Author’s response to reviews

Title: Available, Bed-sided, Comprehensive (ABC) Score to A Diagnosis of Methicillin-Resistant Staphylococcus aureus Infection: A Derivation and Validation Study

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Title: Available, Bed-sided, Comprehensive (ABC) Score to A Diagnosis of Methicillin-Resistant Staphylococcus aureus Infection: A Derivation and Validation Study

Authors: Nori Yoshioka, et al.
Dear Dr. Harris:

Thank you for your careful review and constructive comments on our manuscript. In accordance with the reviewers’ recommendations, we have revised and added discussion to the manuscript. RED indicates modified portions.

We are grateful to you for allowing us to submit our revised manuscript. We hope that this revised manuscript is acceptable for publication in your esteemed journal.

Sincerely yours,

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Comment from Donna M Wolk (Reviewer 1):
The manuscript purpose is useful yet there are some flaws that need to be addresses.
Comment #1

The introduction is accurate but I suggest the authors tailor each concept toward the need for their screening system. Some grammatical and formatting improvements can be made, including merging the last sentence with the paragraph above to avoid a 1 sentence paragraph.

Answer #1

Thank you for your comment. As indicated, we have revised the grammar of the introduction. In addition, the last sentence was moved to the last part of the third paragraph (Page 5: lines 82-84).

Comment #2

Methods should include more description of the study population, for instance, % Adults vs Peds. % in ICU, other? Refer to STARD criterion for suggestions.

Answer #2

Thank you very much for your constructive comment.

We compared the background data of the two cohorts; we summarize this comparison in Supplement 2 (Page 13: lines 225-229).

Comment #3

Methods. The tool is limited in that only one person ranked all data. There is no kappa scores among raters, since there was only one. I suggest discuss of this bias/limitation in the Discussion section.

Answer #3

As you point out, only one person evaluated the clinical diagnosis of MRSA infections in the derivation phase; there were not multiple raters at the time of provisional ABC score evaluation. We therefore evaluated clinical data of the patients with two independent staffs in the validation phase, to increase the accuracy of clinical diagnosis (Page 10: lines 162-165).

We also have noted this limitation in the discussion section. (Page 16: lines 272-273)
Comment #4

Consider placing the provisional information for data tables in the supplement, as it is not the final result.

Answer #4

Thank you for your comment. As recommended, we moved the provisional score from a table to Supplementary Table 1.

Comment #5

Data analysis - why were so many excluded? Describe the large # of exclusions and rationale in more detail. I flow diagram may be helpful.

Answer #5

In the derivation study, there were 25 un-differentiable cases (we rechecked our data and found that un-differentiable cases were 25, not 26), due to the nature of clinical evaluation (retrospective and records-based) (Page 11: lines 192-193). The indeterminate cases were excluded from the target cohort in order to evaluate the provisional ABC score clearly with definite cases.

Details of the cases are summarized in Supplementary Table 3.

Comment #6

A table or flow diagram to describe actual differences between provision and final scoring system would be useful.

Answer #6

We have prepared a new figure that provides an overview of the workflow for this study (Fig. 1).

Comment #7
Without a software program, web based input or even simply a checklist, the usefulness of this model is limited. I suggest the authors develop an actual tool that is useful for the future as they and others move forward to validate their model.

Answer #7

Thank you for your constructive comment.

Surely a simple scoring system would be easier to use than a complex scoring system. As you recommend, a production-ready implementation of our scoring system (as a mobile web application, or as a paper checklist) would be useful. We aim to develop such a user-friendly implementation in the future.

Comment #8

The model text description is difficult to follow.

Answer #8

As you note, the previous manuscript was difficult to understand. We hope that the additional flow diagram (Fig. 1) clarifies our study model.

Thank you for your review.

Comment from Hee-Chang Jang (Reviewer 2):

The authors evaluated the usefulness of clinical score in case of MRSA infection.

I have two major comments.

Comment #1

Gold standard:

the authors compared the ABC criteria with gold standard:
inflammation and clinical signs were apparent at the site where MRSA was detected.

(ii) Systemic inflammation was apparent (fever, elevation of peripheral white blood cells [WBC] or serum C-reactive protein [CRP]).

