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OPEN PEER REVIEW

Comparison of Respiratory Microbiota in Patients with and Without Hospital-Acquired Infection

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

4 comments · 2 May 2023 – 27 May 2023

Banafsheh Mashak Reviewer

MAJOR REVISION 2 May 2023

Dear Author: The manuscript entitled “Respiratory Microbiota in Elderly Impatiens with Hospital Acquired Infection” was carefully studied, and some comments were left in the manuscript.
Title: It would be better to correct the title to “Comparison Respiratory Microbiota in Elderly Patients with or without Hospital Acquired Infection”.
Line9: The elderly are persons >65 years old, not >%50 years old.
-In conclusion: Please use the results from the tables and all findings in the conclusion.
-Line 65: It is better to mention “ location, type of ICU and the type or kind of university”.
Line67: How are the two groups defined?
-Line 107: It is not clear what is meant by “checking platelets in infectious cases, alone ”.
-Explain the definition of the two groups (HAI and NHAI). Clarify the method of recruitment and the distinction between them.
-The roadmap for the methods used to carry out the work is not explained in detail.
-What are the reasons for hospitalization of the NHAI group?
- Tests for infection such as “CBC”, “C/A”, “U/C”, and “LP” should be included.
-I recommend that this article be directed by an infectious disease specialist or an ICU specialist.
My decision: major revision

Referee 1 Reviewer

MINOR REVISION 27 May 2023

Dear Authors
- Please mention the reference used for MIC.
- Which culture media were used for the identification of nosocomial infection isolates?
- In Table 1: If the primers were designed by the authors, they should explain the design method. If not, the authors should provide references for the primers used for each bacterium separately.
- Please list the positive control microorganisms for the antibiotic resistance test separately.
- Please report MDR for antimicrobial susceptibility (antibiotic resistance) of HAI isolates in Table 3.
My decision: minor revision

Amirreza Saadati Reviewer

MINOR REVISION 27 May 2023

Dear authors
-Provide correct and clear definitions and characteristics of variables such as HAI, NHAI, and the age of the elderly.
-Which protocol was used for antibiotic testing (such as CLSI)?
-Please omit "in" in line 219: This was also shown in in vivo studies.....
I recommend its publication with minor revision.
My decision: Minor Revision

Associate Editor

MAJOR REVISION 27 May 2023

Dear Authors
- Which university granted ethical approval for this research? What is the ethical code?
-The title should be corrected to “Comparison Respiratory Microbiota in Elderly Patients with or without Hospital Acquired Infection”.
-Line 9: Elderly persons are >65 years old, not >50 years old.
-In the conclusion: please use the results from the tables and all findings.
-Line 65: It is better to mention “ location, type of ICU and the type or kind of university”.
Line 67: How are the two groups defined?
-Please omit “in” in line 219: this was also shown in in vivo studies
-Line 107: It is unclear what is meant by “checking platelets in infectious cases, alone ”.
-Explain the definition of the two groups (HAI and NHAI). Clarify the method of recruitment and separation into the two groups.
-The roadmap for carrying out the work is not explained in detail.
-What are the reasons for hospitalization in the NHAI group?
- Tests for infection, such as “CBC”, “C/A”, “U/C”, and “LP”, should be included.
-Which protocol was used for antibiotic testing (such as CLSI)?
-Please mention the reference used for MIC.
-Which culture media were used for identification of nosocomial infection isolates?
-In Table 1: If the primers were designed by the authors, they should explain the method of primer design. If not, the authors should provide references for the primers used for each of the total bacteria separately.
-Please list the positive control microorganisms for antibiotic resistance testing separately.
-Please write and add “ Multi-drug resistant (MDR) ” for antimicrobial susceptibility (antibiotic resistance) of HAI Isolates in Table 3.
-Please show an image of qPCR (positive control + negative control + Ladder + positive samples) for each bacterium.
My decision: Major revision

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Chief Editor of

Thank you very much for your e-mail having the referee's comments about our article entitled " Simultaneous genetical detection of *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Haemophilus influenzae* in patients with treatment-resistant respiratory infection ". In response to the comments and suggestions in your letter, I would like to thank you and the referees for your valuable point of views and suggestions. Our changes in the text in response to respected referee are highlighted. **Q** is the question or suggestion raised by each of the respected referee and *Answer* is our explanation in response to the respected referee's suggestion.

Response to respected reviewer #1:

Q1. Correct and clear definitions and characteristics of variables such as(HAI and NHAI and age of Elderly)

Answer: Identification of HAI and NHAI patients were done by microbiological records and confirmation of doctors and nurses. We corrected the aforementioned variables in MS and highlighted by red color.

