Author's response to reviews

**Title:** Clinical outcomes and molecular typing of heterogenous vancomycin-intermediate Staphylococcus aureus bacteremia in patients in intensive care units

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**Author's response to reviews:** see over
Dear editor, 

We would like to submit the revised manuscript MS: 4720391841573669 entitled “Clinical outcomes and molecular typing of heterogenous vancomycin-intermediate Staphylococcus aureus bacteremia in patients in intensive care units” for revision. We deeply appreciate the reviewers’ valuable comments. Our manuscript have been made a comprehensive revision according to these comments point to point. The revised text will be represented by red color in the manuscript. All authors have agreed to the submission and we hope our manuscript may be more logical and readable.

Thank you for your attention.

Sincerely Yours,

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Reviewer reports:

Reviewer #1:
Comments to Author(s): The information below constitutes my objective and unbiased review of the manuscript titled “Clinical outcomes and molecular typing of heterogenous vancomycin-intermediate Staphylococcus aureus bacteremia in patients in intensive care units” (BMC-ID 4720391841573669) for publication consideration in BMC Infectious Diseases. Comments are as follows:

General Comment: Overall interesting retrospective study focused in hVISA bacteremia patients in ICUs. However, the manuscript needs major revisions to make it acceptable as there is a lack of detail, numerous spelling/grammatical errors, and incorrect use of words throughout (association, cause, risk factors, predictors, confounding). Further, without proper statistical methods (multivariate logistic regression) to assess for independent predictors the use of the words “risk factors” and “predictors” in this study is inappropriate. The study appears to be purely descriptive and I caution the authors on how they present and interpret the results.

Major Compulsory Revisions

Abstract:
1. Line 5: The use of the word “bacteremia” is not correct, the source of infection is irrelevant as hVISA can appear in any type of isolate (tissue, sputum, etc).
Response: Thank you for the reviewer’s comment and we delete the word “bacteremia”.

2. Methods: specify molecular typing and outcomes assessed
Response: Thanks the reviewer’s comment about this and we have revised our manuscript as” Multilocus sequence typing (MLST), staphylococcal cassette chromosome mec (SC Cmec) and the accessory gene regulator (agr) typing were performed individually. Clinical outcomes including in-hospital mortality, length of stay in intensive care unit and hospital after MRSA bacteremia of the patients were also analyzed.”

3. Results: lines 16 -18 cannot make this statement using descriptive statistics (X2 or Fishers exact test). Page 3 line 20 and page 4 this statement cannot be made without appropriate statistical analysis.
Response: Thanks the reviewer’s comment and we have revised it with logistic regression analysis.
Introduction:

1. Page 5, line 4: Consider using “blood” or “circulatory system” instead of “bacteremia”. May also consider deleting this sentence and replacing it with a statement that depicts why it is so concerning.
Response: Thanks the reviewer’s comment, we have used “circulatory system” instead of “bacteremia”.

2. Page 5, line 10: Would consider re-wording this statement to “However, recent attention has focused on the emergence of isolates with decreased vancomycin susceptibility.” You mentioned “poor clinical outcomes” here but do not specify until later in the background. Therefore recommend to mention it later.
Response: Thanks the reviewer’s comment.
(1) We have revised our manuscript as your comment.
(2) We have deleted this statement because we have mentioned it later.

3. Page 5, lines 11 – 14: Would consider breaking up and clarifying this sentence. Please also cite this sentence. Consider deleting the word “bacteremia” in “…has been considered a phenotype of MRSA bacteremia…” as the source of infection is not technically a phenotype and including the word “bacteremia” is irrelevant.
Response: Thanks the reviewer’s comment. We break up the sentence and delete the word “bacteremia”.

4. Page 5, lines 15: Consider deleting the word “isolate” after “vancomycin susceptible S. aureus”
Response: Thanks the reviewer’s comment and we have deleted it.

