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REVIEW ARTICLE

Proton pump inhibitors and community-acquired pneumonia risk: a systematic review and meta-analysis

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ABSTRACT

Proton pump inhibitors (PPIs) are the most commonly prescribed medications for acid-related illnesses; however, since 2004, possible concerns have been raised about their relationship with an elevated risk of community-acquired pneumonia (CAP). This review included an extensive discussion of literature on the association between PPI use and the risk of CAP, with an emphasis on studies from large databases released over the last decade. Six studies with almost 700,000 individuals were reviewed using the Newcastle–Ottawa Scale and random-effects meta-analysis. Results showed a significant association between PPI use and higher risk of CAP (hazard ratio [HR] 1.70, 95% confidence interval [CI] 1.59-1.81, $p < 0.01$), representing a 70% higher risk of CAP in PPI users, a random-effects meta-analysis revealed a significant association (HR 1.70, 95% CI 1.59-1.81, $p < 0.01$) with low and statistically non-significant heterogeneity ($I^2 = 0\%$, $p = 0.44$). The included studies found dose–response relationships with a larger risk associated with higher doses of PPI (e.g., ≥90 defined daily doses/year: HR 4.32, 95% CI 2.94-6.33). The risk was especially high in patients with myocardial infarction (adjusted hazard ratio 2.25; 95% CI 1.57-3.21; $p < 0.001$) and congenital heart disease (odds ratio 2.21; 95% CI 1.66-2.94). Some studies observed an elevated risk early in the course of PPI medication. In conclusion, there was a significant association between PPI use and higher risk of CAP, especially in the short term, although caution needs to be exercised when prescribing PPIs, especially in individuals at high risk for pneumonia.

Keywords: CAP, community-acquired pneumonia, proton pump inhibitors, risk, systematic review.

Introduction

Proton pump inhibitors (PPIs) are frequently suggested to avoid the development of gastrointestinal ulcers and to treat upper gastrointestinal problems, which include peptic ulcers and gastroesophageal reflux disease (GERD), resulting from insufficient acid secretion. Following the first discovery in 2004, numerous studies have examined the potential correlation between PPI consumption and a higher incidence of pneumonia [1]. Nevertheless, short-term use might pose some risk. PPIs lower stomach acidity, which can influence both the oral and gut microbiomes. This change might result in micro-aspiration, possibly leading to pneumonia, especially community-acquired pneumonia (CAP) [2]. Furthermore, the respiratory system has been found to contain proton pumps, and suppressing these pumps with PPIs could disrupt microbiota within the respiratory tract; this might contribute to an increased risk of pneumonia. CAP is a prevalent medical diagnosis that contributes to serious health complications and considerable healthcare expenses. In 2006, the United States recorded an estimated 4.2 million visits to outpatient care facilities for CAP.

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Data from Medicare between 2007 and 2008 revealed that the mortality rate within 30 days for CAP ranged from 3.8% to 8.5%. Additionally, the annual medical costs for Medicare fee-for-service patients with CAP are estimated to be approximately $13 billion. According to some research, PPI users might be more susceptible to CAP [3].

A longitudinal analysis of electronic medical records found that PPIs were linked to an increased risk of incident pneumonia in the second year following treatment initiation (prior event rate ratio [PERR]-adjusted hazard ratio [aHR] = 1.82, 95% CI = 1.27-2.54) [4]. In addition, a systematic review and meta-analysis revealed that ambulatory PPI medication increased the incidence of CAP by 1.49 (95% CI 1.16, 1.92; I^2 = 99.2%). During the first month of treatment (odds ratio [OR] 2.10; 95% CI 1.39, 3.16) [3]. However, a population-based study concluded that the association between PPI use and the incidence of CAP is likely to be completely attributed to confounding factors [5]. Therefore, the purpose of the current research was to review the link between the usage of PPIs and the risk of acquiring CAP.

Subjects and Methods

Search strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [6]. Various electronic databases were searched: ClinicalTrials.gov, online trial registrations, Embase, PubMed, and the Cochrane Library. Three authors independently developed the search strategy using the keywords: ("proton pump inhibitors" OR PPIs OR omeprazole OR pantoprazole OR esomeprazole OR lansoprazole) AND ("community-acquired pneumonia" OR CAP OR pneumonia OR "lung infection") AND (adults OR "adult patients") AND ("risk" OR "incidence" OR "association").

Selection of article

After the first database search, titles and abstracts were screened independently by two reviewers to identify studies meeting certain inclusion criteria. They next read the entire texts of the selected articles to see if they were appropriate. The inclusion criteria were studies published in English, studies designed to study the association between PPIs and risk of CAP, studies that included both genders and those who were 18 years and older, and studies published in the last 10 years. The review comprised prospective cohort studies and randomized controlled trials (RCTs). Studies that were neither prospective cohort studies nor RCTs, such as editorials, letters, commentaries, or reviews; studies that did not describe the clinical outcomes of interest; and studies that included patients younger than 18 years were excluded. Studies that did not involve PPIs were also omitted. Some studies were judged to be at substantial risk of bias or low quality in terms of study design, sample size, data collection, analysis methods, and other important domains. Studies found to exhibit substantial bias were also excluded from the review.

