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

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Clinical characteristics of Carbapenem-resistant Klebsiella pneumoniae infection/colonization in the intensive care unit: a 9-year retrospective study</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>wang, ping; Zou, Xiaocui; zhou, boting; Yin, Tao</td>
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VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Tamburro, Manuela University of Molise Department of Medicine and Health Sciences Vincenzo Tiberio</th>
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<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>13-Jul-2022</td>
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<tr>
<td>GENERAL COMMENTS</td>
<td>This study evaluated the trend and epidemiology of carbapenem-resistant klebsiella pneumoniae in intensive care in China from 2012 to 2020. The study presents important findings useful in the field although revisions are required. Although risk factors for carbapenem-resistant Klebsiella pneumoniae (CRKP) infection/colonization in the hospital have been reported. Clinical characteristics of CRKP infection/colonization in the intensive care unit (ICU) remain scarcely investigated. Check this sentence in the abstract. Given the epidemiological and clinical challenges of CRKP isolates in the ICU, a general monitoring of CRKP infection and colonization in the ICU is imperative. Moreover, CRKP bloodstream infections have been widely reported, CRKP infection/colonization of other sites also need attention add references (see doi: 10.1016/j.jiph.2019.01.060). In the discussion something could be included for 2020 in relation to covid.19 especially for data collection. What about younger age? advanced age is more reported as risk factor for these infections. Figure 2b could be deleted as it is of bad resolution or otherwise reporting in another way. Figure 4 should be at better resolution as well. Figure 5 could be avoided. Please check also in the tables spelling.</td>
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<table>
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<tr>
<th>REVIEWER</th>
<th>Shropshire, William The University of Texas MD Anderson Cancer Center</th>
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<tr>
<td>REVIEW RETURNED</td>
<td>04-Dec-2022</td>
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<tr>
<td>GENERAL COMMENTS</td>
<td>This is an incomplete attempt at characterizing the burden of CRKP within the author’s institution. They seemingly did not attempt to define many covariates and results while reviewing EHR thus making their methodology unclear as well as results. There is a potential to better describe the clinical epidemiology here, but</td>
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otherwise, the manuscript simply only characterizes the carbapenem positivity of colonized/infection unique patients within their time frame.

Summary: Wang et al. provide a descriptive epidemiological characterization of carbapenem resistant *Klebsiella pneumoniae* within their institution in Xiangya hospital from 2012 to 2020. While it was alarming to see that an incredibly high proportion of *K. pneumoniae* isolates were carbapenem resistant (42.6%), it wasn’t clear exactly what the burden was given a lack of a population at risk measure. Additionally, the fact that infection vs. colonization was not clearly delineated made it unclear how impactful this level of resistance was in this teaching hospital. While I agree with the authors that local epidemiological investigations of CRKP are necessary, especially to trace local outbreaks, the authors have plenty of additional opportunities to more fully describe the extent of which these carbapenem resistance patterns are changing if they make their covariate/result definitions clearer.

Major comments:
Line 129: Given the retrospective nature of this study and that you’re not measuring baseline levels of colonization without your patient cohort, I would refrain from referring to your infection rates as ‘incidence’, rather, you’re establishing a proportion of total *K. pneumoniae* colonization/infection. You need a baseline ‘at risk’ population (i.e., number of admissions/patients within a time frame) to establish prevalence if you want to report prevalence measures.

Fig 1. The stacked barchart is not clear in presentation. The total fraction of CRKP/CSKP should equal 100, unless the barchart’s y-axis on the right was reflecting prevalence based on an unreported denominator.

Fig 3. Is this reflective of changes in susceptibility over time or the number of carbapenems tested for MICs? This is unclear based on data provided if susceptibility patterns are changing or if testing over time is changing. When you look at Table 1, it looks like it’s just a change in the number of isolates tested against each carbapenem given the small numbers of ETP/MEM/IMI that are non-susceptible to ≤2 carbapenems.

