

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Bacteremia predictive factors among general medical inpatients: retrospective cross-sectional survey in a Japanese university hospital
AUTHORS	Fukui, Sayato; Uehara, Yuki; Fujibayashi, Kazutoshi; Takahashi, Osamu; Hisaoka, Teruhiko; Naito, Toshio

VERSION 1 - REVIEW

REVIEWER	<p>Gerald H. Stein, MD, FACP Courtesy Clinical Assistant Professor, Department of Medicine, College of Medicine, University of Florida, United States of America</p> <p>There may be a perceived competing interests. I not only know several of the authors because I consult with Dr. Naito's Juntendo University department staff twice yearly, but also I am anticipating a faculty appointment in Dr. Naito's department next year, 2016.</p> <p>Nonetheless, I feel I can give an objective opinion and review about this manuscript.</p>
REVIEW RETURNED	07-Dec-2015

GENERAL COMMENTS	<p>I enjoyed reviewing this timely important article as a general internist. Its publication would be beneficial to many international practitioners.</p> <p>I have made modest suggestions for improving this timely manuscript using Microsoft Word 'Markup.' This file is attached and uploaded for the authors and editors.</p> <p>Please note that many of the 'Markups' are formatting changes needed to copy the manuscript to the Word file; I regard all suggested changes as 'minor.'</p> <p>I have not been able to make suggested changes for the Tables with Markup. The suggested Table changes noted below refer to the original Table numbers, not the proposed change in the Table numbers as I wrote in the Markup 'Comments' of the Word file</p> <p>For Table 1 Remove superscript 'a' from top and bottom of Table; change superscript 'b' to '*' I prefer directly under Blood Culture[above the (n=..)], not on the same lines (n=..) + & remove (+); Blood Culture - & remove (-) Change 'Females' to 'Female sex' Change 'History of any operations' To 'Recent surgical procedures' Change 'Use of immunosuppressant to 'Use of immunosuppressive drugs'</p>
-------------------------	--

	<p>Change 'Patient was not admitted from home' > To 'Patient admitted from health facility'</p> <p>Change 'Intraurethral catheter' To 'Indwelling urinary catheter'</p> <p>Suggest moving "Mean+/-SD to Line 'Clinical and laboratory findings, centered in the + Blood Culture and - Blood Culture space Change 'Hemoglobin A1C' to 'Hemoglobin A1c'</p> <p>Table 2 Change title to 'Blood culture (+) patients' diagnosis when BC obtained'</p> <p>In addition my comments in the Word file to change Table 2 to Table 1 and change Table 1 to Table 2. Table 2 is confused by (%) at the top of table and at the bottom of table listing 'Total' in % column</p> <p>Table 3 Bottom: delete 'a' & superscript 'b' change 'b' every to '*'; suggest bottom line 'CI = confidence interval; *p < 0.05</p> <p>Figure 1 (see issues of BMJ Open for proper format of text above & below Figure, Table, References)</p> <p>The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.</p>
--	--

REVIEWER	Lee, Yoon Seon University of Ulsan College of Medicine, Asan Medical Center, Seoul, Kore
REVIEW RETURNED	14-Dec-2015

GENERAL COMMENTS	<p>This study intended to show clinical factors associated with bacteremia and to establish indications for blood cultures among inpatients in general internal medicine. However, I have some concerns below,</p> <ol style="list-style-type: none"> 1. Authors did not describe the standard protocol for blood culture including indications and procedural guidelines if any in their hospital. 2. To answer the authors' questions in a cross-sectional study, the number of study sample is too small to have scientific significance. 3. To my best knowledge, there have been many previous studies which showed predictive factors of bacteremia in various clinical settings. So, this study may not be the first one. 4. Bacteremia is strongly related to patients' immune status and underlying diseases. It does not seem to be generalizable that certain factors are associated with bacteremia in all clinical situations even in cancer and non-cancer patients, or immunocompromized and immunocompetent patients. It looks more reasonable to specify the study group.
-------------------------	--

REVIEWER	Anna Mathew Northwell Health Hofstra Northwell School of Medicine United States
REVIEW RETURNED	20-Jan-2016