Data extraction

Two writers independently extracted data from the included studies and resolved any discrepancies by discussion with the third author. Data extracted from each study included first author name, year of publication, study design, country of origin, sample size, demographic characteristics, details of the PPI intervention (type, dosage, duration), duration of follow-up, and major outcomes (incidence of CAP (hazard ratios [HRs] or ORs), hospitalization statistics, and mortality rates).

Risk of bias assessment

The quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS) [7], which assessed three major domains: (1) selection of study participants (four criteria), (2) comparability of cohorts or cases and controls (two criteria), and (3) assessment of outcomes and adequacy of follow-up (three criteria). Each study was independently reviewed by two reviewers who assigned stars to each criterion met. Discrepancies in ratings were resolved through discussion until consensus was achieved. Each study was given a total NOS score from 0 to 9 stars to assess the quality of the study as "good" (7-9 stars), "fair" (5-6 stars), or "poor" (<5 stars). Studies were not rejected based on NOS quality scores alone, as even "fair" quality studies provided essential narrative data.

Statistical analysis

Meta-analysis was performed using RevMan 5.4.1 [8]. The HRs and 95% confidence intervals (CIs) were pooled from the studies included in current analysis using the general inverse-variance approach with a random-effects model. Sensitivity analysis was performed by the leave-one-out technique, and the meta-analysis was repeated by excluding one study at a time. This tested if any single study had an undue influence on the aggregated effect magnitude.

Publication bias was visually examined by producing a funnel plot of effect estimates against their standard errors. Statistical tests for funnel plot asymmetry (Egger's test) were not performed because of the small number of included studies (n < 10) with insufficient power to distinguish chance from true asymmetry. The subgroup analysis and meta-regression were carried out because of the lack of substantial statistical heterogeneity (I^2 = 0%) and the small number of included papers. No heterogeneity would be present to explain, and hence, no relevant further insights from such studies could be expected.

Results

PRISMA diagram

A total of 269 papers were extracted from databases including PubMed, ClinicalTrials.gov, Cochrane Library, Embase, and Scopus. Of these, 53 were removed due to duplication, and 201 were excluded after screening the titles and abstracts. Additionally, nine papers were excluded after full-text screening. Ultimately, six articles were deemed suitable for the systematic review (Figure 1).

Characteristics of the included studies

The research reviewed, published between 2016 and 2022, indicated substantial variability both in design and methodology. Most of them were retrospective or nested case-control studies from different healthcare systems like South Korea, Denmark, the United States, Taiwan, and the United Kingdom. Sample sizes ranged from a few thousands to over 390,000. The study populations included the general adult population and special populations such as patients with myocardial infarction (MI) or congenital heart disease (CHD). There was also considerable variation between studies in PPI exposure. There were differences in the exact pharmaceuticals including the classification of dosages (standard *vs.* high doses based on the defined daily dose [DDD]), and the period of treatment (30 days to several years). Also, the follow-up times were very

