Peer Review File

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Reviewer A

-Thank you for the opportunity to review this work. Detailed comments about this study are as follows:

-Please correct the spelling of "AST, glutamic oxalacetic transaminase" to "AST, glutamic oxaloacetic transaminase" in a footnote of Table 1.
Response: Thank you for pointing out our error, which I have corrected.

-Please provide the unit of each measurement in Table 2.
Response: Thank you for your suggestion, we have added the units of measurement for the lab data. (Table 1, Table 2)

-Some variables may not be available in the emergency department or the ICU immediately after admission, such as atrial fibrillation (required the period to monitor this dysrhythmia occurred), requirements of dialysis (may be indicated after many days passed), total antibiotics use, fluconazole usage (maybe need to wait for the result of the investigation before using those total antibiotics in some cases). Moreover, those results might be available after 2 or 4 days, which is the outcome of this study. This issue should be discussed, and it should be suggested how to implicate this prediction model in clinical practice, for example, when the physician should use this nomogram to improve the outcome of each patient in current admission.
Response:

Thank you for pointing this out. Regarding the identification of AF, we were based on the hospitalization diagnosis provided in the database. Regarding the use of medication, the time of the patient's medication initiation was provided in the database. Medication initiated after the onset of sepsis was considered ineffective (i.e., the time of sepsis diagnosis minus the time of medication initiation was negative). Therefore, the medication information we extracted was prior to the onset of sepsis and can be considered empirical.

Additionally, we realized that the time points we used for plotting the nomogram were inappropriate, and that the 2-, 4-, and 6-day predictors did not allow for long-term forecasting. Therefore, we modified the time points used for plotting the nomogram. Therefore, we changed the time points used to map the nominations to 3 days, 1 week, 2 weeks, and 1 month. When a clinician realizes that a patient needs a certain medication (which is included in the model), the clinician can predict the sepsis that occurs thereafter. For example, if a patient is thought to need a medication on day 8 of admission, the incidence of sepsis on day 14 and at 1 month can be predicted.

Reviewer B

In reviewing the study titled "A predictive model for the identification of the risk of sepsis in patients with Gram-positive bacteria in the intensive care unit."

Major comments.

1. P2 Line 33-51: Can the authors describe the frequency of sepsis on day 2, 4, and 6, respectively?

Response: Thank you for pointing this out. The incidence of sepsis in the total study cohort was 5.8 %, 4.5 %, and 4.4 % of patients within 2, 4, and 6 days, respectively.
Since we have changed the predicted time points to 3 days, 1 week, 2 weeks, and 1 month, we illustrate the incidence of sepsis at these time points in the results section (Lines 288-289). In addition, we have added the event occurrence curves grouped according to the variables in the nomogram, where the number of sepsis events at each time point can be clearly seen in the risk table of the curves (Figure 3).

2. P4 Line 93-95: What is the prevalence of GNR and GPC infections among sepsis? Please cite the latest papers. This would be relevant to this study.

Response: Thank you for your comment. A study based on 10 million cases of sepsis showed that Gram-positive bacteria accounted for 52.1% of reported sepsis cases in 2000, Gram-negative bacteria accounted for 37.6%, polymicrobial infections accounted for 4.7%, anaerobes accounted for 1.0%, and fungi accounted for 4.6%. This study is based on a large sample size, and we believe the data is credible. In addition, we have not found more recent studies. We also describe this in the "Introduction" section (Lines 118-128).

3. P4 Line 93-95: There was no description in terms of a research gap for identification of sepsis among Gram-positive bacteria. Why did the authors look at only GPC?

Response: Thank you for your comment, we studied Gram-positive bacteria because the largest percentage of causative organisms in sepsis are Gram-positive. However, there are no studies on the risk of sepsis in patients with Gram-positive bacterial infections only. We further describe the research gaps in this area in the Introduction section (Lines 125-128).

4. P4 Line 116-118: How did the authors identify Gram-positive bacteria? Did they look at culture data?

Response: Thank you for pointing out the parts that we did not describe clearly. Sampling times and culture results of microbiologic cultures of patients are provided in MIMIC database. In our study, Gram-positive bacterial infections were determined from the patients' blood culture results. We have added a description of this detail in the Methods section (Lines 160-162).