GENERAL COMMENTS	<p>Fukui et al conducted a retrospective chart review at one hospital in Japan from Jan 1 2011 until December 31, 2012. The objective was to compare clinical parameters to identify predictive factors of bacteremia and who needs blood cultures among general medical inpatients. The authors report that 28.5% of blood cultures drawn were positive. Predictive factors for positive cultures were age > 60, female sex, temperature >38, PMN >80% and ROC area was 0.79.</p> <p>I believe this study would be of interest to BMJ Open readers. However, I suggest the following issues should be addressed:</p> <ol style="list-style-type: none"> 1. Explanation of regression modelling: On page 8, line 128, the authors state that “variables significantly different by univariate analysis and other essential variables were entered into a multivariate logistic regression model”. The authors should explicitly state which variables were initially entered into the regression model, and what selection method was used to obtain the final model variables (i.e step-wise selection, forward selection etc). 2. Table 2 provides limited information beyond what is presented in Table 1 as Final Diagnosis of infection, and could be removed from the manuscript. 3. Limitations of small sample size: The study’s main and serious limitation is small sample size. Only 200 patients with blood cultures drawn are analyzed, and only 57 outcomes (positive blood cultures) are reported. Clinical factors which make intuitive sense such as HIV infection (n=9) and immunosuppressant use (n=12) are not significantly associated with bacteremia, likely due to small sample size. This must be clearly stated in the abstract and discussion sections. 4. Author recommendations: Given the serious limitations of small sample size, the authors final recommendations on how to use their findings should focus on hypothesis generation for future larger and prospective studies, rather than recommendations to change clinical practice based solely on the current findings.
-------------------------	--

REVIEWER	Michelle A. Kendall Center for Biostatistics in AIDS Research Harvard T.H. Chan School of Public Health USA
REVIEW RETURNED	18-Feb-2016

GENERAL COMMENTS	<p>Review of “Analysis of factors predictive of bacteremia among general medical inpatients” Fukui et al. provide a succinct summary of their study findings.</p> <p><u>Major comments</u></p> <ol style="list-style-type: none"> 1. Univariate and multivariate are used throughout. I recommend using univariable and multivariable since the
-------------------------	--

	<p>outcome of interest is univariate. A multivariable analysis is an analysis examining multiple independent variables. A multivariate analysis is an analysis that examines a multivariate dependent variable.</p> <ol style="list-style-type: none"> 2. Study Design: There is no mention of how the participants were selected for this study. What's needed appears in lines 47 and 48 of the Abstract. 3. Study Design (lines 116-123): Not all variables listed here are summarized in Table 1. Many variable names differ from or are less specific than those used in the table (e.g., surgery within a month versus history of any operations). 4. Results (diagnoses): Final diagnoses and infectious diseases seem to be used interchangeably and this is confusing. There are totals not provided in the table and it's not clear how some percentages are calculated (e.g., line 144). The numbers don't agree between Table 1 and Table 2 (e.g., infective endocarditis) and the discussion of the results (lines 142-146) are a little confusing since it's unclear which table is being referenced at which time. I'd recommend moving the diagnosis analysis from lines 151-154 to line 146 so that the discussion of the diagnoses stay together and the discussion of the univariate analysis results and the multivariable analysis will be together. Central line-associated bloodstream infection is missing in line 152. 5. Discussion (lines 189-200): Starting at line 193 (mention of women), it begins to feel like this came out of nowhere. Is this to explain why your study found higher risk in women while the other one found it in men? If so, the data presented here need to be in a table. Table 2 has some of the data, but it's in the bacteremic only. 6. Table 1: The results should be consistently summarized in the total column and the culture status columns. That is, N (%) and mean \pm SD. This lets the table match the text in many places where the text quotes data not in the tables (e.g., overall age reported in the Abstract and Results). Is it final diagnoses or infectious diseases? The percentages in the table are usually column percentages (which make the most sense), but there are 8 that have row percentages (central-line through fever). 7. Table 3: The Methods say that all variables significant in the univariable analysis (age, central venous line, body temperature, heart rate, neutrophils, blood urea nitrogen, and eGFR) and other essential variables (sex and creatinine) were entered in the multivariable model. The model presented does not contain blood urea nitrogen and eGFR, but does contain C-reactive protein. This needs to be corrected. In addition, I'd recommend fitting the univariable regression models just to see the ORs and p-values for all the variables in the multivariable model. If the ORs for each variable are similar (both >1 or both <1) in both the multivariable and the univariable models, then there's no confounding between the variable of interest and the others in the multivariable model. This is an important finding and should be noted (more evidence of independent associations if the p-values are nearly the same). If there is confounding, this also needs to be noted. To simplify the discussion of this additional analysis, the results of the univariable models can be added to Table 3.
--	---