(iii) Inflammation was alleviated upon treatment with MRSA-targeted antimicrobials.

These criteria is not relevant to be used as a gold standard because following reasons.

1) many criteria are also included in ABC scores

2) arbitral: clinical decision not pathological or microbiological confirmation.

3) Gold standard criteria are more simple and convenient to be used. Why another score needed?

Answer #1

Thank you for your comment.

Your comments are very reasonable. However, we would like to insist on our opinion here. The above points [(i) ~ (iii)] alone do not guarantee an optimal clinical diagnosis. A medical doctor in the derivation phase comprehensively differentiated active infection from colonization based on his own judgment, in light of these points. These points [(i) ~ (iii)] are just references for the clinical diagnosis, but they do not provide the comprehensive specification that “gold standard” implies. We are sorry for the misleading sentence. We have revised the corresponding text (Page 7: lines 104-105).

As pointed out, some diagnostic items in the revised ABC score are included in the clinical criteria, which might be simpler. However, the ABC score fills a niche that the clinical criteria do not. The ABC score was developed for infection control practitioners, as well as first-line
physicians, to differentiate MRSA colonization from active infection (Page 15: lines 263-266). The infection control practitioners are not necessarily medical doctors (non-MDs such as nurses, laboratory technicians, pharmacologists, or even clerks are often in charge of collecting clinical data and performing surveillance activities in hospitals); an easy and reliable scoring system for non-MDs is needed (Page 5: lines 78-84).

Since the provisional version of the ABC score was established on the basis of current guidelines and clinical experience (Page 7: lines 116-117), the scoring criteria appeared to be similar to the clinical criteria. However, in the process of developing the score, we evaluated and weighted each criterion according to the k coefficient. Thus, we believe we have established an accessible and reliable scoring system for differentiating MRSA colonization from MRSA infection.

Comment #2

Design. Derivation can be performed from retrospective samples; however, validation usually should be performed in prospective manner.

Answer #2

Thank you for your comment.

We understand that the validation process should be prospective. However, time constraints prevented us from conducting it prospectively. We have added a note of this limitation to the discussion section (Page 16: lines 279-281).

Thank you for your review.

Comment from Shey-Ying Chen (Reviewer 3):

This manuscript developed and validated a scoring system to differentiate between infection and colonization among hospitalized patients with positive MRSA culture. It is important for first-line physicians in their decision in appropriate use of anti-MRSA antibiotics. However, some aspects and limitations prevent this manuscript from being published in current style.
Comment #1

The predictors and assigned score point in the provisional ABC score were arbitrary and were not assessed by appropriate statistical methodology. Though the authors provided a revised score by recruiting new predictors, the decision of selecting predictors in final model by sensitivity/specificity/diagnostic concordance > 50% criteria was inappropriate and introduced the risk of model over-fitting problem.

Also, the author should provide reference how they translated kappa value to score point in this study. Why 1 point for a kappa coefficient ranging from 0.01 to 0.41 but not 0.01 to 0.40.

Answer #1

Thank you for your constructive comments.

In the process of developing the score, we evaluated the sensitivity, specificity, and diagnostic concordance rate. This approach may not be statistically sufficient, as you note. We therefore denote this limitation in the discussion (Page 16: lines 273-276).

The cut-off index of the kappa coefficient in our study was derived from a previous statistical report, which we cited in the manuscript (Landis et al. Biometrics. 1977). The authors of that report insisted that although the categories given may be arbitrary, they provide useful benchmarks. We thus weighted our point scoring in light of Landis et al., as follows:

Cited by the following reference at page 165; Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74.

“0.01 to 0.41” was miswritten. This text should have read “0.01 to 0.40”. We have revised that part (Page 9: Line 156-1598).

Comment #2

Isolation of MRSA from aseptic sample such as blood, ascites, pleural effusion, or spinal fluid should be considered as an invasive MRSA infection and needs prompt anti-MRSA
antimicrobial therapy. These patients need not and should not be determined their infection status by any scoring system in order not to mislead antibiotics treatment decision. I could not image a MRSA endocarditis patient without significant systemic inflammatory response but has persistent bacteremia might be judged as "colonization" by the revised ABC score in this study. Therefore, those patients with MRSA culture from aseptic sample should be excluded from this study.