5. P4 Line 116-118: What if patients already had sepsis at admission? Were they excluded?

Response: Thank you for raising this point. We excluded patients who already had sepsis at admission. The database provides the time to diagnosis of sepsis, and we used the time to diagnosis of sepsis minus the time to admission; if the result was negative or zero, these patients were excluded. Patients diagnosed with sepsis within 24 hours of admission were also excluded by us, considering that there may be a lag in diagnosis. Our description in the Methods section as "Patients who were diagnosed with sepsis within 24 hours after

admission were excluded." may lead to misunderstanding on the part of the reader, and we have therefore made a correction (Lines 176-177).

6. P5 Line 127-128: Can the authors describe how many missing values there were in each variable?

Response: Thank you for your suggestion, cases with missing data have been excluded from the data we included in the analysis. Therefore, none of the variables described in Table 1 contain missing values.

7. P5 Line 132-134: It is not clear when GCS, SOFA score, CVP, vital signs, vasopressor use, and laboratory tests were measured. Were they measured at admission or something else?

Response: Thank you for bringing this up and I apologize that we did not describe it clearly in the manuscript. The data you mentioned are all multiple measurements. The time of measurement is provided in the database for data with multiple measurements. For these data, we used data within 24 hours of admission for analysis. If an indicator was measured multiple times within 24 hours of admission, the first measurement was used. We explain this in the Methods (Lines 186-200).

8. P5 139-140: How did the authors identify proven or suspected infection? Can the authors describe the distribution of infection site (such as pneumonia, UTI, abdominal, etc.) in this cohort?

Response: We diagnosed sepsis based on the officially provided script (sepsis3.sql). Based on the script, the confirmed or suspected infection was recognized based on the ICD codes as well as microbial culture results (We have added relevant explanations in the Methods section) (Lines 170-172). We included patients whose blood cultures revealed Gram-positive bacteria in our study. The blood culture results were provided by the "microbiologyevents" table in the database. Only the sample tested was provided in the results, not the site of infection. Therefore, we regret that we are unable to provide information on the site of infection of the patients.

9. P5 Statistical analysis: Can the authors clarify which variables were initially screened in the Cox model?

Response: Thanks to your comments, the variables described in Table 1 and those in the "Characteristics" column of Table 2 were all included in the initial screening.

10. P6 Line 156-158: How censoring was handled in the Cox model? If patients died between day 2 and 6, how were they handled in the Cox model? Can you please clarify?

Response: Thank you very much for your comments.

1. How censoring was handled in the Cox model?

In the Cox model, right censoring is the most common type of censoring, where we know that an event has not occurred by a certain time point, but we don't know if or when it will occur beyond that point. This type of censoring is typically handled by including censored observations in the analysis. These censored observations contribute partial information up to the time of censoring, but they do not provide information about what

happens after censoring. The Cox model uses this partial information to estimate hazard ratios and survival probabilities.
2. If patients died between day 2 and 6, how were they handled in the Cox model?
In fact, the Cox model can handle data from all time points. To test the performance of the model, we chose three time points for prediction (since 2, 4, and 6 days do not predict long-term sepsis risk, we have now changed to four time points: 3 days, 1 week, 2 weeks, and 1 month) and plotted ROC curves. If we want to know the incidence of sepsis within day 5 or 7, we can also choose day 5 or 7 as the prediction time point. In addition, to show the prediction results of the Cox model at each time point, we plotted time-dependent ROC curves (Fig. 4 L, M), with the X-axis being the patient's follow-up time and the Y-axis being the Cox model's prediction results at each time point.

11. P6 Line 177-178: Can the authors identify MRSA and VRE? It's very meaningful to distinguish resistant organisms in sepsis.
Response: Thank you for your comment, it is very valuable. We have overlooked antibiotic resistance. First, we wanted to identify common resistant Gram-positive bacteria, but we were concerned that the identification was incomplete. Therefore, we extracted the antibiotic sensibility (Intermediate, Resistant, Sensitive) data provided by the database and included it as a variable in the analysis.

12. P6 Line 179-180: Does this mean the prevalence of sepsis was 19,032/19,961 (95.3%)? If so, why do we need this prediction score because most patients with gram-positive bacteria developed sepsis? Can the authors show the frequency of sepsis on day 2, 4, and 6, respectively?
Response: Thank you for your comment. It was not the case. A total of 929 patients (4.7 %) developed sepsis in the total cohort (Table 1). The incidence of sepsis within days 2, 4, and 6 in the total cohort was 5.8 %, 4.5 %, and 4.4 %, respectively. As we realize that 2, 4 and 6 days do not predict long term sepsis risk. Therefore, we have changed the time points to 3 days, 1 week, 2 weeks, and 1 month. We have stated the incidence of sepsis at these four time points in the results section (Lines 288-289).