	<p><u>Minor comments</u></p> <ol style="list-style-type: none"> 1. Abstract Objectives (line 42): The clinical parameters were not compared, they were examined. The rest of the sentence needs to be clarified. Maybe “to determine who needs blood cultures”? 2. Abstract Main Measures (line 52): Fisher's exact test, not the Chi-square, was used per the Methods section. 3. Abstract Main Measures (lines 55-58): The first use of an abbreviation should be written out (OR and CI) and the p-values should match those reported in the Results section. I prefer p-values to 3 decimal places when decisions are based on a 2-decimal cut-off. 4. Abstract Conclusions: These conclusions work well in the context of the Discussion, but they do not flow well from the Abstract Main Measures. Rewording may help. 5. Study Design (lines 113-115): Some blood cultures were coded as negative per some criteria. This is reasonable. However, it would be useful to note how many were coded in this manner. 6. Study Design (line 115): Before the list of clinical information included in the study, I'd recommend adding the text from lines 49 and 50 of the Abstract since it clearly states when and from where the information was gathered. This information appears at the end of the paragraph, but it can be interpreted as applying to only the variables listed in that sentence. 7. Study Design (line 116): BMI is listed here and in line 123. It seems more appropriate in line 123. 8. Study Design (line 128): It should be noted that diagnoses were not entered into the multivariable model and why (small numbers is sufficient justification). 9. Results (lines 147-154): Providing directions of the associations found would be valuable information. 10. Results (line 156): Sex and creatinine were added, not age. 11. Results (lines 160-164): It would be easier to follow the discussion of the results if the discussion matched the order in the table. 12. Results (line 167): It would be good to have the interpretation of the ROC results from lines 212-213 here as well. 13. Discussion (line 186): Please add a reference to this statement. 14. Discussion (line 193): The reference to Table 3 is incorrect. Studies are referenced, but not cited. 15. Discussion (line 207): Stating that an increase in CRP was delayed isn't supported by your data. 16. Discussion (line 210-211): This sentence would be more useful in the Methods section, combined with the sentence in lines 132-133. 17. Discussion (lines 228-230): The last sentence in this paragraph is a better version of the one used at the end of the Conclusions (lines 239-240). I'd recommend moving this one to that location or combining the two in some manner. 18. Table 2: Please comment on why there may be a lower percentage of bacteremia in those with central line-associated bloodstream infection since it seems that everyone with a bloodstream infection would have a positive blood culture. 19. Acknowledgements: Shouldn't this be funding?
--	--

VERSION 1 – AUTHOR RESPONSE

To the reviewer 1

1. I have made modest suggestions for improving this timely manuscript, Tables and Figure.

●All the points that you pointed out in Microsoft Word 'Markup' were revised. Then, we prepared the reply to your comments.

• Comment 1 Are all temperatures corrected from axillary to oral adding 0.5°C?

●The temperature was measured all in axillary and made all corrections as “axillary body temperature”.

• Comment 2 You fail to understand your reason for obtain Blood Cultures(BC) in afebrile patients, when your data indicate a

BT>38°C is a statistical risk factor for bacteremia-Please explain here in in the Discussion paragraph

●We revised the sentences in the abstract and discussion part, following your suggestion to clarify that these factors were independent from each other.

Our results emphasize the importance of taking blood cultures if the body temperature is greater than 38.0°C, from elderly patients, and for ordering a differential white blood cell count.

• Comment 3 Be consistant: heart rate in Table 3 or pulse rate in Methods section.

