Peer Review File

Reviewer Comments

Comment 1: I agree that the proportion of recorded respiratory rates is concerning, given the clinical importance of this parameter. Do you have any comments as to why this was poorly recorded?

Reply 1: In our hospital, vital signs are mainly measured and recorded by nurses, and we could not approach nurses sufficiently. Unfortunately, as a result of many cases in which respiratory rate could not be measured at the initial visit, we were unable to determine the PSI and the CURB-65. We have already noted this in the discussion because we considered it a major limitation that should be mentioned (see Page 7, line 31-35).

Changes in the text: non.

Comment 2: Did you look at procalcitonin as a continuous variable? It appears that you have collected absolute values for other laboratory data including BNP and CRP and used these as continuous variables, but again appear to have reported procalcitonin using a binary cut-off. The quoted cut-off of 0.5mg/dL is usually used to differentiate probable presence of bacterial infection from unlikely bacterial infection (or in my interpretation of the evidence really a low PCT suggests a diagnosis other than bacterial infection as we see a wide range of aetiologies for elevated PCTs). One could therefore argue that all these patients if they have a genuine diagnosis of bacterial pneumonia should have a PCT elevated above 0.5mg/dL. This would equate to using a CRP cut-off of 0.2-1mg/dL depending on the assay used. As a prognostic rather than diagnostic marker I would expect to see procalcitonin assessed as a continuous variable.

Reply 2: We appreciate your advice. We completely agree that it would have been better if PCT could have been evaluated as a continuous variable. The PCT measurement kit employed in this study could only determine PCT as a binary value with a cutoff of 0.5 ng/mL, making it impossible to evaluate it as a continuous variable. As you pointed out, the PCT being a binary value is an important limitation in predicting the prognosis of pneumonia and we added it to the discussion and the conclusion (see Page 7, line 35-38, Page 8, line 12-13).

Changes in the text: Page 7, line 35-38, Page 8, line 12-13

Comment 3: For me, having not reported and evaluated procalcitonin as a continuous variable, this weakens the comparative conclusions between procalcitonin and other parameters assessed (though clearly does not impact on the strength of the conclusion that BNP appears to be a useful prognostic biomarker). I feel this should be acknowledged in your discussion and conclusion.

Reply 3: We agree that this is a very important point, as is comment 2. We added it to the discussion and the conclusion (see Page 7, line 35-38, Page 8, line 12-13).

Changes in the text: Page 7, line 35-38, Page 8, line 12-13

Comment 4: Did you look at whether multiple parameters can enrich each other to better improve the sensitivity and specificity of prognostication? -for example BNP in addition to A-DROP score. This has been demonstrated with various combinations of other scoring systems and biomarkers, for example CRP added to CURB-65 has been shown in multiple studies to improve ability to prognosticate (eg https://erj.ersjournals.com/content/52/suppl_62/PA2041).

Reply 4: We considered it very important in pneumonia practice to combine multiple parameters for a more accurate prognostic tool, so we also examined it. We have added the results as table S1 and appended them to the text. We added BNP ≥179.3 pg/mL as one item to the A-DROP score, resulting in a sensitivity of 64.9%, specificity of 82.3%, positive likelihood ratio of 3.67, and negative likelihood ratio of 0.43. The results suggest that the addition of BNP to the A-DROP score may improve diagnostic accuracy compared to the regular A-DROP score. We added some data and a new table (see Page 5, line 25-27, Page 6, line 28-31, Page 7, line 9-10, Table S1).

Changes in the text: Page 5, line 25-27, Page 6, line 28-31, Page 7, line 9-10, Table S1

Comment 5: Did you capture any microbiological data other than the total number of bacteraemias and if so did you see any associations with this either with procalcitonin or BNP titres or with outcome measures?

Reply 5: When blood cultures were performed and positive findings were obtained, we diagnosed bacteremia and measured the number of cases. However, we did not obtain any other microbiological data. This is an important limitation and we added it to the discussion (see Page 7, line 38, Page 8, line 1-2).

Changes in the text: Page 7, line 38, Page 8, line 1-2

Comment 6: Did you correlate the BNP with ECG and echocardiographic findings to further elucidate whether the elevated BNP is related to RV strain or whether there is concomitant LV dysfunction or ischaemia?

Reply 6: Thank you for your important suggestion. We consulted cardiologists in all patients in this study and used the Framingham score to determine if the patient had congestive heart failure or not. However, we did not obtain data on cardiac dynamics such as ECG or echocardiography. Considering that previous studies have shown that atrial fibrillation and morphological abnormalities of the heart affect BNP, as described in the discussion, it would have been a more meaningful study if these data could have been obtained. We hope to clarify this in future studies. We added it to the discussion (see Page 8, line 2-4).

Changes in the text: Page 8, line 2-4

Comment 7: Neither the 2016 ATS/IDSA guidelines on community-acquired pneumonia removes the healthcare-associated pneumonia subclassification due to it's lack of utility and inferior performance to other risk stratification tools in determining microbiological

aetiology and prognosis. Admittedly the 2011 guidelines in use at the commencement of your study did include the HCAP definition. The 2011 ERS/ESCMID guidelines on community acquired pneumonia did not elect to define such a subcategory. Is it still commonplace in clinical practice in Japan to utilise this diagnosis and do you feel there is a clinical relevance to doing so? Would you expect different results in terms of prognostic value of BNP or any of the other biomarkers described in the HCAP/NHCAP subgroup as compared to the non-HCAP/NHCAP CAP or CAP as a whole?

Reply 7: We appreciate your review and positive suggestions for our manuscript. Certainly, the ATS/IDSA Guideline for CAP recommends removal of HCAP because of its lack of usefulness in antimicrobial selection. However, studies have shown that NHCAP is not only associated with a higher risk of bacterial resistance, but also presents with more end-stage pneumonia, including aspiration pneumonia, and has a higher mortality rate than CAP (Ref. 7,8). Therefore, in Japan, which has become the world's leading aging society, the diagnosis of NHCAP is recognized as highly important due to its high mortality risk, and the NHCAP diagnosis category is still used as a standard in JRS Guideline 2017 (Ref. 6). It is easy to predict that this disease will become a very common problem not only in Japan, but also in the aging society that is expected to prevail worldwide in the future.

NHCAP is known to be caused by a combination of various factors due to aging and functional impairment. Therefore, the prognostic accuracy of prognostic scoring such as PSI, CURB-65, and A-DROP is inferior to that of CAP (Ref. 13). Therefore, we believe it is important to examine prognostic methods for NHCAP and to develop evaluation indices for selecting treatment strategies, including determination of hospitalization and antimicrobial selection. In particular, since prognostic indices for biomarkers have not yet been identified for NHCAP, we examined BNP in this study.

we have modified our text and added two new references as advised (see Page 2, line 35-38, Page 3, line 1, Page 9, line 12-15). Thank you very much.

Changes in the text: Page 2, line 35-38, Page 3, line 1, Page 9, line 12-15

Typographical errors (you pointed out):
We have made the following two corrections. Thanks a lot.
Page2, line 1 - Background
Table 2 - DIC percentage in the survivors group should be 5.4% rather than 54%

Typographical errors (you didn't point out):
We noticed and corrected the following two kinds of errors We apologize.
Page 6 line 1, line 15, Table 1, Table 2, Table 3 - The unit of PCT was written as mg/dL in several places; corrected to ng/mL.
Page 6 line 1, line 15-16, Table 1, Table 2 - Fonts for ≥ have been unified to Times New Roman.