13. P6 183-192: Why cancer and mechanical ventilation were not included in the list? How was Burn defined?
Response: Thank you for your comments. In the updated manuscript we included cancer and ventilation types for analysis. Burns we defined according to ICD disease codes.

14. P7 Line 195-197 and table1: Why were fluconazole and itraconazole included? Also why were fluconazole and itraconazole separately included? How about other antifungal medications?
Response: Thank you for your reminder. We have compiled other commonly used antifungal drugs (including Amphotericin, Anidulafungin, Caspofungin, Fluconazole, Flucytosine, Itraconazole, Ketoconazole, Micafungin, Posaconazole), were analyzed as a variable.

15. P7 Line 195-197 and table1: Can the authors identify whether patients received vancomycin as empiric therapy? More details regarding antibiotic use would be useful.
Response: Thank you for pointing this out. We are very sorry that we did not describe it clearly in the manuscript. The database provides the time when the patient started the medication. In our study, medication initiated after the onset of sepsis was considered ineffective (i.e., the time of sepsis diagnosis minus the time of medication initiation was negative). Therefore, the medication information we extracted was prior to the onset of sepsis and can be considered empirical. We clarify this point in the Methods section (Lines 188-200).

16. P7 Line 195-197 and table1: Why did the authors look at only vasopressin instead of other vasopressors? Can the authors show the proportion of all vasopressor use?
Response: Thank you for pointing this out. In the updated manuscript, we included commonly used vasopressors (including Vasopressin, epinephrine，dopamine, dobutine, Norepinephrine, Phenylephrine)integrated together for analysis. Vasopressors were used by 17.7%, 17.6%, and 18.1% of patients in the total study population, training cohort, and validation cohort, respectively.

17. P13 limitation: Was this a single center study? If so, generalizability is limited.
Response: Thank you for your comment. Yes, this was a single-center study. However, the amount of data we used was large. Also, the center included major ethnic groups such as whites, blacks, and Asians. Therefore, we think the results can be generalized to some extent. Even so, this is a limitation of our study that we will mention in the discussion section.

Reviewer C

The paper is well written and shows interesting data that support the potential usefulness of the proposed model. The authors deserve credit for their effort to critically appraise some of the possible pathophysiological and clinical implications of the nine variables that were considered by their model. Often times, similar modeling efforts exclusively focus on the statistics behind the model but lack contextualization.
I have one question and one suggestion to improve the manuscript:

1) I was a bit surprised that age was not part of the model, given that it is often highlighted in a number of similar modeling studies. However, dementia is. I suppose that dementia is definitely associated with age. More in general, it is well known that age is a predictor of poor outcome, although not necessarily of the risk for sepsis following bacterial infection per se. Any comment on the possible reasons why age was not considered by the model?
Response: Thank you for pointing this out. There is a great deal of heterogeneity in physical condition at the same age. Stepwise Cox regression automatically screens for important variables. It is possible that age was not included in the model because the variables included in the model were more important than age.

2) The discussion on the possible meaning of neutrophil levels is particularly interesting, since it includes a potentially important mechanistic aspect that the model could help better understand. In particular, I suggest expanding a bit this discussion item, given the recent findings about the possible roles of proteolytic enzymes and the relevant clinical implications, that could be cited to bolster the significance of this aspect of the model, e.g.:
Maegele M, et al. New insights into the pathophysiology of trauma and hemorrhage. 2023;59(3S Suppl 1):6-9;
Bauzá-Martinez J, et al. Proteolysis in septic shock patients: plasma peptidomic patterns are associated with mortality. Br J Anaesth. 2018;121(5):1065-1074.
Response: Thank you very much for your suggestions, we have benefited a lot. We have read the literature you mentioned and added a description of protein hydrolases and neutrophils to the discussion section (Lines 567-573).

Reviewer D

1-The Author has to define the criteria of inclusion more clearly, for example, why he includes sepsis patients who stay 1 day while keeping the others
Response: Thank you for pointing this out and we have clarified it in the methods section (Lines 176-177). The reason for the exclusion of sepsis occurring within 24 hours is that we believe that the diagnosis of sepsis is somewhat delayed. We also excluded patients who developed sepsis before admission.