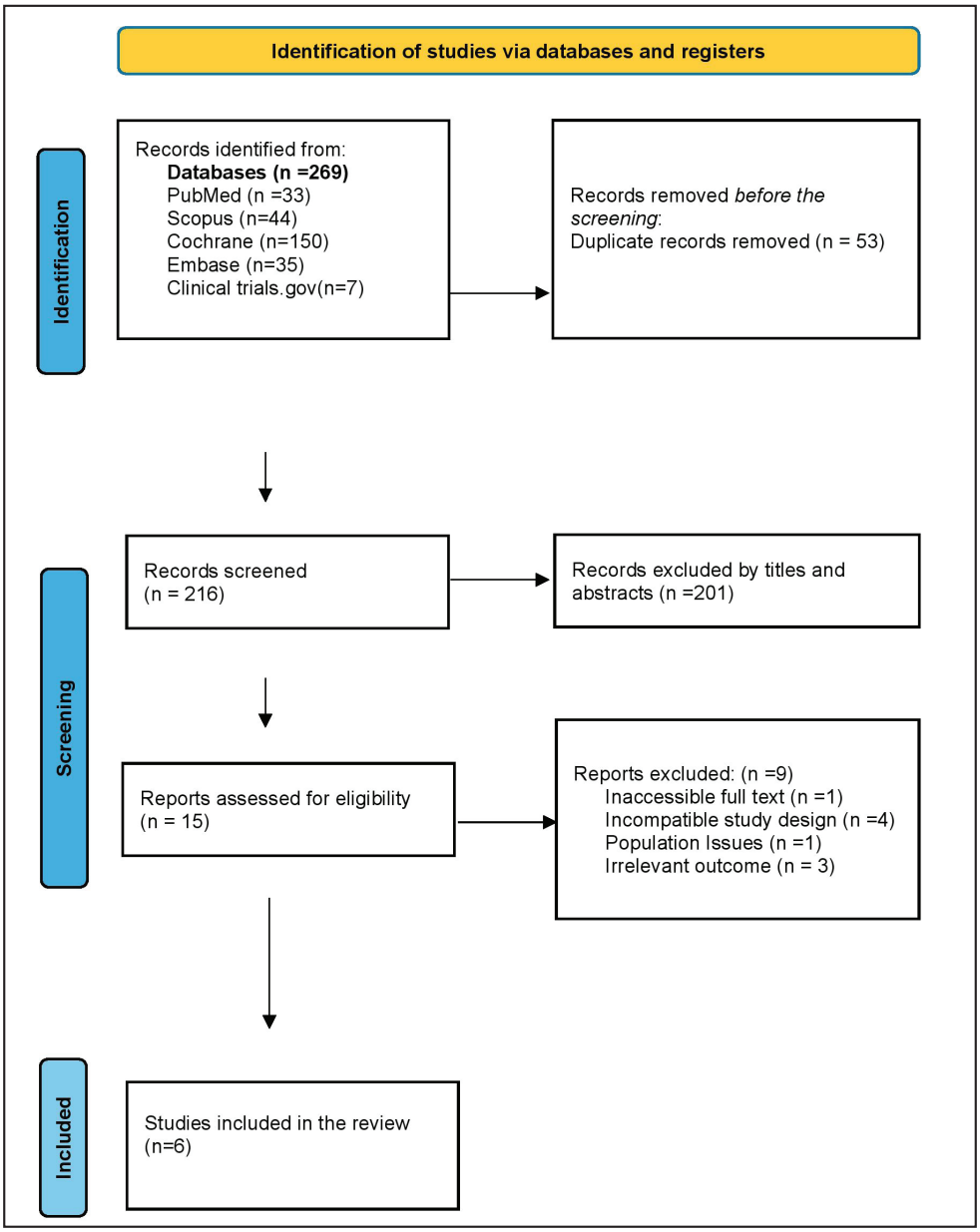


Figure 1. *Schematic representation of the criteria for selecting studies in the systematic review.*

Table 1. *Characteristics of the included studies evaluating the association between PPI use and risk of CAP.*

First author (year)	Study design and country	Sample size	Age (mean [standard deviation]) years	Gender (male/female)	Intervention (PPI type, dose, duration)	Follow-up duration (months)
Jeon et al., 2022 [9]	Retrospective nationwide cohort study in South Korea	**3,701 patients with MI**	**62.01 (12.76)**	**2,664/1,037**	**Type:** Omeprazole, lansoprazole, ilaprazole, rabeprazole, pantoprazole, dexlansoprazole, esomeprazole **Dose:** Low versus high dose based on World Health Organization DDD criteria **Duration:** Time-dependent exposure during follow-up (mean 4.85 years)	**4.85 ± 3.75 years** (around 58 months)
Evers et al., 2021 [10]	Nested case-control study in Denmark	**Cases:** 618 adults with CHD hospitalized with CAP **Controls:** 3,082 adults with CHD without CAP	≥18 years	**Cases:** 285/333 **Control:** 1,422/1,660	Any PPI; dose: low (<1 DDD/day) or high (≥1 DDD/day); duration: current use (prescription filled 7-90 days before index date)	12 months (excluding last 7 days)
Cohen et al., 2019 [11]	Retrospective cohort study in the United States	392,355 patients Pre-PPI use: 103,423 No pre-PPI use: 288,932	Total cohort: 52.9 (15.6); no pre-index PPI: 51.4 (15.8); pre-index PPI: 56.9 (14.2)	145,501/246,854	PPI types: any type Dose and duration: PPI prescribed for 30 days	3 years (36 months)
Lin et al., 2019 [12]	Retrospective cohort study in Taiwan	**Cases:** 988; **Controls:** 3,952	**Cases:** 58.8 (13.4) **Control:** 58.8 (13.2)	**Cases:** 614/374 **Control:** 2,478/1,474	**Types:** Omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole **Dose:** Annual DDD categories: <30, 30-59, 60-89, ≥90 DDDs/year	14 years
Zirk-Sadowski et al., 2018 [4]	Longitudinal cohort study in England	**Cases:** 75,050 **Control:** 75,050	71 (7.3)	31,202/43,848 in each group	**Type:** Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole **Duration:** Long-term use (≥1 year prescription)	24 months
Othman et al., 2016 [5]	Cohort self-controlled case series study in the United Kingdom	**Cases:** 160,000 **Control:** 160,000	56 (16)	**Cases:** 72,000/88,000 **Control:** 72,000/88,000	Any PPI; new user design; median duration: 28 days (interquartile range 28-76)	Average 60 months per patient

heterogeneous, ranging from 24 months to 14 years (Table 1).

The study-specific findings regarding the association between proton pump inhibitor use and community-acquired pneumonia, including hospitalization and mortality outcomes, are summarized in Table 2.