5. Page 5, lines 16 – 18: Consider changing to “…. Frequently occur in isolates with a minimum inhibitory concentration (MIC) within the susceptible range (# 2 mg/L by E-test).”
Response: Thanks the reviewer’s question and comment and we change our manuscript as following: frequently occur in isolates with a minimum inhibitory concentration (MIC) within the susceptible range (\( \geq 2 \) mg/L by E-test)

6. Page 6, lines 5 – 6: Consider deleting this sentence as it is not relevant to you
study and you have already mentioned the prevalence

Response:
Thanks the reviewer’s comment and we have removed this sentence.

7. Page 6, lines 6 – 10: Consider making this statement into the start of a new paragraph and rewording to “Infections caused by hVISA have been associated with vancomycin treatment failure, persistent bacteremia, and prolonged hospital length of stay. However, the impact of hVISA bacteremia on mortality has yet to be determined.” Also consider adding a brief statement on these studies and their limitations as well as any data on hVISA in patient’s in the ICU.

Response:
We deeply appreciate the reviewer’s important comments and we reword it.

8. Page 6, lines 9 – 16: Consider removing this information from background and placing it in your discussion.

Response:
Thanks the reviewer’s comment. We do more detailed description about these information in Discussion section.

9. Page 6, line 17: please specify “risk factors” or define in methods section.

Page 11, line 12 -14 states “risk factors for mortality” but is not described in statistical analysis (see comments for that section). This would be another study aim.

Response:
Thanks the reviewer’s comment on the issue.
(1) We revised our manuscript at Page 6, line 16 as: “The aim of this study was thus to investigate the prevalence and genotype of hVISA among patients in ICUs with MRSA bacteremia. The risk factors for hVISA genotype such as age, primary infection site, comorbidity or history of glycopeptide exposure were also analyzed.”

(2) We have revised the statistical analysis and mentioned in the Method section. We also revised it as secondary aim at Page 6, line 17 as: “A secondary aim was to compared the clinical features and outcomes between these patients with hVISA and ancomycin-susceptible S. aureus (VSSA) bacteremia. Finally, we investigated the independent predictors for in-hospital mortality between survivor and non-survivor.”

10. Page 6, lines 17 – 19: In abstract you mentioned what appears to be a secondary aim comparing survivor and non-survivor groups but it is not mentioned here.
Response:
Thanks the reviewer’s comment and we have revised it at Page 6, line 19 as following: “Finally, we investigated the independent predictors for in-hospital mortality between survivor and non-survivor.”

Methods:
Study design and patients
1. Page 8, line 3: Consider providing more information on the type of medical center (how many beds, number and types of ICUs).
Response:
Thanks the reviewer’s comment on the type of medical center and we revised as following” in a tertiary medical center with a 3700-bed general ward and a 278-bed adult ICU in northern Taiwan.”

2. Page 8, line 4: Please clarify if it was all patients “admitted” to the ICU or in the ICU at the time of the MRSA isolate? How did you define bloodstream infection?
Response:
Thanks the reviewer’s comment.
(1) For the first question, we enrolled patients with MRSA bacteremia and were treated in ICU, we revised our manuscript as: “patients with MRSA bloodstream infection (BSI) and treated in ICUs were eligible for the study.”
(2) For the second question, we define bloodstream infection according to the CDC definition and we add a description at Page 8, line 6 as following” The definition of MRSA BSI was patients with MRSA in blood cultures and met the Centers for Disease Control and Prevention (CDC) criteria for primary bloodstream infection”

3. Page 8, line 7: “only the data of the first episode was analyzed” do you mean the first isolate? How did you define recurrent and persistent bacteremia?
Response:
Thanks the reviewer’s comment to the issue.
(1) We indeed choose the first isolate of MRSA during the admission for molecular typing and collect clinical data of that time. So we revised the manuscript as following: “only the data of the first episode was analyzed.”
(2) The recurrent bacteremia means two separate infection episode during the same admission period. However, persistent bacteremia mean there was still obvious infection signs (fever, dyspnea or leukocytosis) and MRSA-positive in the following blood culture more than 7 days after appropriate glycopeptide therapy

4. General: were patients that had other infections caused by other organisms at
the time of MRSA bacteremia included? Please comment.

Response:
Thanks the reviewer’s comment. As Page 8 mention, only “single pathogen in blood culture were included”. In the 117 screened patients, all were only MRSA- positive in blood culture.