2- In line 116, this should be corrected as 3 types of G-+ bacterial infection at admission at the same time can be included. (at least one of 3 G+ bacteria can be included)
Response: Thank you very much for pointing this out, we have corrected it (Lines 160-161).

3- The definition/criteria of inclusion criteria have to be further explained for example besides the Sepsis-3 definition, (either sepsis or septic shock) , the suspect of sepsis, the lowest duration of admission (3 days) in order to obtain the culture sensitivity result.
Response: Thank you for your comment. We have added the relevant explanation in the Methods section (Lines 169-172).

4- The site and sources of the culture sample (blood, sputum, CCF), were not mentioned.
Response: Thank you for the suggestion that the patients we included were those with positive blood cultures, which we clarified in the Methods section (Lines 161-162).

5- For those patients without isolated culture bacteria samples, how-to included/excluded
Response: Thank you for your comment. We only included patients with blood culture results of gram-positive bacteria.

6- In terms of antibiotic therapy (ex.3AB) , not mentioned whether empirical or definitive therapy was used.

Response: Thank you for your comment. The database provides the time when the patient started the medication. In our study, initiation of medication after the onset of sepsis was considered ineffective (i.e., time to sepsis diagnosis minus time to initiation of medication was negative). Therefore, the medication information we extracted was prior to the onset of sepsis and can be considered empirical. We will clarify this point in the Methods section (Lines 189-201).

7-The clear definition of two arms of the study population (validated and training groups) has to be explained in the methodology

Response: Thanks to your comments, we have further clarified the role of the training and validation cohorts in the statistical analysis section (Lines 214-215).

8- Ethical approval has to be mentioned also and whether consent forms were used or waived

Response: Thank you for your suggestion. The MIMIC-IV program was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Patient information is anonymized so that informed patient consent is not required. We describe this in the Methods section (Lines 147-158).

9- Table -1 has to be divided into 3 sections/ tables (demographic, patient clinical data, lab findings)

Response: Thank you for your suggestions. We have reorganized Table 1 based on your suggestions.

10-Discussion must be summarized, was too lengthy.

Response: Thanks to your suggestion, we have simplified the discussion section.

11- The font size of tables has to be improved

Response: Thank you for your comment, we have improved the font of tables.

Reviewer E

1. The authors mentioned “studies...”, while only one reference was cited. Change “Studies” to “A study” or add more citations. Please revise.

The severity of sepsis is determined, in part, by the pathogen responsible for the initial infection. Initially, it was thought that the pathogens causing sepsis were predominantly Gram-negative pathogens, but more recent epidemiologic studies have shown a greater preponderance of Gram-positive pathogens (14).

Response: Thank you for your comments. We have modified it.

2. Table 1

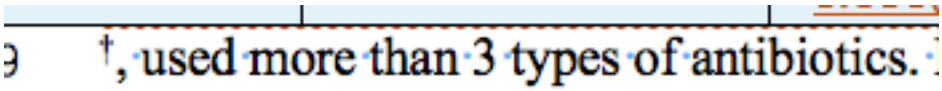
2.1 There seems to be no "*" and "†" in Table 1, while they were explained in the legend. Please check and revise.

943 *, the time of being diagnosed with sepsis or discharge; †, used more than 3 types of
944 antibiotics. Data are presented as n (%) or median [IQR]. AF, atrial fibrillation; COPD,

Response: Thank you for your comments, we have indicated the position of "*" in Table 1.

2.2 There seems to be no "MCV", "NEUT", and "BASO" in Table 1, while they were explained in the legend. Please check and revise.
Response: Thank you for pointing out our oversight. We have checked and modified it.

3. Table 2
3.1There seems to be no "†" in Table 2, while they were explained in the legend. Please check and revise.



Response: Thank you for your comment. We have checked and revised it.

3.2 "AST ≥ 40 U/L" or "AST > 40 U/L"? Which one is correct? Please check and revise.

Main text:

277 1.474; 95% CI: 1.226-1.772; P<0.0001), AST > 40 (adjusted HR, 1.296; 95% CI:

Table 2

Dialysis		2.908(2.54-3.613)	<0.0001		
Laboratory data					
ALT ≥ 40 U/L		1.294(1.089-1.539)	0.0035		
AST ≥ 40 U/L		1.541(1.311-1.810)	<0.0001	1.296(1.101-1.525)	0.0018
Basophils		0.761(0.610-0.950)	0.0160		

Response: Thank you for your comment. We checked and modified it.