●We unified all as “pulse rate”.

• Comment 4 Perhaps change Table 2 to table 1 and change table 1 to table 2. Table 2 is confused by % at the top of table and bottom of table listing totals in % column Perhaps better to modify and show the derivation of 130 pt w/ID Diagnosis(Dx)

Explain $130 + 57 = 187$.. $200 - 187 = 13$ had non ID Dx; yet $45 + 25 = 70$ had non ID Dx??

●We switched Table 1 and Table 2 to each other following your suggestion. In addition, the confusing original Table 2 was revised following your suggestion.

• Comment 5 This paragraph may be shortened with comments that your + BC patients did not have low BT Low (SD 37.1), or the paragraph can be deleted. In its place you might write a paragraph about the differences between bacteremia and sepsis(SIRS) with references.

●We added the reference 26 about the very new (Organ Failure Assessment (qSOFA) suggesting sepsis and changed the sentence as follows.:

These unique phenomena of elderly might cause lack of abnormality in Organ Failure Assessment (qSOFA) score (systolic hypotension [≤ 100 mm Hg], tachypnea [≥ 22 /min], or altered mental status)²⁶
In such patients without signs of sepsis, positive blood culture results could be the only clue to the correct diagnosis, leading to appropriate medical treatment and a good outcome.

• Comment 6 Do you need to have data in the results section for this statement or list a reference?

●We corrected the sentence following your comment, and the speculative sentences below were deleted from the discussion part.

For multivariate analysis, data categorized by usual clinical action values were more practical then use of the continuous data result.

To the reviewer 2

1. Authors did not describe the standard protocol for blood culture including indications and procedural guidelines if any in their hospital.

●We totally agree with the reviewer’s comment. The aim of this retrospective study is to reveal the risk

factors of positive blood culture among hospitalized GIM patients in order to develop the criteria to obtain blood culture. We added some comments about the study purpose, limitation of this study and necessity of prospective research in the future.

2. To answer the authors' questions in a cross-sectional study, the number of study sample is too small to have scientific significance.

●We appreciate your suggestion. We added the following sentences as limitation.

This study is a retrospective study without common criteria for obtaining blood cultures with a small number of patients. In addition, the lower percentage of bacteremia cases with the central line, use of immunosuppressive drugs and HIV infection makes subgroup analysis of each underlying condition difficult in this study.

3. To your best knowledge, there have been many previous studies which showed predictive factors of bacteremia in various clinical settings. So, this study may not be the first one.

●We appreciate your comment. We revised the sentences as follows to avoid the readers' confusion.

This study conducted a direct comparison of patients with positive and negative blood cultures in order to identify factors predictive of bacteremia among general medical inpatients.

4. Bacteremia is strongly related to patients' immune status and underlying diseases. It does not seem to be generalizable that certain factors are associated with bacteremia in all clinical situations even in cancer and non-cancer patients, or immunocompromized and immunocompetent patients. It looks more reasonable to specify the study group.

●We agree with your suggestion. This comment seemed to be related to the second comment. We added the following sentences as limitation.

This study is a retrospective study without common criteria for obtaining blood cultures with a small number of patients. In addition, the lower percentage of bacteremia cases with the central line, use of immunosuppressive drugs and HIV infection makes subgroup analysis of each underlying condition difficult in this study.

To the reviewer 3

1. Explanation of regression modelling: On page 8, line 128, the authors state that "variables significantly different by univariate analysis and other essential variables were entered into a multivariate logistic regression model". The authors should explicitly state which variables were initially entered into the regression model, and what selection method was used to obtain the final model variables (i.e step-wise selection, forward selection etc).

●We analyzed them by forced entry methods after controlling simultaneously for potential confounders. We added the following sentences to the text.

Variables that were significantly different by univariate analysis and other essential variables were entered into a multivariable logistic regression model to determine factors predictive of bacteremia. Univariate and multivariable logistic regression was used to calculate odds ratio (OR) and 95% coincidence interval (CI) after controlling simultaneously for potential confounders. Variables introduced to the model by forced entry method were female sex, age, pulse rate, axially body temperature, central venous line, neutrophil, creatinine and CRP. BUN and eGFR were not entered into multivariable analysis, because of regarding effects of the multicollinearity on creatinine and sex.