Q2. Which protocol have used for antibiotic test(such as CLSI?)

Answer: The CLSI protocols was used for antibiotics test and it was added to the 2.2 subsection of Materials and Methods section.

Q3. Please omit "in"line 219:This was also shown in in vivo studies

Answer: It was applied in Discussion section of MS.

Response to respected reviewer #2:

Q1. Please mention reference that used for MIC.

Answer: The reference was added and highlighted by blue color.

Q2- Which cultured media used for identification of nosocomial Infection isolates?

Answer: The media used for identification of nosocomial Infection isolates included blood agar, chocolate agar and macconkey agar media. All the media were mentioned in MS and highlighted by blue color.

Q3- In Table 1: If primers are designed by the authors, they should explain about the method of designation. If not, authors should bring their references for used primers of each one of total bacteria, separately.

Answer: We used Gene Runner software for designing the sequences of primers. Then, we blasted the sequences in NCBI database (https://www.ncbi.nlm.nih.gov/tools/primer-blast/) and after ensuring the accuracy of the sequences the synthesis of primers was done. This was added in MS and highlighted by blue color.

Q4- Please write control positive microorganisms for antibiotic resistance test, separately.

Answer: In the current study, S. pneumonia ATCC 19615, S. pyogenes ATCC 49619, H. influenza ATCC 33930, Neisseria PTCC 1773, B. fragilis ATCC 25285 and M. catarrhallis ATCC 19976 were used as standard strains. This was added in MS and highlighted by blue color.

Q5- Please write MDR for antimicrobial susceptibility (antibiotic resistance)of HAI Isolates in Table 3

Answer: The MDR was added in Table 3 as a column designated as resistance type.

Response to respected reviewer #3

Q1. Title:is better correct to"Comparison Respiratory Microbiota in Elderly Patients with or without Hospital Acquired Infection"

Answer: The title of MS was changed and highlighted by green color.

Q2. Line9:Elderly are persons >65 year s old not>%50 years old.

Answer: The Elderly was deleted in All part of MS.

Q3. In conclusion: please use results of tables and all finding in conclusion.

Answer: The conclusion was changed based on the results obtained in current study and highlighted by green color.

Q4. Line 65: It is better to mention " location, type of ICU and the type or kind of university

Answer: The current research was conducted in in the ICU-General of Pars hospital, Tehran, Iran which added in MS.

Q5. Line67: How are the two groups defined?

Answer: The Identification of patients was done by microbiological records and confirmation of doctors and nurses. This was added in MS.

Q6. Line 107:It isn't identified "checking platelets in infectious cases, alone ".

Answer: The levels of Platelets were stated in Table 2. Actually, we did not understand the meaning of this question.

Q7. Explain definition of two groups(HAI and NHAI)? Clear the method of recruitment and separation between them. The consent of the participants in research and permission of IRCT were not obtained.

*Answer: In line 68 We stated that "**The informed consent was obtained from human subjects"**. We explained two groups in MS. The Ethical letter was uploaded as supplementary file.*

Q8. the road map in the method of doing the work is not explained in detail.

Answer: We comprehensively described the method section in MS.

Q9. what are the reason for hospilatization of NHAIgroup

Answer: In Table 2 the Diseases section, we stated the reason why NHAI admitted to the ICU.

Q10. Tests for infection such as "CBC","C/A","U/C,"LP" should be included.

Answer: We added the CBC and U/C data.

Associate Editor 1:

Dear Authors

- This research was ethically confirmed by which university? What is the ethical code?

Answer: The research was approved by ethical community of Islamic Azad University, Science and Research Branch. This was added to MS. Also, the ethical letter was uploaded as supplementary file.

-Title is better correct to "Comparison Respiratory Microbiota in Elderly Patients with or without Hospital Acquired Infection"

Answer: The title was changed.

-Line9:Elderly are persons >65 year s old not>50 years old.

Answer: We deleted all Elderly words in MS.

-In conclusion: please use results of tables and all finding in conclusion.

Answer: The conclusion was changed based on study findings.

-Line 65: It is better to mention " location, type of ICU and the type or kind of university"

Answer: all the information were added in MS.

Line67: How are the two groups defined?

Answer: The identification was added in MS.

-Please omit "in"line 219:this was also shown in in vivo studies

Answer: The sentence was corrected.

-Line 107:It isn't identified "checking platelets in infectious cases, alone ".

Answer: The levels of Platelets were stated in Table 2. Actually, we did not understand the meaning of this question.

-Explain definition of two groups(HAI and NHAI)? Clear the method of recruitment and separation between them. The consent of the participants in research and permission of IRCT were not obtained.