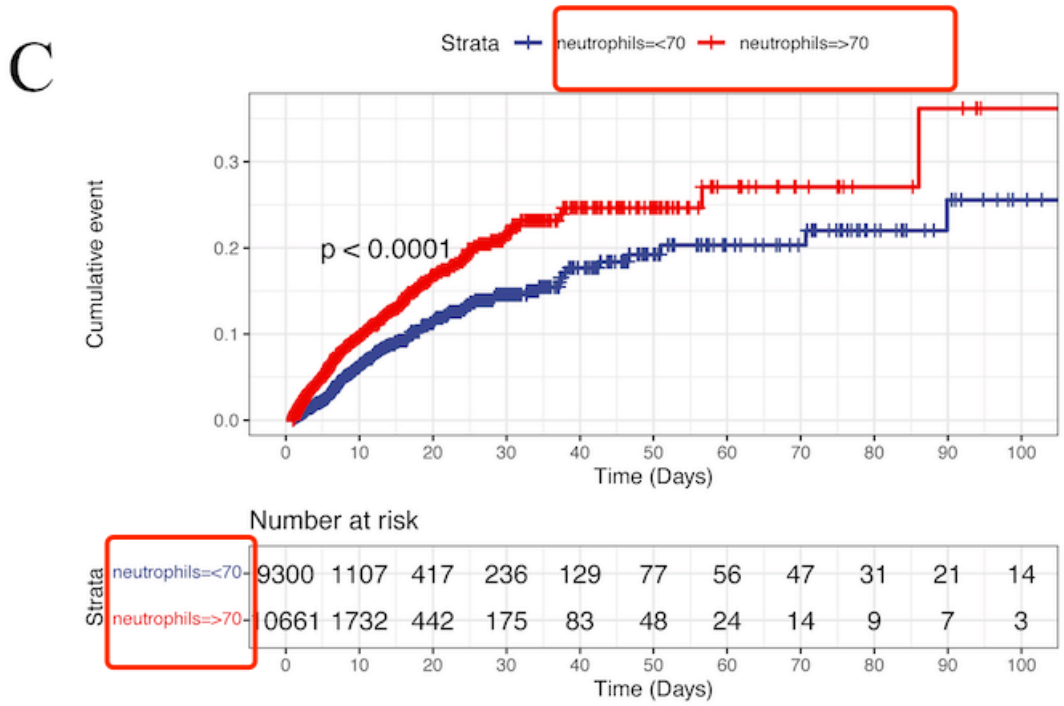
4. Figure 1
Please re-provide Figure 1 editable in Word format.
Response: Thank you for your comments. We have provided the Word version.

5. Figure 2
The situations "Neutrophils＝70" and "Antibiotics＝3" are missing. Please check whether the two points groups are correct.

Response: Thank you for your comment. We checked the Figure 2 and modified it.

6. Figure 3C

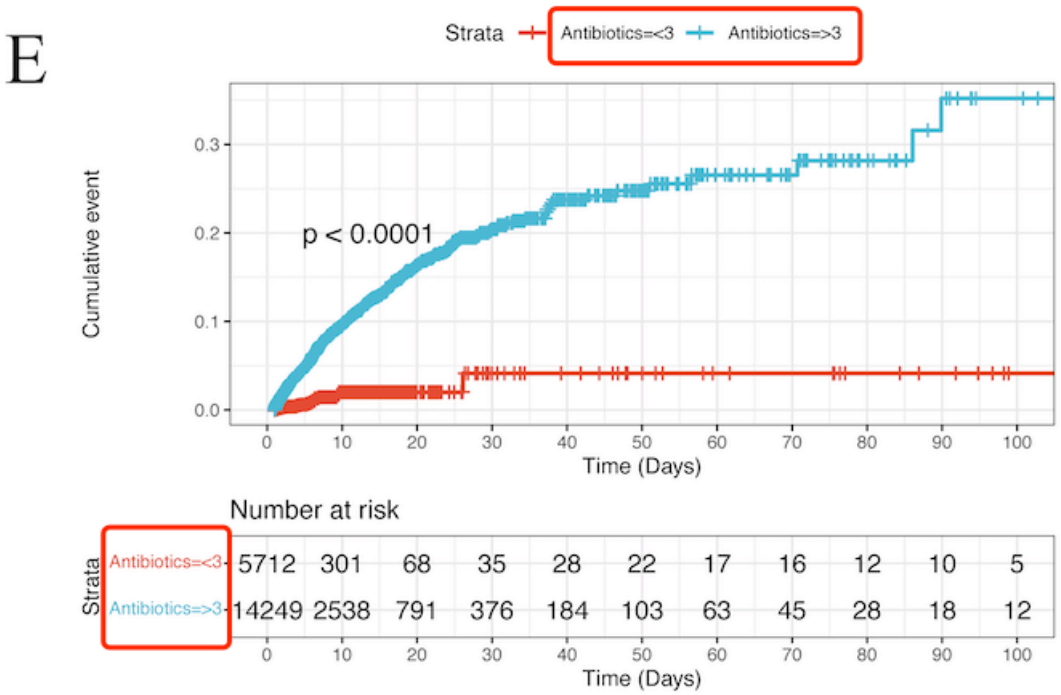
The situations “Neutrophils＝70” is missing. Please check whether the pointed groups are correct.