2 Table 2 provides limited information beyond what is presented in Table 1 as Final Diagnosis of infection, and could be removed from the manuscript.

●Because another reviewer recommended us to switch Table 1 and Table2 to each other and leave them in this manuscript, we revised the tables to make the contents more valuable.

3 Limitations of small sample size: The study's main and serious limitation is small sample size. Only 200 patients with blood cultures drawn are analyzed, and only 57 outcomes (positive blood cultures) are reported. Clinical factors which make intuitive sense such as HIV infection (n=9) and immunosuppressant use (n=12) are not significantly associated with bacteremia, likely due to small sample size. This must be clearly stated in the abstract and discussion sections.

●We appreciate your suggestion. We added the following sentences to limitation.

This study is a retrospective study without common criteria for obtaining blood cultures with a small number of patients. In addition, the lower percentage of bacteremia cases with the central line, use of immunosuppressive drugs and HIV infection makes subgroup analysis of each underlying condition difficult in this study.

4. Author recommendations: Given the serious limitations of small sample size, the authors final recommendations on how to use their findings should focus on hypothesis generation for future larger and prospective studies, rather than recommendations to change clinical practice based solely on the current findings.

● We totally agree with the reviewer's comment. The aim of this retrospective study is to reveal the risk factors of positive blood culture among hospitalized GIM patients in order to develop the criteria to obtain blood culture. We added some comments about the study purpose, limitation of this study and necessity of prospective research in the future.

To the reviewer 4

1. Univariate and multivariate are used throughout. I recommend using univariable and multivariable since the outcome of interest is univariate. A multivariable analysis is an analysis examining multiple independent variables. A multivariate analysis is an analysis that examines a multivariate dependent variable.

●We agree with your suggestion. All "multivariate" in the manuscript was changed to "multivariable".

2. There is no mention of how the participants were selected for this study. What's needed appears in lines 47 and 48 of the Abstract.

●This is a cross-sectional retrospective study all the hospitalized GIM patients with blood culture results. We revised the description of the study design in the abstract.

3. Not all variables listed here are summarized in Table 1. Many variable names differ from or are less specific than those used in the table (e.g., surgery within a month versus history of any operations).

●We revised the variables and unified the names in the text and Table 1 (revised as Table 2) following your suggestion.

4. Final diagnoses and infectious diseases seem to be used interchangeably and this is confusing. There are totals not provided in the table and it's not clear how some percentages are calculated (e.g., line 144). The numbers don't agree between Table 1 and Table 2 (e.g., infective endocarditis) and the discussion of the results (lines 142-146) are a little confusing since it's unclear which table is being referenced at which time. I'd recommend moving the diagnosis analysis from lines 151-154 to line 146 so that the discussion of the diagnoses stay together and the discussion of the

univariate analysis results and the multivariable analysis will be together. Central line-associated bloodstream infection is missing in line 152.

●We appreciate your suggestion. We revised the text, Table 1 (formally Table 2) and Table 2 (formally Table 1) to clarify how percentages were calculated and which table was referenced in the text. We moved the diagnosis analysis from the original position to the new position that you suggested. We added a description about central line-associated bloodstream infection (p=0 .0077).

5. Starting at line 193 (mention of women), it begins to feel like this came out of nowhere. Is this to explain why your study found higher risk in women while the other one found it in men? If so, the data presented here need to be in a table. Table 2 has some of the data, but it's in the bacteremic only.

- We agree with your suggestion. The relationship among women, pyelonephritis and risk of bacteremia could not be analyzed in this study. We deleted the related description from the text to avoid confusion.

6. The results should be consistently summarized in the total column and the culture status columns. That is, N (%) and mean \pm SD. This lets the table match the text in many places where the text quotes data not in the tables (e.g., overall age reported in the Abstract and Results). Is it final diagnoses or infectious diseases? The percentages in the table are usually column percentages (which make the most sense), but there are 8 that have row percentages (central-line through fever).