Answer #2

Thank you for your very reasonable comment.

As you point out, clinicians may not need such a scoring system when patients are critically ill and MRSA is isolated from aseptic samples such as blood. Diagnosis of MRSA infection is obvious in such cases, and the appropriate treatment is beyond doubt. However, some pathogens, including MRSA, can be isolated from aseptic samples as contamination, and our scoring approach will be of help in such cases.

Furthermore, this scoring system has been developed to help first-line physicians, as well as infection control practitioners in hospitals, as described in the introduction and discussion (Page 5: lines 78-82, Page 15: lines 263-266). The infection control practitioners are not necessarily medical doctors; non-MDs such as nurses, laboratory technicians, pharmacologists, and clerks are in charge of collecting clinical data and surveillance activities in hospitals. For them, it is not so easy to differentiate an active infection from colonization. In one respect, our ABC score was developed for such persons. Based on our objective, all cases with MRSA isolation should be included for evaluation.

We hope you understand the goal and role of the scoring system we have developed.

Comment #3

To avoid misclassification, colonization or active infection of a patient with positive MRSA culture from non-sterile sample (sputum, wound, urine, and upper airway) was best judged by two independent ID doctors who were blind to the result of ABC score. A third ID doctor's decision will be need if the first two ID doctors have discrepancy in their judgment.

Answer #3

It is true that in the validation phase, judgment by two independent ID doctors was performed in a blind manner. We asked them to make a five-graded evaluation in each case (5: definite infection, 4: possible infection, 3: undetermined, 2: possible colonization, 1: definite
colonization). We regarded 4 or 5 grades as active infections and 1 or 2 grades as colonization. As a result, there was no discrepancy in their judgment.

Comment #4

I worried about the consistency of the diagnosis of active MRSA infection of study patients in the derivation and validation phase. In derivation phase, 26 out of 172 patients (15.1%) had undifferentiated infection (undetermined infection status?) judged by one ID doctor. However, in the validation phase, none of the 154 cases were judged as undifferentiated infection. I am not sure if patients with undifferentiated infection were excluded in validation phase. If so, this might introduce selection bias and falsely increased the predictability of the revised ABC score as assessed by AUC.

Answer #4

Thank you for your comment.

In the validation phase, there actually were no undetermined cases; there were no exclusions to cause selection bias. The target cases were clearly differentiated as either active infection or colonization, without discrepancy in the clinical diagnoses of the two independent ID doctors.

In addition, during a reanalysis of our data, we found that un-differentiable cases were 25, not 26. We corrected the corresponding text.

Minor comments for authors:

Minor Comment #1

I suggest using criteria for systemic inflammatory response syndrome (SIRS), including HR, RR, BT and WBC count, as the definition of "systemic inflammatory response" in this study. It is well recognized and accepted in the definition of so-called systemic inflammation.

Answer #1

Thank you for your constructive comment.

As pointed out, the definition for SIRS might have been better for determining systemic inflammation. However, due to the retrospective nature of this study, it was impossible to
accurately confirm the SIRS parameters (HR, RR, BT, and WBC count). Thus, we alternatively considered the present parameters (fever, WBC, and CRP) as indicators for systemic inflammation. We agree that your recommendation should be implemented in a future study.

Minor Comment #2

In page 6, line 87, the word should be corrected to "In the derivation phase, all consecutive patients admitted to the hospital from May 2010 to April 2011 with any positive culture for MRSA during hospitalization were enrolled in the study". It is because the authors did not enrolled patients without positive MRSA culture in this study.

Answer #2

Thank you very much for your recommendation.

We have changed the sentence as recommended (Page 6: lines 91-93).

Minor Comment #3

I would like to suggest to change "undifferentiated infection" to "undetermined infection status" or "unknown clinical significance" of MRSA culture.

Answer #3

As suggested, we changed “undifferentiated infection” to “undetermined case” throughout the manuscript. Please refer to each sentence.

Minor Comment #4

The manuscript should be edited by a native English speaker before formal publication.

Answer #4

We have submitted our manuscript for English editing. We attach a certificate verifying this step.
Thank you for your review.