Clinical Epidemiology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association Between Pneumonia Risk and Anticholinergic Burden Among Patients with Different Frailty Levels

Avery Shuei-He Yang[1,2,*], Hsin-Yu Fan Chiang[1,*], Daniel Hsiang-Te Tsai[1,2], Albert Tzu-Ming Chuang[1,2], Edward Chia-Cheng Lai[1,2]

[1]School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Population Health Data Centre, National Cheng Kung University, Tainan, Taiwan

*These authors contributed equally to this work

Correspondence: Edward Chia-Cheng Lai, School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, No. 1, University Road, Tainan, 701, Taiwan, Tel +886-6-2353535, ext. 6820, Email edward_lai@mail.ncku.edu.tw

Objective: We aimed to evaluate the association between recent increase in anticholinergic burden and risk of hospitalised pneumonia, taking frailty levels into consideration.

Setting: We conducted a case-crossover study using data drawn from Taiwan's National Health Insurance Research Database.

Participants: We enrolled patients aged over 65 years old who were hospitalised for pneumonia between 2011 and 2020. Exclusion criteria included prior diagnosis of ventilator dependency, pneumonia and immune dysfunction.

Measurements: The observational period was divided into a hazard period, a washout period and one of four reference periods, based on the 30-day interval before the admission. We calculated the anticholinergic cognitive burden (ACB) scale for the hazard period and one randomly selected reference period. Using a multimorbidity frailty index we classified patients into four groups (ie, fit, mildly frail, moderately frail and very frail).

Statistical Analysis: We used conditional logistic regression to evaluate the risk of pneumonia by comparing the anticholinergic burden between the hazard window and the randomly selected reference window and conducted sensitivity analyses based on case-time control and case-case-time control analysis to examine the robustness of the findings.

Results: The fit group included 188,740 patients, followed by 133,038, 61,805 and 18,198 patients for the mildly, moderately and very frail groups, respectively. Each single point increase in ACB scale was associated with a pneumonia risk increase by 1.35 (95% CI: 1.34–1.35), 1.24 (95% CI: 1.24–1.24), 1.18 (95% CI: 1.17–1.18) and 1.12 (95% CI: 1.11–1.13) times in the fit and mildly, moderately and very frail groups, respectively. The results of the case-time control and case-case-time control analyses remained consistent with the main analysis.

Conclusion: Our study confirmed the association between recently elevated ACB and the risk of hospitalised pneumonia. Even in the less frail, exposure to anticholinergic drugs warrants close monitoring for pneumonia.

Keywords: anticholinergic burden, pneumonia, older people, case-crossover, frailty

Key Messages

Why was the study done?

Previous studies have investigated the association between anticholinergic burden and pneumonia, focusing on specific populations such as patients with schizophrenia or older community-dwelling individuals. However, these studies primarily addressed long-term anticholinergic effects and did not consider frailty, an important factor in the care of older adults.

What did the researchers do and find?

Our study is the first to incorporate frailty status to differentiate susceptibility to anticholinergic burden. Our study further suggested that the degree of frailty may modify the pneumonia risk associated with recent exposure to drugs with

Received: 24 February 2025
Accepted: 16 August 2025
Published: 30 September 2025

anticholinergic burden, which has never been reported before. Specifically, the risk of pneumonia associated with a recent increase in anticholinergic burden was more significantly elevated in patients who were less frail compared to those who were frailer.

What do these results mean?

We found that a recent increase in anticholinergic burden was associated with a higher risk of pneumonia among older adults. Moreover, we observed a more prominent increase in short-term pneumonia risk for less frail patients. Our findings highlight the need for careful monitoring of older adults who have recently been exposed to anticholinergic drugs, even for those less frail.

Introduction

Anticholinergic drugs have been used for multiple diseases and therapeutic purposes; however, with some drugs, their anticholinergic activity is unrelated to their primary therapeutic purpose (eg, tricyclic antidepressants). Moreover, anticholinergic medications are known to be associated with several adverse effects in the older population, including cognitive function decline, falls, dry mouth, constipation, urinary retention, increased heart rate, hospitalisation and mortality.[1] Despite long-standing calls to reduce anticholinergic burdens in older adults,[2] between 30% and 50% of drugs prescribed to older patients have anticholinergic effects.[1] The prevalence of potent anticholinergic use in the older population has increased from 5.7% to 9.9% over the last 20 years.[3]

Previous research has suggested an association between anticholinergic burden and pneumonia, especially for drugs with high anticholinergic potency and in the early phase of treatment.[4–8] However, these studies have focused primarily on the long-term effects of anticholinergic burden. Additionally, based on the pharmacodynamic properties, pneumonia could be caused by recent exposure to or short-term use of drugs with anticholinergic activity.[7] While the relationship between the severity of pneumonia and baseline frailty has been established,[9,10] the relevant studies did not consider the frailty of patients when evaluating the risk of pneumonia and anticholinergic burden. Therefore, our study aimed to evaluate the association between pneumonia risk and anticholinergic burden, taking into consideration patients' different frailty levels. Using case-crossover design, we were able to evaluate recent anticholinergic exposure and the risk of pneumonia, which has not been considered before in previous studies.[4,5,7,11] In addition, we specifically assessed the risk of pneumonia associated with anticholinergic burden across different levels of frailty.

