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RESPONSE TO LETTER

Association Between Pneumonia Risk and Anticholinergic Burden Among Patients with Different Frailty Levels [Response to Letter]

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Dear editor

We appreciated Yang et al for providing comments regarding our study titled "Association between pneumonia risk and anticholinergic burden among patients with different frailty levels".[1] We provided explanation and additional analyses based on those comments in the following contents.

Cognitive dysfunction and psychiatric disorders represented important factors in clinical practice. Patients with cognitive dysfunction and psychiatric disorders are at increased risk of pneumonia through multiple mechanisms, including impaired swallowing and airway protection, functional decline, and immune dysregulation.[2] By employing a case-crossover design within a large population-based database, we mitigated confounding by indication through within-person comparisons.[3] Moreover, we limited our observation period to 180 days, during which we assumed that disease status was unlikely to have changed significantly over this period.[4]

To address time-varying confounding due to acute illness, we conducted a sensitivity analysis with additional adjustments for cerebrovascular disease, use of immunosuppressants, steroid use, heart failure, and chronic obstructive pulmonary disease within the hazard and referent periods, respectively.[5,6] After adjustment using a conditional logistic regression model, we observed an increased risk of hospitalized pneumonia. The odds ratios per ACB score were 1.31 (95% CI: 1.28–1.35), 1.18 (1.15–1.21), 1.14 (1.11–1.17), and 1.09 (1.05–1.13) among the fit, mildly frail, moderately frail, and very frail groups, respectively. These results demonstrate the consistency of our findings.

We acknowledge that different anticholinergic burden scales vary in drug coverage and scoring systems. However, prior studies have demonstrated high agreement across different anticholinergic burden scales.[7] Moreover, scales such as KABS and GABS may include a broader range of medications commonly prescribed in Asian settings, which may better reflect real-world prescribing patterns in Taiwan.[8] We observed consistent associations across all scales, suggesting that our findings are robust in different scales.

We acknowledge that the duration and dosage of medication can substantially affect the risk of pneumonia. To address this issue, we conducted additional analyses that incorporated the defined daily dose (DDD), as defined by the World Health Organization, to standardize the measurement of anticholinergic burden.[7] The odds ratios associated with each unit increase in ACB score were 1.56 (1.53–1.58), 1.32 (1.31–1.34), 1.21 (1.20–1.23), and 1.11 (1.09–1.14) among the fit, mildly frail, moderately frail, and very frail groups, respectively. We also excluded prescriptions with durations of fewer than seven days to account for prescription duration, and the results remained consistent with the main findings. The risk of pneumonia per ACB score was 1.23 (1.22–1.23), 1.19 (1.18–1.20), 1.16 (1.15–1.16), and 1.13 (1.12–1.14) among the fit, mildly frail, moderately frail, and very frail groups, respectively. All above analyses suggested the robustness of our findings.

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β2-agonists have been associated with improved lung function and may attenuated the observed association if they were prescribed concomitantly. However, within 180 days observation period, we assumed that the proportion of β2-agonist use was similar between the hazard and reference periods, which.[9] Therefore, the potential impact of β2-agonists was likely minimal in our case-crossover study.

Finally, we appreciate the comment highlighting that heterogeneity in healthcare systems, prescribing patterns, and population genetic backgrounds may modify the observed associations. Similar to studies that use a single country database, we cannot ensure that the results can be generalized to other countries without further examination. This provides an opportunity for future studies conducted through international collaborative research networks to include a broader range of countries and populations to further validate and generalize these findings across diverse healthcare systems, clinical settings, and ethnicities.[10,11]

Disclosure

The authors report no conflicts of interest in this communication.

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