The majority of studies reported a significantly increased incidence of CAP with PPIs, with aHRs ranging from 1.67 (95% CI 1.55-1.79) to 2.25 (95% CI 1.57-3.21). Several studies showed a significant dose-response association, indicating that the risk of pneumonia was increased with greater doses of PPIs. Lin et al. showed a four-fold greater risk in patients taking ≥90 DDDs/year (HR 4.32; 95% CI 2.94-6.33). Evers et al. [10] discovered higher chances associated with high-dose (OR 2.29; 95% CI 1.60-3.26) than low-dose PPIs (OR 2.11; 95% CI 1.38-3.22). Timing of exposure: Othman et al. [5] identified an increased risk within 30 days of starting a PPI (incidence rate ratio [IRR] 1.19; 95% CI 1.14-1.25), but also an increased risk in the 30 days before starting a PPI (IRR 1.92; 95% CI 1.84-2.00), suggesting confounding by indication. Two studies presented hospitalization data with inconsistent results. Mortality was not significantly elevated after adjustment for covariates.

Table 2. *Study outcomes on the association between PPIs and CAP.*

First author (year)	Risk of CAP	Hospitalization rates	Mortality	Conclusion
Jeon & Kim, 2022 [9]	**PPI:** aHR 2.25 (1.57-3.21), $p < 0.001$ **Histamine-2 receptor antagonist (H2RA):** aHR 1.50 (1.16-1.93), $p = 0.002$ **Mucoprotective agents:** aHR 1.27 (0.98-1.64), $p = 0.074$	Not reported (NR)	NR	Both PPIs and H2RAs notably raise the risk of pneumonia in patients who have had an MI. In contrast, mucoprotective medications do not have this effect. However, the use of mucoprotective agents is linked to a higher risk of gastrointestinal bleeding.
Evers et al., 2021 [10]	**Overall adjusted OR: 2.21** (95% CI: **1.66-2.94**) **Dose-specific adjusted OR: Low-dose PPI (<1 DDD/day): OR = 2.11** (95% CI: **1.38-3.22**) **High-dose PPI (≥1 DDD/day): OR = 2.29** (95% CI: **1.60-3.26**)	The OR for CAP in current PPI users was 2.21 compared to non-users. This risk was higher in males (OR 3.59), those over 65 (OR 2.30), and individuals with severe/univentricular CHD (OR 2.35). For dosage, low-dose PPI users had an OR of 2.11, while high-dose users had an OR of 2.29.	NR	CHD patients who are prescribed PPIs face an increased likelihood of being hospitalized for CAP within the next three months. This risk is notably higher among patients who are on high-dose PPIs, male patients, those over 65 years of age, and individuals with severe or univentricular CHD.
Cohen et al., 2019 [11]	**Absolute risk:** 4.0% (no pre-index PPI) versus 5.3% (pre-index PPI). **Relative increase:** 30%-50% higher likelihood with PPI use.	NR	NR	PPI use was associated with a 30%-50% increased likelihood of CAP in patients with laryngeal/voice disorders, even after adjusting for confounders. The pervasive use of PPIs in this population warrants caution.
Lin et al., 2019 [12]	**Overall PPI use: aHR 1.70 (95% CI: 1.43-2.03)** **Dose-response:** • **<30 DDDs: HR 1.29 (1.03-1.60)** • **≥90 DDDs: HR 4.32 (2.94-6.33)**	NR	NR	The use of PPIs is notably associated with a greater risk of pneumonia in patients with type 2 diabetes mellitus (T2DM), showing a clear correlation with dosage. The strongest effects are observed with omeprazole and in those taking high doses of PPIs.
Zirk-Sadowski et al., 2018 [4]	**PERR-adjusted HR = 1.82 (95% CI: 1.27-2.54)** Unadjusted post-PPI HR = 3.03 (2.60-3.53) Unadjusted pre-PPI HR = 1.67 (1.37-2.02)	NR	NR	The likelihood of developing pneumonia increases among older adults with long-term therapy with PPIs in primary care settings, regardless of higher rates of pneumonia that may have occurred before the initiation of PPI treatment. In our study group, the additional risk appeared to be statistically consistent across various age brackets and comorbidity categories.
Othman et al., 2016 [5]	HR = **1.67** (95% CI 1.55-1.79) → higher risk in PPI users. **30 days after PPI start:** IRR = **1.19** (95% CI 1.14-1.25) **Remaining exposure period:** IRR = **1.49** (95% CI 1.46-1.52) **30 days before PPI start:** IRR = **1.92** (95% CI 1.84-2.00)	**Rates:** • Exposed patients: ~61.4 per 1,000 person-years after PPI. • Before PPI: ~62.1 per 1 000 person-years. • Controls: lower, but increasing over time. • **PERR-adjusted HR:** 0.74 (95% CI 0.69-0.97). • Suggests **no excess hospitalization risk** attributable to PPI itself.	No significant increase in pneumonia-related mortality was observed after PPI initiation, once confounding factors were accounted for. About **5% of patients died within 90 days** of pneumonia diagnosis in the case series analysis.	The findings suggest that there is no strong evidence connecting the use of proton PPIs with a heightened risk of developing CAP. The observed association may be attributed to the existing health issues of patients, who often have an elevated risk for pneumonia before they begin using PPIs. This greater susceptibility likely relates to individual health factors, prior medical conditions, and the severity of GERD, rather than the PPIs themselves.