Methods

Study Population

We used data from Taiwan's National Health Insurance Research Database (NHIRD) between 2011 and 2020 to enrol patients aged over 65 years old with hospital-diagnosed pneumonia for the study. The diagnosis of pneumonia in the NHIRD has been validated in previous studies with a high sensitivity rate (92.3%).[12] Patients with ventilator dependency and immune dysfunction (ie, solid malignancy, haematological malignancy, acquired immunodeficiency syndrome, autoimmune disorder, and tuberculosis) within 1 year before the pneumonia hospitalisation were excluded from the analysis. To avoid including cases of recurrent pneumonia, we excluded patients with any pneumonia diagnosis within one year prior to the date of pneumonia hospitalisation. The assessment period for the exclusion criteria began on 1st January 2010 to ensure a comprehensive evaluation of the exclusion conditions. The NHIRD is maintained in conjunction with Taiwan's National Health Insurance programme and contains anonymised, patient-level data of approximately 23 million individuals (nearly 99.9% of Taiwan's total population).[13] Detailed information on the eligibility and disease definitions is provided in Supplementary Table 1.

Measure

We identified anticholinergic drug exposure using Anatomical Therapeutic Chemical (ATC) codes and used various anticholinergic burden scales to measure the cumulative anticholinergic activity. Five anticholinergic burden scales, including the Anticholinergic Cognitive Burden Scale (ACB),[14] Anticholinergic Drug Scale (ADS),[15] Modified Anticholinergic Cognitive

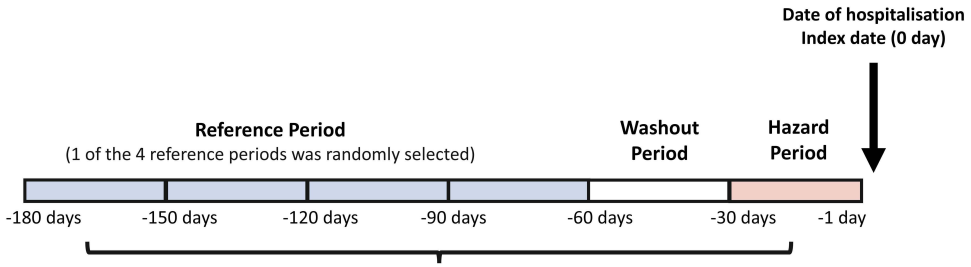
Burden (m-ACB),[16] German Anticholinergic Burden Scale (GABS),[17] and the Korean Anticholinergic Burden Scale (KABS)[18] were calculated based on the medication coverage during the study period. These medication records included data from outpatient and inpatient visits, as well as pharmacy refill records, obtained from the NHIRD. We assumed that, given the comprehensive coverage of reimbursement, the NHIRD was able to identify each individual's use of non-over-the-counter (non-OTC) medications. We defined the date of the first pneumonia admission as the index date. We divided the study period into hazard-, washout- and reference periods, based on the intervals relative to the index date (Figure 1). The hazard period was defined as the 30 days prior to the index date. We also implemented a 30-day washout period before the hazard period to allow patients to return to their original unexposed status. One reference period was randomly selected from four possible intervals (ie, 61 to 90, 91 to 120, 121 to 150, and 151 to 180 days) prior to the index date. The rationale for selecting the 30-day observational intervals derived from the average duration of drug supply in Taiwan. We tested this assumption by changing the length of each observational period in the sensitivity analysis.

Covariates

The covariates included the baseline comorbidities (Supplementary Table 2), anticholinergic burden scales (Supplementary Table 3) and multimorbidity frailty index (Supplementary Tables 4 and 5) captured within one year prior to the index date. We defined the comorbidities based on previous literature,[5,19] and clinical risk factors associated with pneumonia. We derived the multimorbidity frailty index from previous studies that defined frailty as the proportion of deficits a patient had, relative to several pre-specified deficits, and this index has been validated for the prediction of all-cause mortality, unplanned hospitalisation, and the use of ICU services in the NHIRD.[20,21]

Statistical Analysis

For the analysis of baseline characteristics, we presented categorical variables as number and percentage and continuous variables as mean and standard deviation. We modelled the anticholinergic burden as a continuous variable,[22] with the risks calculated as risk increase per unit of burden score increase. To investigate the impact of frailty on the risk of pneumonia associated with anticholinergic use, we categorised the patients into four groups: fit, mildly-, moderately-, and very frail, based on the multimorbidity frailty index percentile derived from the study population.[20,21] The cut-off points for the frailty subgroups were defined based on the quantile of population frailty distribution: <50.0% for the fit group, 50.0–66.3% for the mildly frail group, 66.4–82.6% for the moderately frail group, and ≥82.7% for the very frail group.



Odds Ratio of case-crossover:

Odds ratios were derived by comparing the exposure status between hazard and randomly selected reference period within individuals, and only discordant pairs contributed to the risk estimate.

Formula of conditional logistic regression model to estimate the odds ratio:

$$P_{(H,R)} = \prod_{i=1}^{N} \frac{\exp(\beta X_{iH})}{\exp(\beta X_{iH})+\exp(\beta X_{iR})} = logit^{-1}\{\beta(X_{iH} - X_{iR})\}$$

- When $X_{iR} = X_{iH}$; $P = \frac{1}{2}$
- When $X_{iR} \neq X_{iH}$; Odds ratio $= \exp(\hat{\beta})$ and 95% confidence intervals $= \exp(\hat{\beta} \pm 1.96SE(\hat{\beta}))$

N: Population size; X_{iH}: cumulative anticholinergic burden in hazard period in individual *i*;
X_{iR}: cumulative anticholinergic burden of randomly selected reference period in individual *i*

Figure 1 Illustration of case-crossover design.

https://doi.org/10.2147/CLEP.S524645

This data-driven approach was adopted from previous studies used to classify patients with different frailty status.[20] We also conducted sensitivity analyses to test our assumption of the cut-off point definition by using the quantile as cut-off point. We used conditional logistic regression to evaluate the odds ratios (OR) with 95% confidence intervals (95% CI) associated with the anticholinergic burden, by comparing the hazard window and the randomly selected reference window. All analyses were performed using Statistical Analysis System (SAS® 9.4, North Carolina State University).