- There was the same suggestion from other reviewers. We consistently summarized the results in the total column and revised in Table1 (formally Table 2).

7. The Methods say that all variables significant in the univariable analysis (age, central venous line, body temperature, heart rate, neutrophils, blood urea nitrogen, and eGFR) and other essential variables (sex and creatinine) were entered in the multivariable model. The model presented does not contain blood urea nitrogen and eGFR, but does contain C-reactive protein. This needs to be corrected. In addition, I'd recommend fitting the univariable regression models just to see the ORs and p-values for all the variables in the multivariable model. If the ORs for each variable are similar (both >1 or both <1) in both the multivariable and the univariable models, then there's no confounding between the variable of interest and the others in the multivariable model. This is an important finding and should be noted (more evidence of independent associations if the p-values are nearly the same). If there is confounding, this also needs to be noted. To simplify the discussion of this additional analysis, the results of the univariable models can be added to Table 3.

- I added the below sentences in the method part.

Univariate and multivariable logistic regression were used to calculate odds ratio (OR) and 95% coincidence interval (CI) after controlling simultaneously for potential confounders. Variables introduced to the model by forced entry method were female sex, age, pulse rate, axially body temperature, central venous line, neutrophil, creatinine and CRP. BUN and eGFR were not entered into multivariable analysis, because of regarding effects of the multicollinearity on creatinine and sex.

- We added the results of the univariable models in Table3. From the results, we added the comments about confounding factors to the text as follows.

As shown in Table 3, pulse rate and placement of central venous line were thought to have significant affect by the univariate logistic regression, but the confounding factor might be present and these do not affect by the multivariable analysis. Similarly, female sex and axially body temperature could be recognized as the true risk factors by multivariable logistic regression analysis under the influence of confounding factor.

8.

(Minor comments)

1-19

- Thank you for your suggestions for improving this manuscript, Tables and Figure. All the points that you pointed out were revised.

VERSION 2 – REVIEW

REVIEWER	<p>Gerald H. Stein, MD, FACP, Courtesy Clinical Assistant Professor Department of Medicine College of Medicine University of Florida Gainesville, Florida, USA</p> <p>I not only know several of the authors because I consult with Dr. Naito's department staff twice yearly, but also I am anticipating a faculty appointment in Professor Naito's department next year, 2016.</p>
REVIEW RETURNED	03-Apr-2016

GENERAL COMMENTS	<p>Now your article reads much smoother. I appreciate your agreement with most of my 'Markup' comments.</p> <p>I am pleased you found and incorporated the recent JAMA article on severe sepsis into your Discussion section. BMJ readers enjoy noting new timely information.</p> <p>The rewriting of the tables with subsequent 'Results' changes greatly improves your manuscript. Thank you for making the time to make these changes suggested by all of the reviewers.</p> <p>Here are my minimal suggested changes to your manuscript for acceptance for publication:</p> <p>1. I had some difficult with the sentences below, from the Discussion section, from Page 14, Line 496:</p> <p>As shown in Table 3, pulse rate and placement of central venous line were thought to have significant affect in the univariate logistic regression, but the confounding factor might be present and these do not affect in the multivariable analysis. Similarly, female sex and axially body temperature could be recognized as the true risk factors by multivariable logistic regression analysis under the influence of confounding factor.</p> <p>Here is my suggested changes for these sentences:</p> <p>As shown in Table 3, the variables pulse rate and placement of central venous line, did have significant impact on the univariate logistic regression model. However, these two variables had no affect on the multivariable analysis suggesting a confounding factor might be present. Similarly our multivariable logistic regression analysis showed female sex and axillary body temperature were significantly important risk factors, perhaps under the influence of a confounding factor.</p> <p>2. 'axillary' is mistyped throughout the manuscript as 'axially.' Please change to correct spelling in text and tables.</p> <p>3. Further suggested changes for your improved Table 2:</p> <p>Table 2</p> <p>Total Blood culture + Blood culture - Line 5 n=200(% BC) n=57(% BC+) n=143(% BC-)</p>
-------------------------	---