Table 3. *Risk of bias assessment of the included studies using the NOS tool.*

First author (year)	Selection (out of 4)	Comparability (out of 2)	Outcome (out of 3)	Total score (out of 9)	Quality
Jeon & Kim, 2022 [9]	★★★★	★★	★	7/9	Fair
Evers et al., 2021 [10]	★★★★	★	★★★	8/9	Good
Cohen et al., 2019 [11]	★★★★	★★	★★★	9/9	Good
Lin et al., 2019 [12]	★★★★	★★	★★	8/9	Good
Zirk-Sadowski et al., 2018 [4]	★★★★	★★	★★	8/9	Good
Othman et al., 2016 [5]	★★★★	★★	★★★	9/9	Good

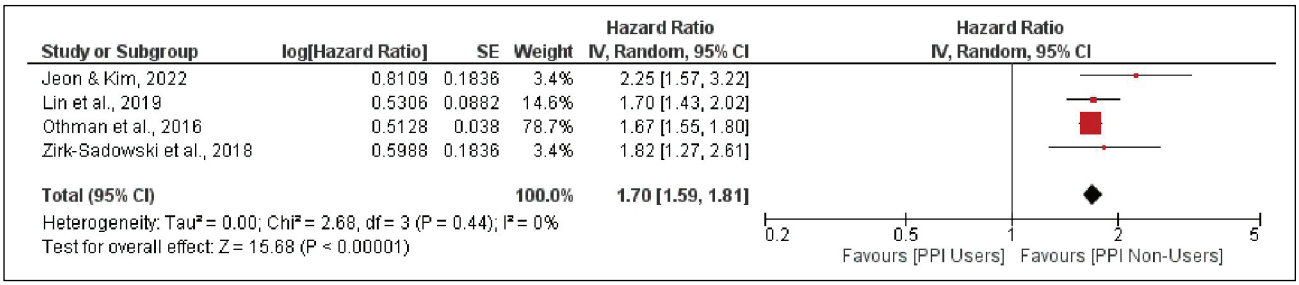


Figure 2. *Forest plot of the association between PPI use and risk of CPA.*

However, the self-controlled design suggested that the association might largely be explained by confounding by indication and other patient characteristics, rather than a direct causal effect of the medications themselves. This idea was strengthened by data that demonstrated an elevated risk even before starting PPI therapy. Data on hospitalization from CAP were limited; however, one study did report a strong association. Importantly, when confounding factors were addressed, the pneumonia-related mortality rate did not reveal a statistically significant increase associated with PPI use. The conclusions, however, were mixed; while several studies caution against overuse of PPIs due to the possible risk of pneumonia, one large study largely attributed the link to confounding variables.

Risk of bias assessment

The quality of the research included in the review was assessed using the NOS (Table 3), and it was mostly high. Five of the six studies were rated "Good" with scores of 8 to 9 out of 9, suggesting good cohort selection and similar groups and good control of confounding variables. "Fair" was the rating given to one study, mostly due to a lower score in the assessment of outcomes. The low risk of bias in most studies enhances the credibility and reliability of the findings (Table 3).

Those who take a PPI had an extremely high risk of CAP. PPI use was associated with a 70% increased risk of developing pneumonia compared with non-PPI users (pooled HR = 1.70, 95% CI: 1.59-1.81, $p < 0.01$). The differences amongst the studies were not very large (Tau² = 0.00; Chi² = 2.68, df = 3, $p = 0.44$; $I^2 = 0\%$). The studies did not vary much, as they all had large sample sizes, which decreased sampling error, and the results were all in the same direction. The systematic review included six articles. Four of them provided HRs that could be combined in a meta-analysis with a 95% CI. Two studies were not included in the quantitative overview but were included in the narrative review. This is because Evers et al. [10] used ORs rather than HRs, and Cohen et al. [11] only reported absolute risks with no HR or OR with CIs (Figure 2).

Sensitivity analysis using the leave-one-out method demonstrated that the pooled HR remained stable, ranging from 1.71 (95% CI 1.55-1.88) to 1.80 (95% CI 1.56-2.07) when individual studies were sequentially excluded. All estimates remained statistically significant ($p < 0.01$) and were consistent with the original pooled HR of 1.70 (95% CI 1.59-1.81). This indicated that the overall finding was robust and not driven by any single study (Figure 3).

A) Excluding Jeon & Kim [9], B) excluding Lin et al. [12], C) excluding Othman et al. [5] and D) excluding Zirk-Sadowski et al. [4].

The funnel plot showed a roughly symmetric distribution of studies around the pooled effect estimate, suggesting no substantial publication bias. However, this finding should be interpreted cautiously because of the limited number of studies (Figure 4).