Answer: All of these applied in MS.

-the road map in the method of doing the work is not explained in detail.

Answer: We revised the methods of study.

-what are the reason for hospilatization of NHAIgroup

Answer: The reason for hospitalization were described in disease section of MS.

- Tests for infection such as "CBC","C/A","U/C,"LP" should be included

Answer: We added the CBC and U/C data.

-which protocol have used for antibiotic test?(Such as CLSI)?

Answer: The Ref was added in method section of MS.

-Please mention reference that used for MIC.

Answer: The ref was added.

-Which cultured medias used for identification of nosocomial Infection isolates?

Answer: All the media were mentioned in article.

-In Table 1: If primers are designed by the authors, they should explain about the method of designation. If not, authors should bring their references for used primers of each one of total bacteria, separately.

Answer: The method for primer design was described in MS.

-Please write control positive microorganisms for antibiotic resistance test, separately.

Answer: All the control bacteria were mentioned in MS.

-Please write and add" Multi-drug resistant (MDR) "for antimicrobial susceptibility (antibiotic resistance)of HAI Isolates in Table 3 .

Answer: This was applied in MS.

-please show image of qPCR(positive control +negative control +Ladder +positive samples)for each bacteria.

Answer: the image of qPCR was added in MS (Figure 3).

Best regards,

2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Chief Editor of

Thank you very much for your e-mail having the referee's comments about our article entitled " **Comparison Respiratory Microbiota in Patients with or without Hospital Acquired Infection** ". In response to the comments and suggestions in your letter, I would like to thank you and the referees for your valuable point of views and suggestions. Our changes in the text in response to respected referee are highlighted. **Q** is the question or suggestion raised by each of the respected referee and *Answer* is our explanation in response to the respected referee's suggestion.

Response to respected reviewer #1:

Q1. Correct and clear definitions and characteristics of variables such as(HAI and NHAI and age of Elderly)

Answer: Identification of HAI and NHAI patients were done by microbiological records and confirmation of doctors and nurses. We corrected the aforementioned variables in MS and highlighted by red color in Line 69-70 of MS.

Q2. Which protocol have used for antibiotic test (such as CLSI?)

Answer: The CLSI protocols was used for antibiotics test and it was added to the 2.2 subsection of Materials and Methods section and highlighted in Line 81 of MS.

Q3. Please omit "in"line 219:This was also shown in in vivo studies

Answer: It was applied in Discussion section of MS and highlighted in Line 227-228 of MS.

Response to respected reviewer #2:

Q1. Please mention reference that used for MIC.

Answer: The reference was added and highlighted by blue color and highlighted in Line 83.

Q2- Which cultured media used for identification of nosocomial Infection isolates?

Answer: The media used for identification of nosocomial Infection isolates included blood agar, chocolate agar and macconkey agar media. All the media were mentioned in MS and highlighted by blue color and highlighted in Line 73-74 of MS.

Q3- In Table 1: If primers are designed by the authors, they should explain about the method of designation. If not, authors should bring their references for used primers of each one of total bacteria, separately.

Answer: We used Gene Runner software for designing the sequences of primers. Then, we blasted the sequences in NCBI database (https://www.ncbi.nlm.nih.gov/tools/primer-blast/) and after ensuring the accuracy of the sequences the synthesis of primers was done. This was added in MS and highlighted by blue color and highlighted in Line 96-99 of MS.

Q4- Please write control positive microorganisms for antibiotic resistance test, separately.

Answer: In the current study, S. pneumonia ATCC 19615, S. pyogenes ATCC 49619, H. influenza ATCC 33930, Neisseria PTCC 1773, B. fragilis ATCC 25285 and M. catarrhallis ATCC 19976 were used as standard strains. This was added in MS and highlighted by blue color and highlighted in Line 83-86 of MS.

Q5- Please write MDR for antimicrobial susceptibility (antibiotic resistance)of HAI Isolates in Table 3

Answer: The MDR was added in Table 3 as a column designated as resistance type and highlighted in line 164-165 of MS.

Response to respected reviewer #3

Q1. Title:is better correct to"Comparison Respiratory Microbiota in Elderly Patients with or without Hospital Acquired Infection"

Answer: The title of MS was changed and highlighted by green color in Line 1-2 of MS.

Q2. Line9:Elderly are persons >65 year s old not>%50 years old.

Answer: The Elderly was deleted in All part of MS in Line 8.

Q3. In conclusion: please use results of tables and all finding in conclusion.

Answer: The conclusion was changed based on the results obtained in current study and highlighted by green color in Line 227-233 of MS.