	<p>[Please be careful with the left column indentations and alignments. For example:]</p> <p>Female sex History of malignant diseases Recent surgical.... Use of... HIV... Patients admitted... Preceding antimicro...</p> <p>Medical Devices Nasogastric tube ETC</p> <p>Thank you for your contribution to the medical literature advancing our understanding of bacteremia.</p>
--	--

REVIEWER	Michelle Kendall Harvard T.H. Chan School of Public Health, USA
REVIEW RETURNED	06-Apr-2016

GENERAL COMMENTS	<p>The authors provide a succinct summary of their study findings. I have made some modest suggestions for clarifying and improving this manuscript.</p> <p>Major comment</p> <p>The Methods say that all variables significant in the univariable analysis and other essential variables were entered in the multivariable model. The significant variables were age, central venous line, body temperature, pulse, neutrophils, blood urea nitrogen, and eGFR . It is explained in Methods why BUN and eGFR are excluded (lines 151-152), but the Results (lines 183-184) say that eGFR is included since it explains why female sex and creatinine are added (the essential variables). Since eGFR is dependent on age, sex, and creatinine, it is not surprising that collinearity was detected. However, eGFR needs to be adjusted by age, sex, and creatinine, so all four should be in the multivariable model. If it is decided that eGFR needs to be excluded due to the detected collinearity, then sex and creatinine need to be excluded as well. In addition, either CRP needs to be removed from the model or an explanation needs to be added to explain why this non-significant variable was included.</p> <p>Minor comments</p> <ol style="list-style-type: none"> 1. Abstract (line 76): It might be better to reword this sentence as "Our criteria included age... neutrophilia; these are readily available clinical action values." 2. Study Design (line 127-128): There is no mention of the timing of the participants selected. What's needed appears in lines 50-51 of the Abstract. For example, "The blood culture results were collected retrospectively from the clinical laboratory database from all general inpatients who had blood cultures taken from January 1, 2011 to December 31, 2012." 3. Study Design (line 137): Axillary is spelled wrong here and in
-------------------------	---

	<p>many other places.</p> <p>4. Study Design (line 140): Glucose was extracted from the charts, but not summarized in Table 2.</p> <p>5. Study Design (lines 150-160): This section needs a little work. The sentence that begins “Variables introduced” (line 157) can be deleted since a similar sentence begins in line 149. The sentence about why diagnoses were not considered in the model should be moved to after the sentence ending in line 152. The sentence about the ROC curve should be moved to after the other sentences describing model creation.</p> <p>6. Results (lines 185-187): I feel the true reason for using neutrophils only instead of total WBC, neutrophils, and lymphocytes is that the three variables are highly correlated.</p> <p>7. Discussion (line 229): What is meant by “under the influence of confounding factor”?</p> <p>8. Conclusions (Abstract line 66 and main text lines 268 and 272): Female sex was significant in the multivariable model, but was omitted from the conclusions in both the Abstract and the main text.</p>
--	--

VERSION 2 – AUTHOR RESPONSE

To the reviewer 1

1. I had some difficulty with the sentences below, from the Discussion section, from Page 14, Line 496
2. 'axillary' is misspelled throughout the manuscript as 'axially.' Please change to correct spelling in text and tables.
3. Further suggested changes for your improved Table 2:
 - Thank you for your suggestions for improving this manuscript. We agree with all your suggestions. All the points that you pointed out were revised.

To the reviewer 4

1. Major comment

The Methods say that all variables significant in the univariable analysis and other essential variables were entered in the multivariable model. The significant variables were age, central venous line, body temperature, pulse, neutrophils, blood urea nitrogen, and eGFR. It is explained in Methods why BUN and eGFR are excluded (lines 151-152), but the Results (lines 183-184) say that eGFR is included since it explains why female sex and creatinine are added (the essential variables). Since eGFR is dependent on age, sex, and creatinine, it is not surprising that collinearity was detected. However, eGFR needs to be adjusted by age, sex, and creatinine, so all four should be in the multivariable model. If it is decided that eGFR needs to be excluded due to the detected collinearity, then sex and creatinine need to be excluded as well. In addition, either CRP needs to be removed from the model or an explanation needs to be added to explain why this non-significant variable was included.