Visual inspection of the funnel plot suggested relative symmetry, with studies distributed roughly equally around the pooled estimate. However, with only

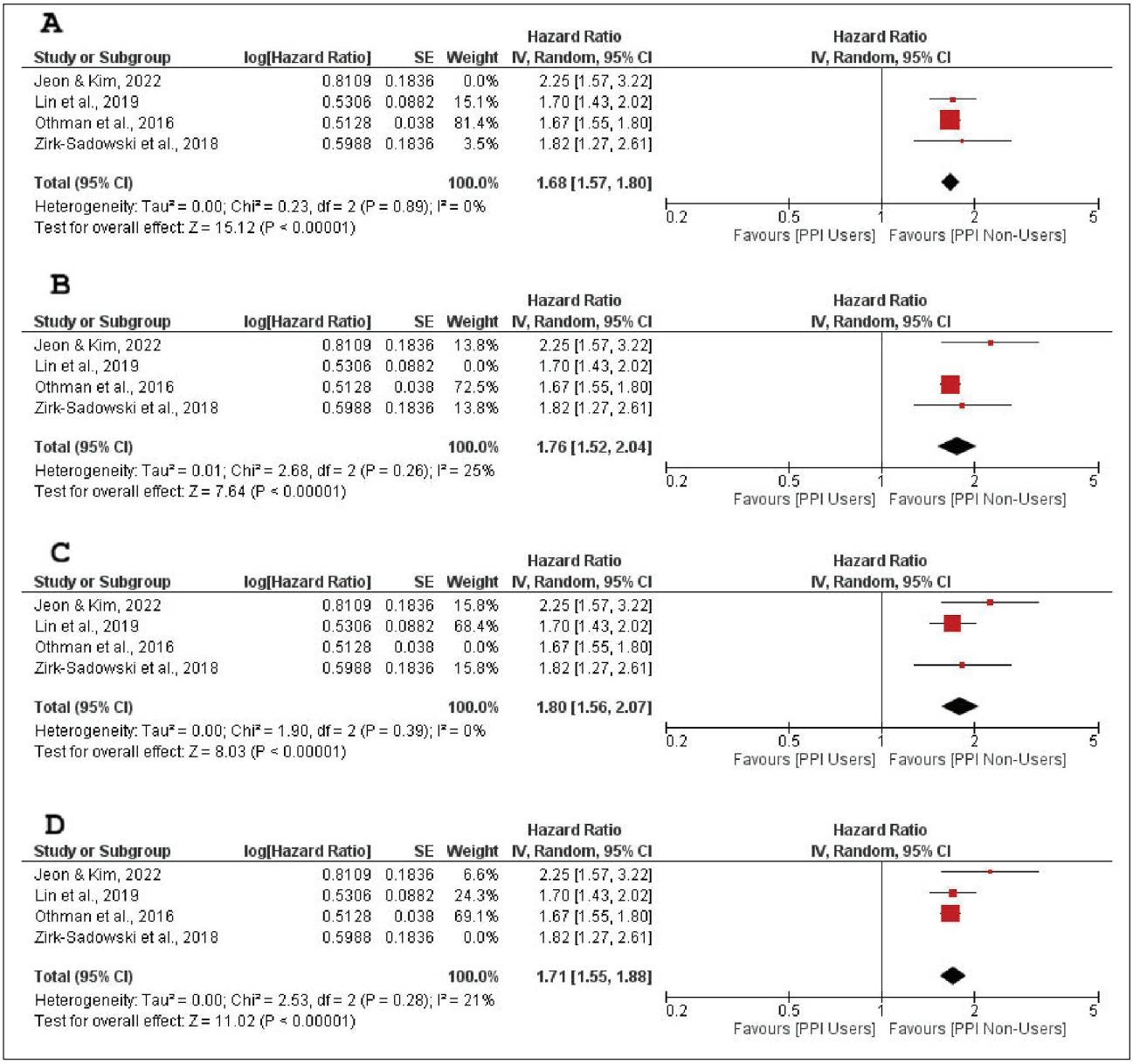


Figure 3. *Sensitivity analysis using the leave-one-out method.*

four studies in the meta-analysis, the power to detect asymmetry was limited, and these results should be interpreted cautiously.

Discussion

PPIs are commonly prescribed for acid-related upper gastrointestinal conditions, such as GERD, peptic ulcer disease, and protection of the stomach from injuries in patients at high risk. While PPIs are thought to be efficacious and safe when used appropriately, their possible adverse events have become of increasing concern as well due to the growing number of cases that include enteric infections, bone fractures, and pneumonia, among others[13-17]. The possibility of acid-suppressing drugs' role in the development of CAP was first suggested in several observational studies, such as the study by Laheij et al., where higher odds of CAP were found in users of gastric acid-suppressive medications [17]. Since that time, many studies and meta-analyses have been conducted on this issue; however, whether there is any causal link between these two phenomena is still questionable, since PPI users tend to have a larger number of comorbidities and thus a greater risk of infection [2,3,5].