Sensitivity Analysis

We performed case-time control (CTC) and case-case-time control analyses (CCTC) to account for the effect of exposure time-trend and protopathic bias,[23] respectively. For the CTC analysis, a group of individuals without pneumonia was included to adjust for the population trend in anticholinergic drugs exposure (Supplementary Figure 1).[24] We selected 3,000,000 subjects with no pneumonia episodes from the NHIRD as a control population, and randomly assigned an index date to each individual prior to death or the end of the study period. The disease risk scores were then calculated using logistic regression, based on baseline comorbidities identified within one year prior to the index date. Pneumonia patients were matched with the controls by the index date (ie, admission date for pneumonia) and disease risk score using a 1:1 greedy match with calliper set at 0.2 standard deviation of the logit of disease risk score.[25,26] By contrast, the CCTC recruited controls from the subjects that were to become cases in the future, ie, the control was derived from the original case cohort, but with their index date shifted earlier to align with the matched cases in calendar time (Supplementary Figure 2).[27] We implemented 1:1 greedy matching that required future cases to match exactly on sex, have an age difference of no more than five years, and pneumonia admission date 60–180 days later, compared with the matched cases. In the CTC and CCTC analysis, the OR of case-crossover was divided by the OR of control crossover to yield the adjusted OR. To further examine the impact of protopathic bias, we also introduced a 7-day or 14-day grace period, which omitted prescription records from the period before the index date to exclude exposures to medication prescribed for the prodrome of pneumonia. To validate the operative definitions for our main analysis, we first classified anticholinergic burdens exceeding 7 days of prescription as the exposure of interest, which eliminated drugs for single use or empirical therapy. Second, we changed the length of the washout period from 30 days to 15, 60, and 120 days to examine whether the length of the observational period would influence our findings. Third, we varied the lengths of the

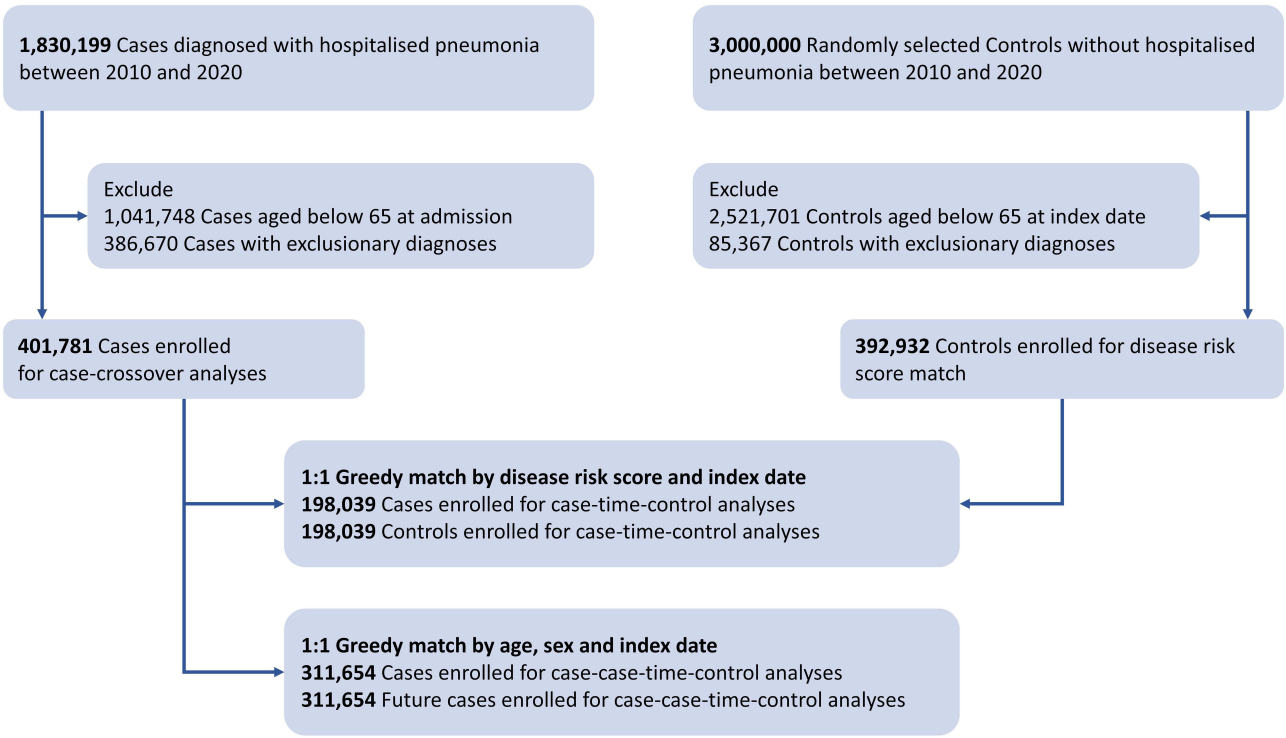


Figure 2 Patient eligibility flowchart.

hazard and reference periods to 15, 45 and 60 days to assess the validity of our assumption regarding the observation period. Finally, we modified the cut-off point for each frailty subgroup from the literature-based cut-off point to quartiles: 0–24% for the fit, 25–49% for the mildly frail, 50–74% for the moderately frail, and 75–100% for the very frail.

Results

A total of 401,781 patients were enrolled, after the exclusion of patients aged under 65 years and those diagnosed with pneumonia, immune dysfunction, ventilator dependence or tuberculosis infection within one year prior to the index date (Figure 2). The baseline multimorbidity frailty index ranged from 0 to 0.66, with a mean of 0.13 and a median of 0.125. The corresponding index distribution is provided in Supplementary Figure 3.