- Thank you for your suggestions for improving this manuscript. We agree with your suggestion. We entered eGFR into the multivariable model and removed CRP. The results were changed: Age greater than 60 years old, female sex, pulse rate greater than 90/minute and neutrophilia were the independent risk factors for the positive blood culture results. So we rewrote results, discussion, conclusions and abstract.

Minor comments

- 1 Abstract (line 76): It might be better to reword this sentence as “Our criteria included age... neutrophilia; these are readily available clinical action values.”
2. Study Design (line 127-128): There is no mention of the timing of the participants selected. What's needed appears in lines 50-51 of the Abstract. For example, “The blood culture results were collected retrospectively from the clinical laboratory database from all general inpatients who had blood cultures

taken from January 1, 2011 to December 31, 2012.”

3. Study Design (line 137): Axillary is spelled wrong here and in many other places.

- We agree with your suggestion. The all points that you pointed out were revised.

4. Study Design (line 140): Glucose was extracted from the charts, but not summarized in Table 2.

- Glucose was not extracted from the charts. We deleted it and evaluated HbA1c.

5. Study Design (lines 150-160): This section needs a little work. The sentence that begins “Variables introduced” (line 157) can be deleted since a similar sentence begins in line 149. The sentence about why diagnoses were not considered in the model should be moved to after the sentence ending in line 152. The sentence about the ROC curve should be moved to after the other sentences describing model creation.

6. Results (lines 185-187): I feel the true reason for using neutrophils only instead of total WBC, neutrophils, and lymphocytes is that the three variables are highly correlated.

- We agree with your suggestion. The all points that you pointed out were revised.

7. Discussion (line 229): What is meant by “under the influence of confounding factor”?

- Because it was hard to be understood, we rewrote it.

8. Conclusions (Abstract line 66 and main text lines 268 and 272): Female sex was significant in the multivariable model, but was omitted from the conclusions in both the Abstract and the main text.

- We rewrote result, discussion, conclusion and abstract mentioning female sex.

VERSION 3 - REVIEW

REVIEWER	Gerald H. Stein, MD, FACP Department of Medicine College of Medicine University of Florida Gainesville, Florida, USA I not only know several of the authors because I consult with Dr. Naito's department staff twice yearly, but also I am anticipating a faculty appointment in Professor Naito's department next year, 2016.
REVIEW RETURNED	13-May-2016

GENERAL COMMENTS	I find your manuscript ready for publication. The confusion about body temperature elevation has been removed, suggested by another reviewer. Table 2 re-formatting has improved it. Now your important study more clearly suggests that the basic clinical markers of age greater than 60 years old, female sex, pulse rate greater than 90 BPM, and neurophilia greater than 80%, predict the increased risk for bacteremia with its need for blood cultures.
-------------------------	---

REVIEWER	Michelle Kendall Harvard T.H. Chan School of Public Health Boston, MA, USA
REVIEW RETURNED	18-May-2016

GENERAL COMMENTS	There are issues with the logistic regression models that can be resolved either through clarification or re-fitting of the models. Please see the attached Track-changed Word version of the manuscript. I did not review the references. The reviewer also provided a marked copy with additional
-------------------------	--

	comments. Please contact the publisher for full details.
--	--

VERSION 3 – AUTHOR RESPONSE

To the reviewer 1

- Thank you for your supportive opinion for publication.

To the reviewer 4

1. Why is creatinine included in the model? It was not significant in Table 2. Either explain why creatinine is included (essential or confounder or what) or remove creatinine from Table 3 (and update the multivariable model).

- Thank you for your suggestions for improving this manuscript. The p-value of creatinine in univariate analysis in Table 2 was revised as significant, because it was incorrectly described. The other variables were checked again and confirmed to be correct.

VERSION 4 – REVIEW

REVIEWER	Michelle Kendall Harvard T.H. Chan School of Public Health, USA
REVIEW RETURNED	13-Jun-2016

GENERAL COMMENTS	<p>This has become a very nice paper. Thank you for letting me review it. I found one small but important discrepancy in the Results. Please see the attached Word document correcting the issue.</p> <p>The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.</p>
-------------------------	--