Peer Review File

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Reviewer A

Comment (C) 1. Would be ideal to include carbapenems as these are anti-pseudomonal beta lactams.
Response (R) 1. Thank you for bringing our attention to this point, which we have not fully explained why carbapenems was excluded from the anti-pseudomonal beta-lactams for empiric therapy for HAP in the original manuscript. However, antimicrobial stewardship to restrict use of carbapenem has been suggested, since epidemiological studies have shown a link between increased use of carbapenems and resistance by Gram-negative bacilli. Therefore, cefepime and piperacillin/tazobactam are most commonly prescribed for initial antimicrobial regimens for HAP in practices. In our full database, very few patients were prescribed carbapenems, but even a small number of patients were excluded due to concerns that the inclusion of these patients could introduce bias in the assessment of clinical outcomes. We added this information in the Discussion section of the revised manuscript.

C2. Would want to know which fluoroquinolones are being used.
R2. Thank you for your comment. We choose levofloxacin or moxifloxacin, which are most commonly prescribed for respiratory infections in Korea. We added this information in methods section.

C3. Is the 7-day readmission rate different in low-risk HAP patients?
R3. As shown in Table 2, the readmission rate within 7 days in the "non-high-risk HAP" group was 1.9% for the "without quinolones" group and 2.1% for the "with quinolones" group. The odds ratio for readmission between these two groups both before and after adjusting for variables had a 95% CI including 1.0, showing no statistically significant difference. So, according to our results, there was no difference in readmission rate within 7 days according to the use of quinolones in the “non-high-risk HAP” group. We briefly added this information in results section.

C4. Grammar and spelling revision is needed throughout. E.g. fluoroquinolones (plural) should be used throughout the manuscript when referred to as individual drugs within the class (this is due to the fact that there are more than one fluoroquinolone). Okay to use fluoroquinolone (singular) when using in the context of combination therapy.
R4. We apologize for our carelessness and thank you for your careful review of our manuscript. We revised these expressions throughout the manuscript. In addition, the manuscript was proofread by a commercial English-language editing service (http://www.enago.co.kr, INQ- 815765323) to address this matter.

C5. Line 54 – 56 suggest fluoroquinolones are relatively safe and effective compared to other classes. The cited article mirrors this thought process, but fluoroquinolones all have multiple warnings and potentially severe adverse effects associated with use, which has deterred use in overall treatment. Would consider revision of this statement.
R5. Thank you for your important comment from the reviewer. We also totally agree with the reviewer. We modified that sentence and added a reference.

C6. Line 81 – 82: The study mentioned within the text (9) does not refer to antipseudomonal beta lactams specifically, is this statement accurate? Inclusion criteria lists “received antibiotics during their hospitalization”. I also do not see a supplementary appendix or list of antibiotic agents that patients received in the cited study.
R6. We apologize for lack of clarity and thank you for your careful reading of our previous publication. We referred to the cited study (BMC Pulm Med. 2022 Jan 12;22(1):21.) for detailed information on the method, including how to diagnose HAP with claim codes and to measure study variables. However, the present study used data from the KNHIS database, not HIRA-NIS that used in the cited study, we

should have cited other study using same KNHIS database, which has been recently published so that we can cite in the revised manuscript (Antibiotics. 2023 May 30;12(6):984.). As this study primarily targeted to compare clinical outcomes of patients treated with cefepime and those treated with piperacillin/tazobactam for HAP, the study population was limited to 9955 patients received cefepime or piperacillin/tazobactam with or without fluoroquinolones. Therefore, we should have clarified the inclusion criteria with 'age of ≥20 years who were diagnosed with HAP during hospitalization for more than 3 days in a tertiary or general hospital and were treated with cefepime or piperacillin/tazobactam'. We modified the inclusion criteria in the revised manuscript and changed it to a reference that can be cited.