Based on the pre-specified cut-off points, 188,740 patients were classified as fit (46.98%), 133,038 patients were classified as mildly frail (33.11%), 61,805 patients were moderately frail (15.38%), and 18,198 patients were very frail (4.53%). The mean ages were 80.26, 81.36, 82.03 and 82.48 years old for the fit, mildly frail, moderately frail and very frail subgroups, respectively (Table 1). We observed an increase in comorbidities aligned with an increase in frailty levels in the baseline characteristics. For instance, the proportion of patients with coronary artery disease was higher among the very frail group (10,331; 56.77%), compared to the fit group (22,137; 11.73%), the mildly frail group (36,536; 27.46%), and the moderately frail group (25,270; 40.89%).

Table 1 Baseline Characteristics Among hospitalised Pneumonia Patients Classified by Multimorbidity Frailty Index

	Frailty Subgroups			
Baseline Characteristics	**Fit (n=188,740)**	**Mildly Frail (n=133,038)**	**Moderately Frail (n=61,805)**	**Very Frail (n=18,198)**
Range of multimorbidity frailty index	< 0.125	0.125 to 0.207	0.208 to 0.292	> 0.292
Male sex (N, %)	103,235 (54.70%)	71,404 (53.67%)	34,086 (55.15%)	10,793 (59.31%)
Female sex (N, %)	85,505 (45.30%)	61,634 (46.33%)	27,719 (44.85%)	7405 (40.69%)
Age (mean, SD)	80.26 (8.51)	81.36 (7.90)	82.03 (7.52)	82.48 (7.10)
Frailty index (mean, SD)	0.06 (0.03)	0.15 (0.02)	0.24 (0.03)	0.35 (0.05)
Comorbidities (N, %)				
Acute kidney injury	2643 (1.40%)	5798 (4.36%)	4787 (7.75%)	2053 (11.28%)
Bipolar disorder	2192 (1.16%)	2650 (1.99%)	1632 (2.64%)	734 (4.03%)
Cerebrovascular events	36,528 (19.35%)	49,131 (36.93%)	30,130 (48.75%)	11,008 (60.49%)
Chronic kidney disease	27,131 (14.37%)	34,302 (25.78%)	21,451 (34.71%)	7614 (41.84%)
Chronic Obstructive Pulmonary Disease	20,825 (11.03%)	35,133 (26.41%)	24,317 (39.34%)	10,761 (59.13%)
Congestive heart failure	9845 (5.22%)	22,066 (16.59%)	17,943 (29.03%)	7960 (43.74%)
Coronary artery disease	22,137 (11.73%)	36,536 (27.46%)	25,270 (40.89%)	10,331 (56.77%)
Dementia	28,718 (15.22%)	35,598 (26.76%)	21,114 (34.16%)	7596 (41.74%)
Depression	7758 (4.11%)	8995 (6.76%)	5767 (9.33%)	2317 (12.73%)
Diabetes mellitus	57,968 (30.71%)	52,336 (39.34%)	26,219 (42.42%)	8026 (44.10%)
Epilepsy	3452 (1.83%)	4025 (3.03%)	2472 (4.00%)	890 (4.89%)
Fall and related fracture	17,031 (9.02%)	19,353 (14.55%)	11,469 (18.56%)	4288 (23.56%)
Hypertension	99,651 (52.80%)	99,311 (74.65%)	51,469 (83.28%)	16,070 (88.31%)
Hyperlipidemia	38,109 (20.19%)	32,330 (24.28%)	16,172 (26.17%)	4840 (26.60%)
Osteoporosis	8184 (4.34%)	13,142 (9.88%)	8924 (14.44%)	3715 (20.41%)
Peripheral arterial occlusion disease	3593 (3.01%)	3431 (5.04%)	2489 (6.77%)	990 (9.97%)
Senile cataract	23,439 (12.42%)	22,245 (16.72%)	11,693 (18.92%)	3712 (20.40%)
Schizophrenia	1635 (0.87%)	1061 (0.80%)	440 (0.71%)	131 (0.72%)
Urinary tract infection	4509 (2.39%)	7301 (5.49%)	5253 (8.50%)	2222 (12.20%)

https://doi.org/10.2147/CLEP.S524645

Table 2 Association Between Anticholinergic Burden and Risk of hospitalised Pneumonia Among Frailty Subgroups

Risk of hospitalised Pneumonia among Frailty Subgroups				
Anticholinergic Burden Scale	**Odds Ratio (95% Confidence Interval)**			
	Fit	**Mildly Frail**	**Moderately Frail**	**Very Frail**
ACB	1.35 (1.34–1.35)	1.24 (1.24–1.24)	1.18 (1.17–1.18)	1.12 (1.11–1.13)
m-ACB	1.31 (1.31–1.32)	1.21 (1.21–1.22)	1.15 (1.15–1.16)	1.10 (1.10–1.11)
ADS	1.35 (1.35–1.36)	1.24 (1.24–1.25)	1.18 (1.17–1.18)	1.12 (1.11–1.13)
GABS	1.35 (1.35–1.36)	1.24 (1.24–1.24)	1.18 (1.17–1.18)	1.13 (1.12–1.13)
KABS	1.32 (1.31–1.32)	1.22 (1.21–1.22)	1.16 (1.15–1.16)	1.11 (1.10–1.11)

Abbreviations: ACB, Anticholinergic Cognitive Burden Scale; m-ACB, Modified Anticholinergic Cognitive Burden; ADS, Anticholinergic Drug Scale; GABS, German Anticholinergic Burden Scale; KABS, Korean Anticholinergic Burden Scale.