Clinical data
1. Page 8, line 10: Using the word “all” is confusing throughout this manuscript as it can have several implications. Consider avoiding the word “all” unless it is defined (i.e. all patients included in the study, all patients in the hVISA group, etc). For this line consider stating “Data collection from patient medical records included: “
Response:
Thanks the reviewer’s comment that we have revised manuscript as recommendation.

2. Page 8, lines 10 – 14: Do you mean Charlson comorbidity index? Please explain how you identified the primary site of infection, was it by assessment of other MRSA-positive cultures at the time of the MRSA blood culture or by medical notes in chart? Why choose the previous one month for vancomycin exposure? Other studies have done 3 - 6 months previous exposure. For receipt of chemotherapy or immunosuppressive therapy, was a certain dose chosen as the threshold of immunosuppression? What was it? Was there a time period of these treatments-- previous 1 month or was it longer? Please specify “other” immunosuppressive therapy in parenthesis. For “drugs used in this episode” do you mean concomitant antibiotics used? Please specify “status at discharge (alive? Deceased? Persistently infected?).
Response:
We deeply appreciate the reviewer’s important comments.
(1) Yes, it was Charlson comorbidity score and we have corrected it.
(2) We determined the primary site of infection was by assessment of other MRSA-positive cultures at the time of the MRSA blood cultures, we add this definition in the paragraph.
(3) To survey the correlation of hVISA and vancomycin exposure, some studies choose 3-6 months previous exposure, but others may choose previous 30 days (Casa pao et.al Antimicrob Agents Chemother. 2013 Jun 24; van Hal SJ et al. PLoS One 2011 Jun 21 ). We choose the previous 30 days because most of our patients developing MRSA bacteremia within the 30 days after admission and none of them was re-admission within the recent 3 months.
(4) The time period of chemotherapy or immunosuppressive therapy was previous
1 month. We also add the definition of other immunosuppressive therapy in the Page 8 line 18 as following” Other immunosuppressive therapy included $\geq 10$ mg/day prednisone or equivalent for more than 2 weeks or any dose of another immunosuppressant.”

(5) Yes, that was concomitant antibiotics used and we revised it.

(6) We add “(alive or deceased)” to specify the status at discharge.

3. Page 8, lines 14 – 19: Please clarify “in-hospital mortality after MRSA bacteremia”. Length of hospital stay, does this include ICU length of stay (LOS), LOS before positive culture and/or after positive culture? Page 10, line 12 -14 you mention other types of LOS that were not defined in your methods section. Please include the definitions in methods section.
Response:
Thanks the reviewer’s comment on these issues.
(1) We defined in–hopital mortality at Page 9, line 11 as: “In-hospital mortality means patients’ status at discharge were deceased.”
(2) We revised our manuscript to define the length of ICU and hospital stay after MRSA bacteremia at Page 9, line 12 as: “Length of hospital stay after MRSA bacteremia was the numbers of days from the first positive blood culture to discharge or death.”
(3) We add a description to define the LOS in hospital before first MRSA bacteremia at Page 9, line 8 as following: “We also calculated the admission days to first culture, that mean the numbers of days from admission to performing blood culture.”

4. Please include how non-surnvivor and survivor groups were defined.
Response:
Thanks the reviewer’s comment. We add the definition of non-survivor and survivor groups in the Method paragraph Page 9, line 15 as following: “For the purpose of analysis, patients were stratified into survivor and non-survivor group according to the status of discharge (alive or deceased).”

5. General comment: Did you collect time to clearance of bacteremia between the hVISA and VSSA groups, vancomycin treatment failure, how the MRSA bacteremia was treated or time to appropriate therapy? Or history of MRSA infection?
Response:
Thanks the reviewer’s comment.
(1) It’s sorry that in our hospital, only when patient has persistent fever or other infection sign, such as cough, dyspnea and chest x-ray progression, we will re-do b
lood culture. We do not follow up blood culture after MRSA bacteremia regularly, so cannot clarify the time to clearance of bacteremia.

(2) The MRSA bacteremia was treated according to the guideline and standard dose (in our hospital, the dose of Vancomycin was 1 g q12h, may adjust dose according to the renal function, age and Ccr). In general, patients will receive 2 weeks treatment course.