Six observational studies were selected for the current systematic review and meta-analysis in order to assess the relationship between the use of PPIs and the risk of CAP. According to the results of the pooled analysis, there is a significantly elevated risk of CAP in those using PPIs in comparison with non-users, with a pooled

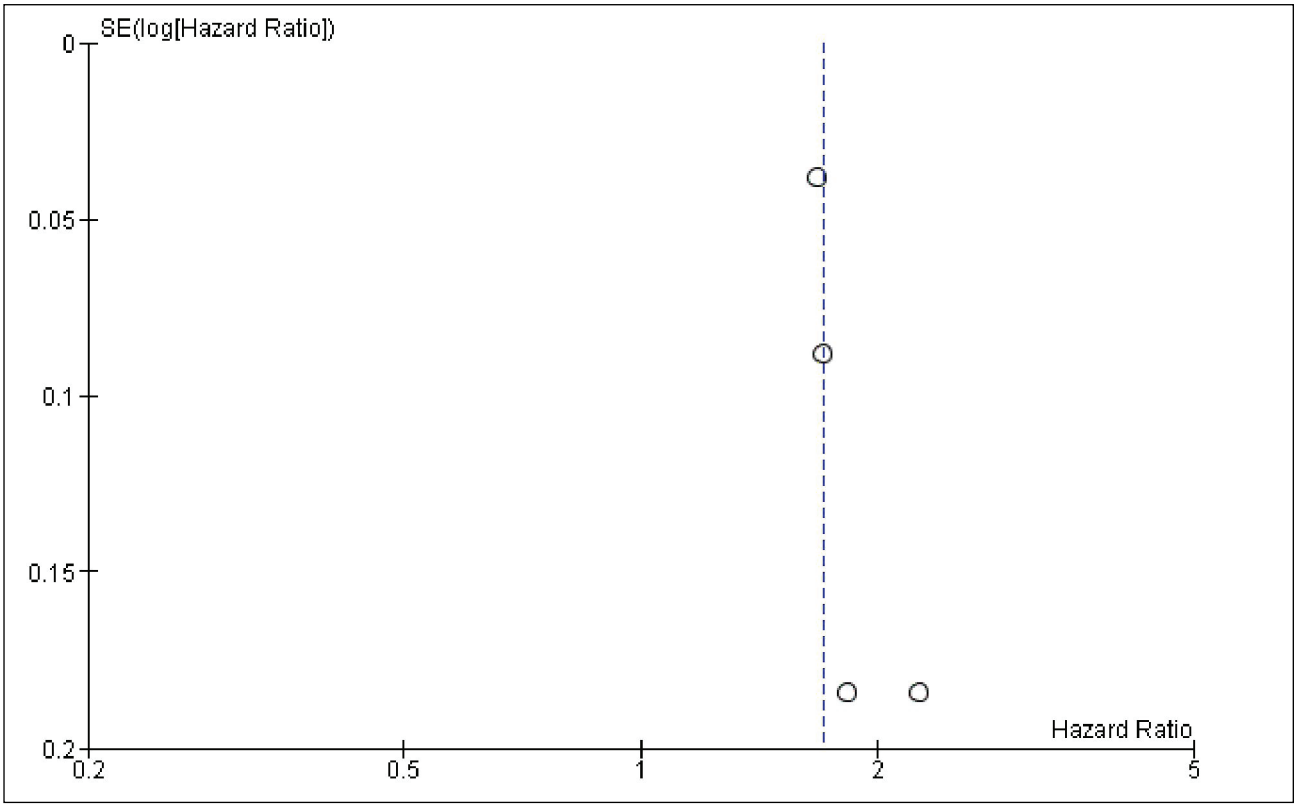


Figure 4. *Funnel plot assessing publication bias for studies evaluating PPI use and CAP risk.*

HR of 1.70 (95% CI, 1.59-1.81). These results indicated an approximate 70% increased risk of CAP among PPI users. The included studies have been performed on various study populations, such as older people, T2DM patients, adults with CHD, and those who had a previous MI [4,5,9-12]. However, it should be noted that despite the significance of the pooled effect and heterogeneity being low, the interpretation of the results should be cautious due to the nature of the selected studies.

Increased risks of CAP in PPI users were indicated by several studies in the review. Jeon and Kim showed that individuals with a history of MI taking PPIs were at least twice as likely to suffer from pneumonia as non-users (aHR, 2.25; 95% CI, 1.57-3.21) [9]. Also, Evers et al. demonstrated a relationship between PPI exposure and higher odds of CAP admissions among adults with CHD where low-dose and high-dose PPI intake increased the odds [10]. Similarly, Lin et al. indicated a dose-response relationship between PPI and pneumonia among patients with T2DM, where the highest category of exposure (≥90 DDDs per year) was associated with a significantly increased risk of pneumonia [12]. It is worth noting that such results have particular significance since the population with diabetes is already at high risk for infections, including pneumonia, and the presence of diabetes is known to be related to poorer prognosis for pneumonia in population-based studies [18-20].