We found an increased risk of pneumonia for patients with recently increased anticholinergic burden, both in the whole study population (Supplementary Table 6) and across all frailty subgroups (Table 2). We found the risk of pneumonia in the fit group increased 1.35 times per 1-point increase in ACB score (OR: 1.35; 95% CI: 1.34–1.35), in the mildly frail group it increased 1.24 times per 1-point increase in score (OR: 1.24; 95% CI: 1.24–1.24), in the moderately

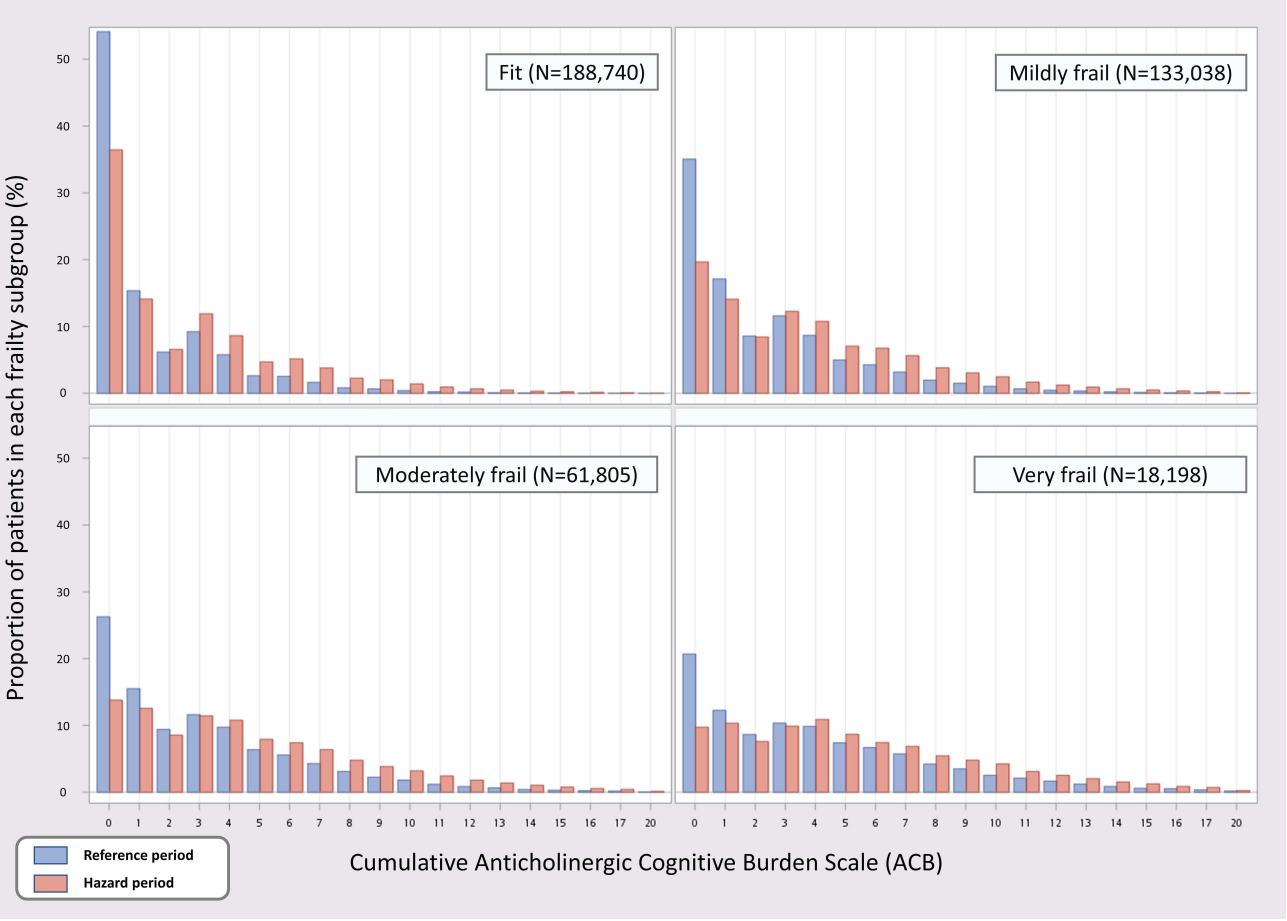


Figure 3 Distribution of Anticholinergic Burden of Hazard and Reference Period in the Case-Crossover Analysis, as Measured by the Anticholinergic Cognitive Burden Scale (ACB).

https://doi.org/10.2147/CLEP.S524645

frail group it increased 1.18 times per 1-point increase in score (OR: 1.18; 95% CI: 1.17–1.18), and in the very frail group it increased 1.12 times per 1-point increase in score (OR: 1.12; 95% CI: 1.11–1.13). We observed a notable shift in anticholinergic burden towards higher levels in the hazard period, particularly for the fit group (Figure 3). The distribution of the anticholinergic burden when measured by other anticholinergic burden scales (ie, ADS, m-ACB, GABS and KABS), remained consistent with ACB (Supplementary Figures 4 to 7).