Microbiological and molecular methods
1. Page 9, line 9. This is generally a short methods section. Specific detail on certain tests would be helpful. For example, how was agr dysfunction defined? How was a reduction of delta-hemolysin defined?
Response:
Thanks the reviewer’s comment.
(1) We defined agr dysfunction as manuscript mention: “agr dysfunction may result in a reduction or absence of of δ-hemolysin production”
(2) The screen of delta-hemolysin production by method of Cafiso v et al. reported (J Clin Microbiol, 2012). We also have made a brief description in the Method paragraph Page 10, line 11 and revised the reference.

2. How long were the isolates stored for before being tested? The can affect the expression of the hVISA phenotype.
Response:
Thanks the reviewer’s comment. The stored time of the isolates may affect the hVISA expression, so our isolates were frozen in the absence of vancomycin and rewarmed only one time and passaged at least 2 times on blood agar plate without vancomycin before testing.

Statistical analysis
1. Please state the type of analysis (logistic regression?) used to identify independent predictors “risk factors” of in-hospital mortality (?) while adjusting for confounding variables.
Response:
We deeply appreciate the reviewer’s important comments on the issue. We have revised our method of analysis and add the description of logistic regression to make our manuscript more readable.

2. If logistic regression was not used – the terms “predictors” and “risk factors” throughout the manuscript are incorrectly used and the results of this study are purely descriptive. Please advise as this will need to be adjusted in the manuscript.
Response:
Thanks the reviewer’s comment and we have adjusted the statistical method.

Results:
1. Page 10, lines 2 – 3: A large number of patients were excluded, but the exclusion criteria are not strict. Were the 69 excluded patients children or had multiple pathogens isolated? Please breakdown reasons for exclusion and the number for each (example: < 18 yo (n=3), etc)
   Response: Thanks the reviewer’s comment and we revised our manuscript at Page 12, line 3 as following:”In the 69 excluded patients, 2 were VISA and others were treated at ward.”

2. Page 10, lines 3 – 5: Consider combining these two sentences: “Of the 48 isolates, 14 (29.2%) harbored the hVISA phenotype.” Do not need to mention the method as it is already stated in the methods section.
   Response: Thanks the reviewer’s comment and we have revised it.

3. Page 10, line 10: A large number of patients in the hVISA group could not locate the origin of the infection. This has been previously found to be a risk factor for mortality, and as such is a possible confounder in this study. Was this considered in your statistically analysis? Please comment?
   Response: We deeply appreciate the reviewer’s important comments. Indeed a large number of patients could not locate the primary site of infection in the hVISA group. However, in outcome study, it seem to not relate to mortality (p= 0.632), so we do not enroll this factor in multivariate analysis.

4. Page 10, line 12: The hVISA group had a longer stay in the hospital prior to culture. The MLST results show that these isolates are genetically similar, but there were 2 different SCCmec types. Is it possible that these isolates are clones, and spread patient to patient within the hospital?
   Response: Thanks the reviewer’s comment. We also are afraid of the possibility of spreading patient to patient. We reviewed these patients medical records, and they belonged to different type of ICU and got the MRSA BSI at different time point, so the possibility should be low.

5. Page 10, lines 12 – 17: LOS was evaluated in multiple ways but not defined entirely in methods section (LOS in hospital, LOS in ICU, LOS prior to bacteremia (+ MRSA blood culture), LOS after bacteremia onset). Please define
in methods section.
Response:
Thanks the reviewer’s comment and we have added definition about these data in Method section.

6. Page 11: Where are the results for the broth microdilution MICs? Do they correlate well to the Etest?
Response:
Thanks the reviewer’s comment. The correlate between the roth microdilution MICs and Etest is well, we do not show it in text.

7. Page 11, lines 2 – 4: Please clarify this statement.
Response:
Thanks the reviewer’s comment on the statement. As some earlier studies mention, MRSA strains with high MIC increases the risk to ococu hVISA, our study also seemt to has the same result.

8. Page 11, line 9: Please comment on how you defined hospital-acquired infection and include in methods.
Response:
Thanks the reviewer’s comment. We revised our manuscript at Page 9, line 1 as f ollowing: “Hospital-acquired infection was defined as the positive blood cultures obtained more than 48 hours after admission.” in Method section.