The results from this review are similar to past meta-analysis studies. For example, Lambert et al. indicated that PPI use among outpatients was linked to an increased incidence of CAP, especially within the first month after initiation, implying that the period of exposure is key [3]. Similarly, Eom et al. showed that acid-suppressing medications like PPIs and H2RAs increased the risk of pneumonia, although the included studies had heterogeneity issues and were mostly observational [21]. More recently, Nguyen et al. showed that the use of PPIs was related to a greater risk of CAP overall and even demonstrated significant relationships based on subgroups involving current, recent use, dose, duration, and hospitalization risk [22]. Nevertheless, the past findings suggested the same direction of relationship as in this current review but at the same time demonstrated how challenging it can be to separate the real impact of the medication from patient-related risks.

One plausible biological basis for the relationship between PPI usage and CAP could be the possibility of fostering an environment conducive for bacteria in the upper gastrointestinal (GI) due to decreased acidity in the stomach. This might lead to increased microbial colonization and micro-aspirations, causing a greater probability of developing pneumonia. Another biological explanation for this relationship was that PPIs can affect the microbiome of both the gut and the respiratory system, leading to greater risks of infection [1,2,14]. Nevertheless, biological plausibility is not enough to

prove causation since patients taking PPIs are not the same as those who do not take them.

The concept of confounding becomes even more critical. Othman et al. proved that the risk of developing pneumonia existed prior to the start of PPI treatment and that self-controlled analysis helped decrease the strength of the argument for a direct relationship [5]. Likewise, Maret-Ouda et al. applied self-controlled case series methodology and pointed out that the relationship between PPIs and pneumonia might be influenced by time-dependent covariates and protopathic bias [2]. The protopathic bias is likely to happen when symptoms of an underlying condition precede the development of the disease, and patients are prescribed PPIs due to those symptoms. This question is also relevant in the broader context of studying PPI safety. In their study of PPIs and mortality, Lo et al. used an adjusted lag-time method in order to avoid reverse causation [23].

There was more inconsistent reporting of hospitalizations within the included studies. Evers et al. observed increased likelihood of PPI-associated hospitalizations for CAP in patients with CHDs [10]. On the contrary, Othman et al. observed no association between PPI use and hospitalization due to CAP after adjusting for confounders [5]. In addition, there was also an association between PPI use and increased likelihood of CAP-related hospitalization in a previous meta-analysis by Nguyen et al. [22]. This inconsistency demonstrated that hospitalization is likely to be affected by a number of different factors, including the specific characteristics of the study population. Thus, one cannot consider the results of hospitalization analysis as definitive evidence of the harmful impact of PPI use.

Information on the mortality rate was also insufficient within the included studies. According to Othman et al., there was no statistically significant increase in mortality from pneumonia after the initiation of PPI therapy, accounting for all confounding variables [5]. Therefore, while there is evidence of PPIs' ability to increase the risk of CAP, it is not possible to determine whether PPI use increases the mortality rate in people who suffer from pneumonia.

In summary, the results of this review indicated that the use of PPIs increases the likelihood of developing CAP, at least in higher-risk groups, as well as early and high-dose exposure. Nevertheless, it must be emphasized that since the data used are based on observational studies, it is impossible to establish any causation from the results presented. It is important to note that the results do not mean that the use of PPIs should be completely avoided; rather, it showed the need for prudent prescription of these drugs. It is crucial to re-evaluate the need for PPIs and avoid unnecessary long-term treatment with PPIs while using the lowest effective dosage in vulnerable populations.

There were a few key limitations to this review. All the studies reviewed were observational in nature, and hence, cause and effect is difficult to establish. There were residual confounding concerns, especially with increases in pre-PPI risk. In addition, there was substantial heterogeneity in the definitions of PPI exposure and the measurement of CAP outcomes, which affects the validity of findings. The generalizability of the findings was also limited since the populations studied often had specific health issues. To improve the legitimacy and usefulness of future findings, research should focus on RCTs and uniform criteria.

Conclusion

PPIs have been found to be associated with an increased risk of CAP, which is an intriguing finding. The incidence of this danger was found to be particularly significant at the beginning of treatment and when the dose is substantial. This demonstrated how critical it is for medical professionals to exercise caution while administering PPIs. They should select the lowest dose that is effective for the shortest amount of time and continue to re-evaluate the necessity of continuous treatment, particularly in high-risk categories such as elderly people. According to the review, it is also recommended that safer options, such as H2RAs, be investigated whenever it is feasible to do so.

List of Abbreviations

aHR	Adjusted hazard ratio
CAP	Community-acquired pneumonia
CHD	Congenital heart disease
CI	Confidence interval
DDD	Defined daily dose
GERD	Gastroesophageal reflux disease
H2RA	Histamine-2 receptor antagonist
HR	Hazard ratio
IRR	Incidence rate ratio
MI	Myocardial infarction
NOS	Newcastle–Ottawa Scale
NR	Not reported
OR	Odds ratio
PERR	Prior event rate ratio
PPI	Proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
T2DM	Type 2 diabetes mellitus

Conflict of interest

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Not applicable.

Author details

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