Minor Comments:

Line 95 – 100: Were these *K. pneumoniae* cultures arising from infection, colonization, or both?
Line 95 – 100: How were sources of culture infection/colonization determined?
Line 97: Should be “testing” not “texting”.
Line 111: Broth Microdilution
Line 125: Any other criterion for inclusion of covariates besides a backward stepwise variable selection method? Were any covariates chosen based on previous literature? What was the total number of observations included in the model? It should be explicitly stated what you’re modelling with your logit function (presumably CR status).
6. Response to comment(Reviewer 1): Although risk factors for carbapenem-resistant Klebsiella pneumoniae (CRKP) infection/colonization in the hospital have been reported. Clinical characteristics of CRKP infection/colonization in the intensive care unit (ICU) remain scarcely investigated. Check this sentence in the abstract.

Response: according to the reviewer’s suggestion, we have advised the sentence. Lines 33-38

7. Response to comment(Reviewer 1): CRKP infection/colonization of other sites also need attention add references (see doi: 10.1016/j.jiph.2019.01.060).

Response: according to the reviewer’s suggestion, we have added the reference. Line 110

8. Response to comment(Reviewer 1): In the discussion something could be included for 2020 in relation to covid.19 especially for data collection

Response: Thank you for your advice, there were no covid.19 patients in our hospital from January 2020 to November 2022, so we had no data of these patients.

9. Response to comment(Reviewer 1): What about younger age? advanced age is more reported as risk factor for these infections

Response: Thank you for your advice, we tried our best to verify the result. In similar studies, they[1-3] also found the median age of CRKP patients was younger than CSKP patients. Although we cannot explain this finding, it is possible that it constitutes a risk factor, and further studies are required to confirm the finding. Advanced age is more reported as a potential risk factor for the death of patients with CRKP infection/colonization[3, 4].

Four examples were list as below:

10. Response to comment(Reviewer 1): Figure 2b could be deleted as it is of bad resolution or otherwise reporting in another way

Response: according to the reviewer’s suggestion, we have deleted the original Figure 2B, resubmitted the new Figure 1. Line 329

11. Response to comment(Reviewer 1): Figure 4 should be at better resolution as well

Response: according to the reviewer’s suggestion, we have modified the Figure 3(original Figure 4). Line 344

12. Response to comment(Reviewer 1): Figure 5 could be avoided

Response: sources of CRKP and CSKP isolates were showed in Figure 4 (original Figure 5), and it helps us to explore whether KP originated in our ICU or transferred from other wards, allowing us to tailor surveillance actions based on our local circumstance. So we have retained Figure 4 (original Figure 5). Line 347
13. Response to comment(Reviewer 1): Please check also in the tables spelling

Response: according to the reviewer's suggestion, we have checked the spellings in the tables. Line 351

14. Response to comment(Reviewer 2): This is an incomplete attempt at characterizing the burden of CRKP within the author's institution.

Response: according to the reviewer's suggestion, we have added the statements of the burden of CRKP in our ICU. Lines 91-94

15. Response to comment(Reviewer 2): They seemingly did not attempt to define many covariates and results while reviewing EHR thus making their methodology unclear as well as results.

Response: according to the reviewer's suggestion, we have modified the definition of covariates and added the statements in the results. Lines 141-142, 159-160, 187-190

16. Response to comment(Reviewer 2): There is a potential to better describe the clinical epidemiology here, but otherwise, the manuscript simply only characterizes the carbapenem positivity of colonized/infection unique patients within their time frame.

Response: Thank you for your advice, which is very important. According to reviewer's suggestion, I have revised the description of epidemiology, and I will improve my scientific research level and make more achievements in the future.

In all, I found the editor and review's comments are quite helpful, and I revised my paper point-by-point. Thank you and the review again for your help.

VERSION 2 – REVIEW

REVIEWER | Shropshire, William
The University of Texas MD Anderson Cancer Center

REVIEW RETURNED | 24-Apr-2023

GENERAL COMMENTS
Summary: Wang et al. have improved on their initial manuscript to more accurately interpret their results related to the proportion of CRKP changes over time within their study population. There are some interpretation/clarification issues as well as minor grammatical/spelling issues though that should be addressed (e.g., Line 142: 'cephalosporins'). Listed below are further comments.