9. Page 11, line 12: This mortality rate is very high, for both hVISA and VSSA. Other sources cite 20-30%. However, other factors associated are not discussed. For example, what antibiotics did these patients receive? Is there a vancomycin dosing protocol in the institution? Were vancomycin troughs taken, and were they in the target range?
Response:
Thanks the reviewer’s comment on the issue.
(1) Indeed, the in-hospital mortality of our patients is higher than other studies. There is several possible reason, first, the population is different. We focus on the patients treated in the ICU, so the severity of patients may be higher than others. Besides, we choose the in-hospital mortality as target of study, but not in ICU or 30-day mortality, this also may cause the different result.
(2) All the enrolled patients receive glycopeptide therapy, the dosage is according to the suggestion of guideline and adjusts according to the patients’ age, renal function and Ccr. At that time, there is no routine check trough level of vancomycin as treatment target in our hospital.
10. Page 11, line 12 – 16. Please include odds ratios and 95% confidence intervals for the hVISA phenotype, SOFA score, receipt of hemodialysis and CVA and which covariates were included in your (logistic?) model? If a multivariate logistic regression was not used an example of the interpretation of the results are as follows: patients in the non-survivor group had significantly higher SOFA score, presence of hVISA, and receipt of hemodialysis.

Response:
We deeply appreciate the reviewer’s important comments on the issue.
(1) We have added the odds ratios and 95% confidence intervals of these factors in our manuscript.
(2) We add the result of multivariate logistic regression analysis in the Result section, Page 13, line 18 as following” In a multivariate logistic regression analysis, SOFA score (OR 1.39; 95% CI 1.07-1.8; p=0.014) and hVISA (OR 11.8; 95% CI 1.1-127.0; p=0.042) were found to be independent predictors of in-hospital mortality.”, which is also shown in Table 4.


Response:
Thanks the reviewer’s comment and we add the definition in Method section, Page 9, line 5 as following: “During the treatment course of MRSA bacteremia, if patients received norepinephrine treatment more than 5 µg per minute or an equivalent dose of other vasopressor for 4 hours or more was defined as shock episode.”

Discussion:
1. General comment:
Response:
Thanks the reviewer’s comment.

2. Page 12, line 5 - 11: Consider combining these statements, they are repetitive.
Response:
Thanks the reviewer’s comment. We have deleted some statements.

3. Page 12, lines 11 – 17: Please clarify statement, not sure what point is trying to be made here. Please comment how this is relevant to your study as it was not previously stated that glycopeptide treatment failure was assessed herein.
Response:
Thanks the reviewer’s comment. In this statement, we re-mention the possible adverse effect of MRSA bacteremia cause by hVISA reported by earlier studies, but we did not observe the similar result in our study. We just want to emphasize that the effect of hVISA is still unclear and needs to be investigated continuously.
4. Page 13, lines 7 – 9: Please rephrase this statement. The use of the word “will” implies that this has been proven would consider substituting with “may”. Unclear on how “virulence factors” is related as the previous studies mentioned are about ST type and clinical outcomes.

Response:
Thanks the reviewer’s comment.
(1) “will” has been substituted by “may”.
(2) In this statement, we want to explain that although the same genotype( ST-239), but there is variable impact on clinical outcomes in different study. Other factor, like agr dysfunction, may be also play a role in the virulence and affect the outcome.

5. Page 13, lines 10 – 12 : Please reference this statement

Response:
Thanks the reviewer’s comment and we add a reference for this statement.

6. Page 13, lines 12 – 17: Please rephrase and include more detail on the studies that are being referenced (what outcomes did they evaluate). Please comment on how “the SCCmec type did not produce any adverse outcomes” in your study. This was not included in the results or methods/statistical analysis.

Response:
Thanks the reviewer’s comment on the issue.
(1) We revised our manuscript as following” but there no significant effect on outcomes such as vancomycin failure or persistent bacteremia were found in either study”.
(2) We revised our statement as “produce similar adverse outcomes”. Besides, we define the persistent bacteremia in the Method section.