The results of both the CTC and CCTC analyses confirmed a higher OR was observed in the fit subgroup, followed by the mildly frail, moderately frail and very frail subgroups. For the CTC analyses (Figure 2), we enrolled 392,932 individuals after applying the eligibility criteria; a total of 198,039 patients were 1:1 matched with the control population, based on the disease risk score. The results consistently indicated a higher risk of pneumonia linked to an increase in ACB; specifically, for each point increase in ACB, the risk of pneumonia increased 1.33 times, 1.23 times, 1.17 times and 1.09 times in the fit, mildly frail, moderately frail and very frail groups, respectively (Supplementary Table 7). In the CCTC analyses (Figure 2), a total of 311,654 future cases were 1:1 matched with cases by age, sex and index date. The results confirmed the association between recently increased ACB and the risk of pneumonia. For each point increase in ACB, we observed increased risks of pneumonia in the fit (1.31 times), mildly frail (1.18 times), moderately frail (1.13 times), and very frail groups (1.09 times), consistent with the main finding (Supplementary Table 8). In the sensitivity analyses, we introduced a grace period of either 7 or 14 days, excluded prescription records lasting less than 7 days, modified the washout period, substituted the cut-off point with quarters for each frailty subgroup, and altered the lengths of the risk and reference periods. In all analyses, the results consistently demonstrated the association between a recent increase in anticholinergic burden and pneumonia, across the different frailty subgroups (Supplementary Table 9 to 13). However, we observed a decrease in the magnitude of the odds ratio between recent ACB exposure and the risk of pneumonia when a grace period was introduced prior to the index date and the observational period was extended to 45 and 60 days.

Discussion

In this case-crossover study, we found that a recently elevated anticholinergic burden was associated with an increased risk of pneumonia among older adults. Furthermore, we observed that the magnitude of risk increase varied among patients with different frailty levels. The increase of pneumonia risk associated with anticholinergic drug burden was more pronounced in patients who were less frail. This may be due to the baseline pneumonia risk being lower in these patients, making the relative impact of anticholinergic drugs greater. Our study draws clinical attention to the risk of pneumonia in patients with recently elevated anticholinergic burden, even for those patients with lower frailty levels.

Previous studies have shown that there is an association between long-term exposure to anticholinergic burden and the risk of pneumonia.[4,5,7] Several mechanisms potentially leading to pneumonia have been postulated, including blockade of the muscarinic receptor, decrease in saliva secretion, and decrease of oesophageal sphincter pressure, which subsequently leads to dysphagia and aspiration pneumonia.[11] Moreover, anticholinergic medications may contribute to pneumonia by reducing mucociliary transport, extending the retention of bacteria in the lungs, and exerting sedative and central depression effects that impair pulmonary hygiene.[7] This lends biological plausibility to the association observed in our study. To further mitigate the issue of confounding factors, we used a case-only study design (ie, case-crossover study design) to estimate the effect of anticholinergic burden within individual patients with hospitalised pneumonia. As a result of the case-only design, the analysis was free from bias caused by time-invariant confounders (eg, comorbidities, residency, sex and health behaviours),[27] which we believe may be a major concern when studying the effects of anticholinergic burden.[27,28] We applied several sensitivity analyses to test the result accordingly, whereby the results remained consistent after adjusting for exposure time-trend and protopathic bias. These results strengthened the likelihood that the observed association between recently elevated anticholinergic burden and risk of pneumonia may be the result of causation.

Notably, the risk of pneumonia increased more prominently in patients whose frailty profile was classified as fit at baseline, compared to patients classified as very frail at baseline. Because the baseline pneumonia risk was higher in more frail patients, adding medications with anticholinergic activity might have contributed only a relatively small additional effect, compared to their baseline risks. Moreover, we observed that patients with high frailty levels were already receiving high amounts of anticholinergic drugs. Previous studies have revealed the upregulation of acetylcholine receptors during chronic competitive antagonism of acetylcholine receptors. Higher plasma levels of antagonists may be

required to achieve a comparable effect.[29,30] Therefore, we consider those exposed to high amounts of anticholinergic drugs more likely to tolerate additional anticholinergic adverse effects, leading to a lower magnitude of drug influence.

Previous studies have mostly focused on long-term effects of anticholinergic medications.[7] This current study suggests that adverse effects can occur even after short-term use. These results underscore the need for careful consideration of the trade-off between therapeutic benefits and side effects, in line with the "First, do no harm" principle,[31] especially when initiating new medications for older adults. Anticholinergic effects are sometimes overlooked as they are often not the primary effect of the drug;[32] therefore, a multidisciplinary approach involving pharmacists and other healthcare professionals is recommended.[2] This study can serve as a reference in consultation, aiding in decisions regarding the continuation or discontinuation of current, unnecessary medication use, especially medications with anticholinergic activity.

In conducting this study, we leveraged the advantages of self-controlled design which uses the subject's own experience as reference, thereby controlling for time-invariant within-person confounders (eg, genetic, socio-economic status, genotype).[33,34] However, some limitations to our study should be acknowledged. First, the claims database contained only the records of reimbursed medications, and the omission of self-paid or over-the-counter medications may have led to an underestimation of the pneumonia risk. Second, there was no standard definition for the cut-off points of the multimorbidity frailty index score. However, based on previous study,[20] we assumed the cut-off points at 50.0%, 66.3% and 82.6%. To test these assumptions, we conducted sensitivity analyses with quarter-based cut-off points, whereby the consistency of the results demonstrated the robustness of our findings. Third, the multimorbidity frailty index implemented in our study did not capture the functional impairment (ie, Instrumental Activities of Daily Living scale, physical activity, cognitive function).[20] However, previous studies have indicated a strong correlation between survey-based frailty index, which provides information regarding the functional impairment, and claims-based frailty index.[35,36] Furthermore, the multimorbidity frailty index has been used in several studies to predict clinical outcomes.[21,37–39] In our study, employing the multimorbidity frailty index developed from the same data source allowed us to more accurately capture the frailty status of our study population. Fourth, an inherent limitation of the case-crossover design was its susceptibility to exposure time trend, which may have biased the observed association due to the different likelihood of exposure between the hazard and reference periods.[34] In our sensitivity analyses, we conducted CCTC and CTC analyses to investigate the impact of exposure time trend, and the results showed little to no change after considering the time trend. Finally, although we proposed two potential explanations for the inverse relationship between baseline frailty status and the increased risk of pneumonia following exposure to drugs with anticholinergic burden, the exact mechanism remains unclear due to limitations of the database. Further research is needed to clarify this association and to enhance understanding of the interplay between frailty and anticholinergic burden.