Major comments:
Line 120: As presented, this is not a case-control study. If so, you would be sampling based on a specific ratio of case/controls based on your definitions. In such a case where you sample based on outcome of interest, you cannot measure proportion changes in CRKP over time. I think initially as presented (a retrospective, single-center cohort study) is more appropriate.
Line 187 – 194: This is a really remarkable change of susceptibilities to each of the three carbapenems. I can't help, but think that this may be due to an information source bias. Did the Xiangya Hospital change AST protocol between 2012 and 2020? There are significantly less CRKP observations in 2012, but I would make sure that the hospital had consistent AST protocols throughout the study frame.
Minor comments:
Line 66: I would refrain from making the claim that this is the first study to explore characteristics of CRKP colonization/infection in the ICU. Perhaps this is true within your hospital system, but I don’t think it’s a necessary claim.
Line 134: MRNs are not demographics.
Line 261: I doubt pulmonary sources of Kp are colonization.

VERSION 2 – AUTHOR RESPONSE

1. Response to comment: There are some interpretation/clarification issues as well as minor grammatical/spelling issues though that should be addressed (e.g., Line 142: ‘cephalosporins’).

Response: Thank you for your advice, which is very important. According to the reviewer’s suggestion, we have made a careful revision, and all changes are marked in red in the manuscript.

2. Response to comment: As presented, this is not a case-control study. If so, you would be sampling based on a specific ratio of case/controls based on your definitions. In such a case where you sample based on outcome of interest, you cannot measure proportion changes in CRKP over time. I think initially as presented (a retrospective, single-center cohort study) is more appropriate.

Response: Thank you for your advice, and we also thought about it for a long time. According to the reviewer’s suggestion, we have revised it as originally presented.

3. Response to comment: Line 187–194: This is a really remarkable change of susceptibilities to each of the three carbapenems. I can’t help, but think that this may be due to an information source bias. Did the Xiangya Hospital change AST protocol between 2012 and 2020? There are significantly less CRKP observations in 2012, but I would make sure that the hospital had consistent AST protocols throughout the study frame.

Response: Thank you for your careful work. Yes, our hospital had consistent AST protocols throughout the study frame, and the antimicrobial susceptibility testing was carried out by bioMerieux VITEK-2 (bioMerieux). The carbapenems on the gram-negative Susceptibility Card are not fixed, which includes options such as one carbapenem (meropenem/imipenem/ertapenem), two carbapenems (meropenem + imipenem, meropenem + ertapenem, imipenem+ ertapenem), or three carbapenems (meropenem + imipenem + ertapenem). In 2012 and 2013, AST of KP isolates were tested against one or two carbapenems and did not test three carbapenems simultaneously. Consequently, the proportion of CRKP isolates that were non-susceptible to all three carbapenems was zero during those years (Figure 2). We deleted the origina Table 1, which resulted in missing some of the explanations for Figure 2. For better display of the results, we have redrawn Figure 2.

4. Response to comment: Line 66: I would refrain from making the claim that this is the first study to explore characteristics of CRKP colonization/infection in the ICU. Perhaps this is true within your hospital system, but I don’t think it’s a necessary claim.

Response: according to the reviewer’s suggestion, we have advised the sentence.

5. Response to comment: Line 134: MRNs are not demographics.

Response: according to the reviewer’s suggestion, we have deleted it.

6. Response to comment: Line 261: I doubt pulmonary sources of Kp are colonization

Response: Thank you for your careful work. In the study, we investigated clinical characteristics of KP infection and colonization. It has been reported that in the ICU, the colonization of K. pneumoniae
may increase the incidence of corresponding KP infections, and patients with CSKP colonization at admission were more likely to acquire CRKP colonization. 31% of patients who were colonized by carbapenemase-producing CRKP progressed to infection. In another article, we counted the number of CRKP respiratory tract infections and colonizations and found that in the ICU, CRKP infection was present in most of the patients with pulmonary sources of CRKP. The number of CRKP respiratory tract colonizations is less than the number of infections. KP respiratory tract colonizations also need attention.


All in all, we found the editor’s and review’s comments quite helpful, and we revised my paper point-by-point. Thank you again for your help.