7. Page 14, lines 5 – 7: “The agr dysfunction did not cause persistent bacteremia in our report” Persistent bacteremia was not previously mentioned in the methods or results of this manuscript. Further, due to the study design causation cannot be assessed, therefore the use of the word “cause” is inappropriately applied. Please comment and include in methods and results how this was defined and evaluated.

Response:
Thanks the reviewer’s comment.
(1) We have defined the “persistent bacteremia” in Method section.
(2) We delete the statement to avoid confusion.

8. Page 14, lines 8 – 9: Besides small sample size, the purpose of this study was
not to evaluate agr dysfunction on mortality. Would consider deleting this statement.
Response:
Thanks the reviewer’s comment and we have deleted this statement.

9. Page 14, lines 11 -17: Please clarify the relevance of these studies, unsure what point is being made here.
Response:
We deeply appreciate the reviewer’s important comments. In this statement, we want to emphasize the significant impact of MRSA bacteremia on the critical ill patients. There is also study reveals patients with MRSA bacteremia and transitted to ICU is independent predictors of mortality. However, study that investigate the clinical outcome of hVISA and predictors on critically ill patients is scarce, that’s why we want to conduct this study.

10. Page 14, lines 19: The term “confounding” is not used properly in this sentence.
Response:
Thanks the reviewer’s comment and we substitute the “confounding” with “predictive”.

11. Page 15, line 3: However there was no difference MRSA attributable mortality between hVISA and VSSA can you comment on this.
Response:
Thanks the reviewer’s comment. According to the definition of attributable mortality and clinical outcome analysis, genotype (hVISA or VSSA) is not a significant risk of mortality at the bacteremia episode, however, it can be a independent factors of mortality in in-hospital mortality.

12. Page 15, lines 5 – 6: Please specify “incomplete for some factors”.
Response:
Thanks the reviewer’s comment on the issue. Because this is retrospective study, some data, like CRP, Procalcitonin, Vancomycin trough level or even follow up blood culture to survey the time of bacteremia clearance cannot be collected completely. This may affect the result of data analysis.

13. Page 15, lines 8 – 9: Please comment on why the number of enrolled cases was not expanded
Response:
Thanks the reviewer’s comment. This study is retrospective and the period of our proposal is only 2 years, so we do not expand our data base. As the Conclusion
section mention, if expands the sample size, maybe we can get a more solid or different result. We hope there is a large scale study in the near future.

14. General comment: other limitations include single center, how long were the isolates stored for before they were tested? Prolonged storage can lead to loss of the hVISA phenotype, is it possible that some may have been missed? If the source of infection was not removed, this may have also confounded the results. Variables that were not collected (i.e. time to appropriate therapy) may also have impacted the results.

Response:
Thanks the reviewer’s comment. Indeed, these factors also may affect the patients outcomes and this is our limitation because we did not collect these data. We add a statement about these limitation in the Discussion section.

15. General comment: would focus on any data that described hVISA bacteremia in patients in addition to those in the ICU and compare it to the findings of this study. Consider referring to Casapao and colleagues (Antimicrob Agents Chemother. 2013 Jun 24) conducted a retrospective multicenter cohort study titled “Clinical outcomes in patients with heterogeneous vancomycin-intermediate Staphylococcus aureus (hVISA) bloodstream infection.

Response:
Thanks the reviewer’s comment.

(1) As previous mention, the data can be obtained was limited because retrospective study, but we still do our best and try to drive a beneficial result. We hope by our work may improve the quality of care in the field of critical care.

(2) We refer this paper and thanks for your suggestion.

Conclusions:
1. As previously stated the use of the word “predictors” is not appropriate.

Response:
Thanks the reviewer’s comment. We analyze the outcomes by multivariate analysis as your comment, so maybe “predictors” is appropriate after revising the data.

Tables:
1. Hemodialysis, shock after infection, and adequate antibiotic treatment is included in table 3 but not in table 1. Please comment why this was not included in table 1 and add the definition of these variables in the methods section under clinical data.

Response:
Thanks the reviewer’s comment. We revise our manuscript and add the data in table 1. We also add definition of these variables in Method section.
(1) Hemodyalysis meant patients ever receiving renal replacement therapy, either regularly or acute episode, during the bacteremia treatment.