Conclusion

We found that a recent elevation in anticholinergic burden was associated with an increased risk of pneumonia among older adults. The increase in pneumonia risk caused by anticholinergic drugs was more pronounced in less frail patients compared to the more frail. Our findings suggest the need for close monitoring for pneumonia in older adults who have recently received drugs with anticholinergic activity, even in non-frail older adults.

Data Sharing Statement

The datasets generated and analysed during the current study are not publicly available due to the data protection regulations established by the National Health Insurance Research Database (https://nhird.nhri.edu.tw/en/Data_Protection.html) but are available from the corresponding author upon reasonable request.

Ethical Approval

The current study has been approved by the NCKU hospital's Institutional Review Board (No: HEREC-E-110-453-2).

Acknowledgments

We appreciate the help from Dr. Wei-Ching Huang in terms of the study material preparation, which includes the anticholinergic burden score summary table and study scheme illustration. The authors thank Ministry of Health and Welfare Data Centre at National Cheng-Kung University for providing administrative support.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; they took part in drafting, revising or critically reviewing the article; they gave final approval of the version to be published, agreed on the journal to which the article would be submitted, and consent to be held accountable for all aspects of the work.

Funding

This study was supported in part by grants from the National Science and Technology Council of Taiwan (NSTC 114-2628-B-006-005-) and the National Health Research Institutes of Taiwan (NHRI-11A1-CG-CO-04-2225-1; NHRI-12A1-CG-CO-04-2225-1; NHRI-13A1-CG-CO-04-2225-1; NHRI-14A1-CG-CO-04-2225-1) to ECCL. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lavrador M, Castel-Branco MM, Cabral AC, Veríssimo MT, Figueiredo IV, Fernandez-Llimos F. Association between anticholinergic burden and anticholinergic adverse outcomes in the elderly: pharmacological basis of their predictive value for adverse outcomes. *Pharmacolog Res*. 2021;163:105306. doi:10.1016/j.phrs.2020.105306
2. Kouladjian O'Donnell L, Gnjidic D, Nahas R, Bell JS, Hilmer SN. Anticholinergic burden: considerations for older adults. *J Pharm Pract Res*. 2017;47(1):67–77. doi:10.1002/jppr.1303
3. Grossi CM, Richardson K, Savva GM, et al. Increasing prevalence of anticholinergic medication use in older people in England over 20 years: cognitive function and ageing study I and II. *BMC Geriatrics*. 2020;20(1). doi:10.1186/s12877-020-01657-x.
4. Lee CY, Cheng YD, Cheng WY, Tsai TH, Huang KH. The prevalence of anticholinergic drugs and correlation with pneumonia in elderly patients: a population-based study in Taiwan. *Int J Environ Res Public Health*. 2020;17(17):1.
5. Lampela P, Tolppanen AM, Tanskanen A, Tiihonen J, Hartikainen S, Taipale H. Anticholinergic exposure and risk of pneumonia in persons with alzheimer's disease: a nested case-control study. *J Alzheimers Dis*. 2017;56(1):119–128. doi:10.3233/JAD-160956
6. Paul KJ, Walker RL, Dublin S. Anticholinergic medications and risk of community-acquired pneumonia in elderly adults: a population-based case–control study. *J Am Geriatrics Soc*. 2015;63(3):476–485. doi:10.1111/jgs.13327
7. Wu M, Li Z, Zheng W, et al. Association between anticholinergic medication uses and the risk of pneumonia in elderly adults: a meta-analysis and systematic review. *Ann Med*. 2023;55(1):2209736. doi:10.1080/07853890.2023.2209736
8. Luykx JJ, Correll CU, Manu P, et al. Pneumonia risk, antipsychotic dosing, and anticholinergic burden in schizophrenia. *JAMA Psychiatry*. 2024;81(10):967. doi:10.1001/jamapsychiatry.2024.1441
9. Iwai-Saito K, Shobugawa Y, Aida J, Kondo K. Frailty is associated with susceptibility and severity of pneumonia in older adults (A JAGES multilevel cross-sectional study). *Sci Rep*. 2021;11(1):7966. doi:10.1038/s41598-021-86854-3
10. Park CM, Kim W, Rhim HC, et al. Frailty and hospitalization-associated disability after pneumonia: a prospective cohort study. *BMC Geriatr*. 2021;21(1):111. doi:10.1186/s12877-021-02049-5
11. Chatterjee S, Carnahan RM, Chen H, Holmes HM, Johnson ML, Aparasu RR. Anticholinergic medication use and risk of pneumonia in elderly adults: a nested case-control study. *J Am Geriatr Soc*. 2016;64(2):394–400. doi:10.1111/jgs.13932
12. Su VYF, Liu CJ, Wang HK, et al. Sleep apnea and risk of pneumonia: a nationwide population-based study. *Canad Med Assoc J*. 2014;186(6):415–421. doi:10.1503/cmaj.131547
13. Hsieh CY, Su CC, Shao SC, et al. Taiwan's national health insurance research database: past and future. *Clin Epidemiol*. 2019;11:349–358. doi:10.2147/CLEP.S196293
14. Boustani M, Campbell N, Munger S, Fox C, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4:311–320. doi:10.2217/1745509X.4.3.311
15. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol*. 2006;46(12):1481–1486. doi:10.1177/0091270006292126
16. Ah YM, Suh Y, Jun K, Hwang S, Lee JY. Effect of anticholinergic burden on treatment modification, delirium and mortality in newly diagnosed dementia patients starting a cholinesterase inhibitor: a population-based study. *Basic Clin Pharmacol Toxicol*. 2019;124(6):741–748. doi:10.1111/bcpt.13184