Response: Thank you for your comment. We checked the Figure 3 C and modified it.

7. Figure 3E

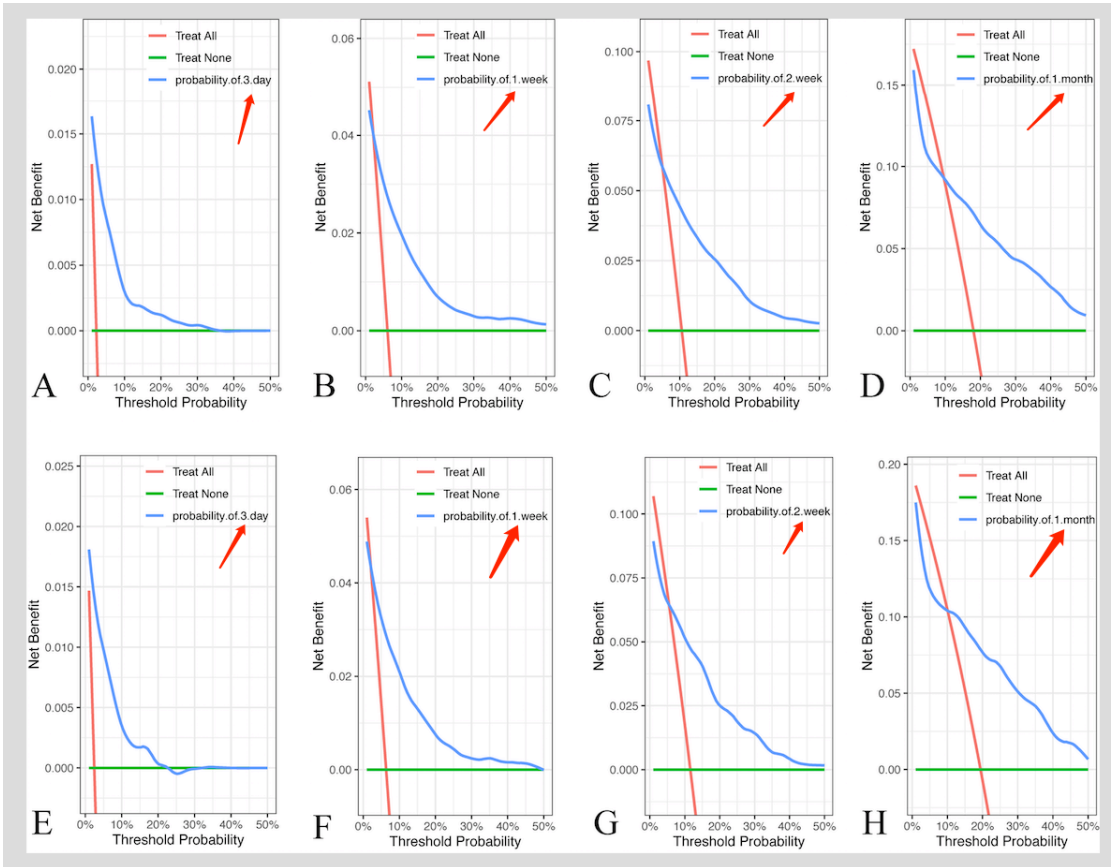
The situations “Antibiotics＝3” is missing. Please check whether the two points groups are correct.



Response: Thank you for your comment. We checked the Figure 3 C and modified it.

8. Figure 6

Should the pointed content be “3-day”, “1-week”, “2-week”, “1-month” or “3 days”, “1 week”, “2 weeks”, “1 month”? Please check and revise.



Response: Thank you for your comment. We checked figure 6 and modified it.