, we removed 'recent hospitalization' as an identified risk factor from the manuscript including abstract and main manuscript.

3. Again, I am a little puzzled by the scoring system. It is ambitious to figure out a model to pick up patients suspected to have MRSA pneumonia based on only limited number of cases. I would like to omit this part.

To my opinion, Without scoring system, the paper still has value to be published.

Reply: As the reviewer recommended, we deleted scoring system parts from the manuscript. (page 3, line 42; page 3, line 52; page 5, line 82; page 15, line 282).

**References**

Reviewer: B.D. Lidewij Broekhuizen

Reviewer's report:

This is a well written article on predicting MRSA related pneumonia. First of all I would like to underline that I am a general practitioner so I may not completely oversee the field of tertiary hospital care. Nonetheless I miss a few aspect in this manuscript (major revisions):

1. The authors state that the developed risk prediction model for MRSA related pneumonia can help to start empirical antibiotic treatment in patients admitted with pneumonia. I was wondering which treatment the authors suggest? It should be mentioned I think.

Reply: As the reviewer recommended, we have added more details about anti-MRSA treatment in the discussion section (page 13, line 247).

For years, vancomycin was the only antibiotic available for the treatment of MRSA pneumonia [1], and linezolid is an alternative choice achieving greater levels in lung epithelial lining fluid than in plasma [2]. Further study is underway to clarify which agent is more superior for the treatment of MRSA pneumonia [1].

2. Furthermore I miss comments on the advantages and disadvantages of such empirical therapy against MRSA.

Reply: As the reviewer commented, there are advantages and disadvantages of such empirical therapy against MRSA. We have described these two aspects of treatment in the manuscript (page 13, line 252).

Rapid institution of appropriate antibiotic therapy in patients with highly suspected MRSA pneumonia is strongly recommended according to several guidelines [1, 3, 4]. Delay of effective antibiotic therapy was associated with increased mortality in patients with ventilator associated pneumonia or septic shock [5, 6]. Among the patients with MRSA bacteremia, inappropriate empirical antibiotic therapy and non-eradicable foci including pneumonia were independent risk factors for mortality [7]. However, unnecessary broad-spectrum antibiotic therapy may promote the emergence of resistant organisms in the patients and the environment. Therefore, antibiotics de-escalation should be considered according to patient’s clinical response and the final results of cultures.

3. A minority of the patients classified with high risk has MRSA (32.6 %). Is it realistic to start empirical treatment in case of high risk? I can imagine that it is unwanted that too many patients who do not have MRSA receive the (last resort) antibiotic treatment against MRSA as this will increase resistance under pathogens in pneumonia?

Reply: The purpose of developing MRSA risk scoring system was to provide useful guidance in selecting initial antibiotics in non-nosocomial pneumonia patients. Therefore, this risk scoring strategy is not definitely recommending the physicians to start anti-MRSA treatment to all high risk group. However, as the reviewer pointed out, only one-third of high risk group showed MRSA pneumonia and the total number of MRSA patients included in this study was small to figure out a model. This problem was also commented by another reviewer. Therefore, we have decided to delete the risk scoring system and show only the multivariate
4. Finally, how long does it take to await the microbiological results on presence or absence of MRSA in days, and could the authors discuss whether that may be too long to await?

Reply: In our hospital, depending on the burden of bacteria, regular culture takes at least 48 hours and up to 72 hours for the results to come out. This period seems to be usual duration as shown in several guidelines where the continuous empirical antibiotic therapy for 48-72 hours is recommended until culture results are finalized [1, 3].

5. I think that patient may have been colonised by MRSA while this bug was in fact NOT the cause of pneumonia The authors should discuss the issue of carrier ship of MRSA and the lated risk of bias in their study.

Reply: We totally agree with the reviewer’s opinion. The diagnostic value of respiratory cultures for identifying MRSA pneumonia is not well established. Therefore, a positive culture of MRSA may reflect colonization rather than true infection for some cases. We have added this limitation in the discussion section (page 14, line 269).

References