Q4. Line 65: It is better to mention " location, type of ICU and the type or kind of university

Answer: The current research was conducted in in the ICU-General of Pars hospital, Tehran, Iran which added in MS and highlighted in Line 66-67 of MS.

Q5. Line67: How are the two groups defined?

Answer: The Identification of patients was done by microbiological records and confirmation of doctors and nurses. This was added in MS and highlighted in Line 69-70 of MS.

Q6. Line 107:It isn't identified "checking platelets in infectious cases, alone ".

Answer: The levels of Platelets were stated in Table 2 in Line 123. Actually, we did not understand the meaning of this question.

Q7. Explain definition of two groups(HAI and NHAI)? Clear the method of recruitment and separation between them. The consent of the participants in research and permission of IRCT were not obtained.

*Answer: In line 68 We stated that "**The informed consent was obtained from human subjects"**. We explained two groups in MS and highlighted in Line 69-72. The Ethical letter was uploaded as supplementary file.*

Q8. the road map in the method of doing the work is not explained in detail.

Answer: We comprehensively described the method section in MS and highlighted in Line 66-86.

Q9. what are the reason for hospilatization of NHAIgroup

Answer: In Table 2 the Diseases section, we stated the reason why NHAI admitted to the ICU and highlighted in line 124.

Q10. Tests for infection such as "CBC","C/A","U/C,"LP" should be included.

Answer: We added the CBC and U/C data in Table 2 in Line 124.

Associate Editor 1:

Dear Authors

- This research was ethically confirmed by which university? What is the ethical code?

Answer: The research was approved by ethical community of Islamic Azad University, Science and Research Branch. This was added to MS and highlighted in Line 75-76. Also, the ethical letter was uploaded as supplementary file.

-Title is better correct to "Comparison Respiratory Microbiota in Elderly Patients with or without Hospital Acquired Infection"

Answer: The title was changed and highlighted in line 1-2.

-Line9:Elderly are persons >65 year s old not>50 years old.

Answer: We deleted all Elderly words in MS.

-In conclusion: please use results of tables and all finding in conclusion.

Answer: The conclusion was changed based on study findings and highlighted in Line 227-233.

-Line 65: It is better to mention " location, type of ICU and the type or kind of university"

Answer: all the information were added in MS and highlighted in Line 66-67 of MS.

Line67: How are the two groups defined?

Answer: The identification was added in MS and highlighted in Line 69-72.

-Please omit "in"line 219:this was also shown in in vivo studies

Answer: The sentence was corrected.

-Line 107:It isn't identified "checking platelets in infectious cases, alone ".

Answer: The levels of Platelets were stated in Table 2 in Line 123. Actually, we did not understand the meaning of this question.

-Explain definition of two groups(HAI and NHAI)? Clear the method of recruitment and separation between them. The consent of the participants in research and permission of IRCT were not obtained.

Answer: All of these applied in MS and highlighted in Line 68-72 of MS.

-the road map in the method of doing the work is not explained in detail.

Answer: We revised the methods of study and highlighted in Line 66-86.

-what are the reason for hospilatization of NHAIgroup

Answer: The reason for hospitalization were described in disease section of MS and highlighted in Line 124.

- Tests for infection such as "CBC","C/A","U/C,"LP" should be included

Answer: We added the CBC and U/C data. In table 2 and highlighted in Line 124 of MS.

-which protocol have used for antibiotic test?(Such as CLSI)?

Answer: The Ref was added in method section of MS and highlighted in line 81-82.

-Please mention reference that used for MIC.

Answer: The ref was added and highlighted in Line 83 of MS.

-Which cultured medias used for identification of nosocomial Infection isolates?

Answer: All the media were mentioned in article and highlighted in Line 73-74.

-In Table 1: If primers are designed by the authors, they should explain about the method of designation. If not, authors should bring their references for used primers of each one of total bacteria, separately.

Answer: The method for primer design was described in MS and highlighted in Line 96-99 of MS.

-Please write control positive microorganisms for antibiotic resistance test, separately.

Answer: All the control bacteria were mentioned in MS and highlighted in Line 83-86 of MS.

-Please write and add" Multi-drug resistant (MDR) "for antimicrobial susceptibility (antibiotic resistance)of HAI Isolates in Table 3 .

Answer: This was applied in table 3 and highlighted in Line 164.

-please show image of qPCR(positive control +negative control +Ladder +positive samples)for each bacteria.

Answer: the image of qPCR was added in MS (Figure 3) and highlighted in Line 176.

Best regards,

3 Revision 2

0 comments

No public comments in this round.