(1) Antibiotic treatment was considered adequate if the used drug was susceptible to the isolated MRSA.

(2) During the treatment course of MRSA bacteremia, if patients received norepinephrine treatment more than 5 µg per minute or an equivalent dose of other vaso pressor for 4 hours or more was defined as shock episode.

2. Prior vancomycin therapy is included in table 1 but not in table 3. Please comment
   Response:
   Thanks the reviewer’s comment and we add the data in table 3.

3. Spell out CRP in table 1 and 2
   Response:
   Thanks the reviewer’s comment and we have revised it.

4. Please change Charlson score to Charlson comorbidity score in tables 1 and 2.

5. Table 2. Were the isolates with agr dysfunction associated to a certain SCCmec type or agr subgroup?
   Response:
   Thanks the reviewer’s comment.

   (1) We have changed the text.

   (2) The isolates with agr dysfunction associated to SCC mec II and III, 5 isolates belonged to II and 8 was III. 10 isolates are agr subgroup 1.
Reviewer #2: This retrospective study compared the in-hospital mortality attributed to heterogenous vancomycin-intermediate Staphylococcus aureus (hVISA) and vancomycin-susceptible Staphylococcus aureus (VSSA) bacteremias in 48 adults with MRSA-bloodstream infections hospitalized in ICUs of a Taiwanese tertiary medical center. Fourteen (29%) of the 48 isolates had the hVISA phenotype. Overall in-hospital mortality was 72.9% and significantly higher for the hVISA (92%) than VSSA phenotype (65%). However, mortality attributable to MRSA was similar for the two groups. Authors concluded that, for patients in ICUs with MRSA bacteremia, the hVISA phenotype was a factor predictive of mortality. The paper is clear and well-written. As underlined by the authors, the major limitations are the retrospective, single-center design and the small sample size.

Discretionary Revisions:
1. The overall mortality seems to be high compared to the literature and this point should be discussed as it could hamper the extrapolation of these results to other centers.
   Response: Thank you for the reviewer’s important comment. We add a statement “The results showed that the overall mortality in our study was relatively high, choosing the serious population only and selecting in-hospital mortality as an aim may correlate to the poor outcome.” in the Discussion section to make our manuscript more readable.

2. It would also be of informative to provide more detailed information on previous vancomycin therapy (length of treatment, dose) and compare it between the two groups.
   Response: Thanks the reviewer’s comment. It is really an important factor on outcome. Due to the limitation of retrospective study, we lack comprehensive data so we do not compare it between the two groups. In our institution, MRSA infection was treated according to the guideline and standard dose (in our hospital, the dose of Vancomycin was 1 g q12h, may adjust dose according to the renal function, age and Cr).

Minor essential revisions:
1. The sentence at the end of the second paragraph of the Discussion, “We did not observe any significant effect of treatment failure caused by hVISA in our study” is unclear and should be revised.
   Response: Thanks the reviewer’s comment. We revised our manuscript as following:” we did not observe the similar adverse effect caused by hVISA in our study”. From this statement, we want to emphasize that we will re-do blood culture in symptomatic patients, and although there is reports that hVISA will cause glycopeptide treatment...
failure or persistent fever, we did not observe the same adverse effect.

2. Tables that appear in the “supplemental materials” should be included in the text.
Response:
Thanks the reviewer’s comment and we have attached the Tables in the text.

Typographical error
1. In Methods: bioMérieux instead of bioM’erieux
Response:
Thanks the reviewer’s comment and we have corrected it.

2. In the Discussion
(1) End of 3rd paragraph: delete but (their results…)
Response:
Thanks the reviewer’s comment and we delete “but”.

(2) Verify the sentence in the 4th paragraph : “In a previous study, SCCmec II … in either study”
Response:
Thanks the reviewer’s comment and we revised the sentence as following:
In previous studies, SCCmec II was the predominant genotype and associated with reducing vancomycin susceptibility and increasing the presence of hVISA [26,27], but there no significant effect on outcomes such as vancomycin failure or persistent bacteremia were found in either study.