17. Kiesel EK, Hopf YM, Drey M. An anticholinergic burden score for German prescribers: score development. *BMC Geriatr*. 2018;18(1):239. doi:10.1186/s12877-018-0929-6
18. Jun K, Hwang S, Ah YM, Suh Y, Lee JY. Development of an anticholinergic burden scale specific for Korean older adults. *Geriatr Gerontol Int*. 2019;19(7):628–634. doi:10.1111/ggi.13680
19. Luo J, Tang W, Sun Y, Jiang C. Impact of frailty on 30-day and 1-year mortality in hospitalised elderly patients with community-acquired pneumonia: a prospective observational study. *BMJ Open*. 2020;10(10):e038370. doi:10.1136/bmjopen-2020-038370
20. Lai HY, Huang ST, Chen LK, Hsiao FY. Development of frailty index using ICD-10 codes to predict mortality and rehospitalization of older adults: an update of the multimorbidity frailty index. *Arch Gerontol Geriatr*. 2022;100:104646. doi:10.1016/j.archger.2022.104646
21. Wen YC, Chen LK, Hsiao FY. Predicting mortality and hospitalization of older adults by the multimorbidity frailty index. *PLoS One*. 2017;12(11):e0187825. doi:10.1371/journal.pone.0187825
22. Hanlon P, Quinn TJ, Gallacher KI, et al. Assessing risks of polypharmacy involving medications with anticholinergic properties. *Annals Fam Med*. 2020;18(2):148–155. doi:10.1370/afm.2501
23. Wang S, Linkletter C, Maclure M, et al. Future cases as present controls to adjust for exposure trend bias in case-only studies. *Epidemiology*. 2011;22(4):568–574. doi:10.1097/EDE.0b013e31821d09cd
24. Huang WC, Yang AS, Tsai DH, Shao SC, Lin SJ, Lai EC. Association between recently raised anticholinergic burden and risk of acute cardiovascular events: nationwide case-case-time-control study. *BMJ*. 2023;382:e076045. doi:10.1136/bmj-2023-076045
25. Wyss R, Glynn RJ, Gagne JJ. A review of disease risk scores and their application in pharmacoepidemiology. *Current Epidemiol Rep*. 2016;3(4):277–284. doi:10.1007/s40471-016-0088-2
26. Wang Y, Cai H, Li C, et al. Optimal caliper width for propensity score matching of three treatment groups: a Monte Carlo study. *PLoS One*. 2013;8(12):e81045. doi:10.1371/journal.pone.0081045
27. Hallas J, Pottegard A. Use of self-controlled designs in pharmacoepidemiology. *J Intern Med*. 2014;275(6):581–589. doi:10.1111/joim.12186
28. Gault N, Castaneda-Sanabria J, De Rycke Y, Guillo S, Foulon S, Tubach F. Self-controlled designs in pharmacoepidemiology involving electronic healthcare databases: a systematic review. *BMC Med Res Methodol*. 2017;17(1):25. doi:10.1186/s12874-016-0278-0
29. Hogue CW Jr, Ward JM, Itani MS, Martyn JA. Tolerance and upregulation of acetylcholine receptors follow chronic infusion of d-tubocurarine. *J Appl Physiol*. 1992;72(4):1326–1331. doi:10.1152/jappl.1992.72.4.1326
30. Kuribara H, Tadokoro S. Development of tolerance to ambulation-increasing effect of scopolamine dependent on environmental factors in mice. *Jpn J Pharmacol*. 1983;33(5):1041–1048. doi:10.1016/S0021-5198(19)52450-7
31. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. *Med J Aust*. 2014;201(7):390–392. doi:10.5694/mja14.00146
32. Hilmer SN, Gnjidic D. The anticholinergic burden: from research to practice. *Aust Prescr*. 2022;45(4):118–120. doi:10.18773/austprescr.2022.031
33. Cadarette SM, Maclure M, Delaney JAC, et al. Control yourself: ISPE-endorsed guidance in the application of self-controlled study designs in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2021;30(6):671–684. doi:10.1002/pds.5227
34. Huang WC, Lai EC. Future-case control crossover analysis for adjusting bias in case crossover studies. *BMJ*. 2023;382:p2136.
35. Guaraldi G, Malagoli A, Theou O, et al. Correlates of frailty phenotype and frailty index and their associations with clinical outcomes. *HIV Med*. 2017;18(10):764–771. doi:10.1111/hiv.12527
36. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring frailty in medicare data: development and validation of a claims-based frailty index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980–987. doi:10.1093/gerona/glx229
37. Ga H, Won CW, Jung HW. Use of the frailty index and FRAIL-NH scale for the assessment of the frailty status of elderly individuals admitted in a long-term care hospital in Korea. *Annals Geriatric Med Res*. 2018;22(1):20–25. doi:10.4235/agmr.2018.22.1.20
38. Bensken WP, Schiltz NK, Warner DF, et al. Comparing the association between multiple chronic conditions, multimorbidity, frailty, and survival among older patients with cancer. *J Geriatr Oncol*. 2022;13(8):1244–1252. doi:10.1016/j.jgo.2022.06.011
39. Short R, Carter B, Verduri A, Barton E, Maskell N, Hewitt J. The effect of frailty on mortality and hospital admission in patients with benign pleural disease in Wales: a cohort study. *Lancet Healthy Longev*. 2024. doi:10.1016/S2666-7568(24)00114-4