C7. Line 152 – 153: Combination therapy was not associated with mortality benefit?
R7. As described in the Results section, the mortality risk was similar between the fluoroquinolones combination therapy group and the monotherapy group of patients with high-risk HAP. Rather, the mortality rate was higher in the fluoroquinolones combination therapy group among the patients with non-high-risk HAP. Based on these results, we summarized this information in the first paragraph of the Discussion section.

Reviewer B

C1. The title needs to correctly indicate the research focus of this study, the relationship between fluoroquinolone administration and mortality and re-hospitalization, as well as the clinical research design, i.e., a retrospective cohort study based on the health insurance claims data.
R1. Thank you for your comment. We modified the title of our manuscript as follow; Clinical outcomes of fluoroquinolones combination therapy in patients with hospital-acquired pneumonia: a retrospective cohort study using national health insurance claims data in Korea

C2. The abstract needs some revisions. The authors did not briefly describe the rationale for this research focus and what the knowledge gap is. The methods need to describe the inclusion of subjects, what the adjusted variables, and how the outcomes were measured. The results need to briefly summarize the clinical characteristics of the study sample and the incidence rates of mortality and re-hospitalization. The conclusion needs comments for the clinical implications of the findings.
R2. In the original manuscript, we couldn't include all contents you pointed out because we wrote it in a 'brief report' format and matched it to a limited number of characters. In particular, it was difficult to provide a lot of information about research methods. However, all the information should have been provided as much as possible. We modified the abstract as you suggested.

C3. In the introduction of the main text, the authors need to review what has been known on the relationship between mortality and antibiotics use, in particular fluoroquinolone, alone or their combination, have comments on the knowledge gap, and clearly indicate the potential clinical significance of this study. The current version focus on the provision of clinical evidence for the fluoroquinolone use for HAP, but the current retrospective data are not able to provide such answers, so the rationale needs more comments from other perspectives.
R3. Thank you for your comment. However, in the present study using real world data, we intended to analyze only the fluoroquinolone combination treatment recommended by the existing guidelines rather than fluoroquinolone alone treatment in the management of HAP, since evidence supporting the fluoroquinolone combination treatment for treating HAP remains weak. We apologize for lack of clarity, but the potential clinical significance of this study has been indicated more clearly in the revised manuscript.

C4. In statistics, please explain whether the current adjustment analysis of the selected covariates is adequate. The methodology part of this papers needs to be organized under the subtitles of subjects, covariates and outcomes, procedures, and statistics.
R4. For the multivariable model, we adjusted for age, sex, hospitalization history, comorbidities, and ICU admission based on a literature review. Then, we checked the absence of multicollinearity and the improvement of the Akaike information criterion of the model compared with the crude model. Therefore, the current adjustment analysis of the selected covariates is adequate. We added this information in the Methods section. In addition, we reorganized the Methods section under the subtitles you suggested.

C5. Please consider to cite several related papers: 1. Kim Y, Park GW, Kim S, Moon HJ, Won S, Chung W, Yang HJ. Fluoroquinolone and no risk of Achilles-tendinopathy in childhood pneumonia under eight years of age—a nationwide retrospective cohort. J Thorac Dis 2021;13(6):3399-3408. doi: 10.21037/jtd-20-2256. 2. Zhu C, Li Y, Yu Y, Lu L. Duration of antibiotic therapy in systemic lupus erythematosus patients with hospital-acquired bacterial pneumonia in eastern China. Ann Palliat Med 2021;10(3):2898-2906. doi: 10.21037/apm-20-584. 3. Li X, Yang S, Tan Z, Chen L, Hu X. Clinical analysis of hospital acquired mycoplasma pneumoniae infection after cardiac surgery: a case series. J Thorac Dis 2022;14(12):4763-4772. doi: 10.21037/jtd-22-1491.
R5. Thank you for your kind suggestions. We additionally cited these references except for ‘J Thorac Dis 2022;14(12):4763-4772. doi: 10.21037/jtd-22-1491.’, which is not relevant to our study objective and results.