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Original Article

Chronic obstructive pulmonary disease is associated with increased recurrent peptic ulcer bleeding risk

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ABSTRACT

Background: The association between chronic obstructive pulmonary disease (COPD) and the risk of recurrent peptic ulcer bleeding (PUB) remains unclear. In this study, we compared the risk of recurrent PUB between patients with and those without COPD.

Methods: Using the Taiwan National Health Insurance Research Database, we first selected patients newly diagnosed with PUB in 2002–2009. Two groups comprising 13,732 COPD cases and 13,732 non-COPD matched controls were created using propensity score matching, thereby making the differences in basic demographics, medication use, and disease conditions between the two groups negligible. Cox proportional hazard regression was used to evaluate the risk of recurrent PUB during the follow-up period.

Results: The cumulative recurrence rate of PUB was significantly higher in the patients with COPD than in the non-COPD matched controls (2 years: 10.8% vs 9.3%; 6 years: 18.3% vs 15.7%, P all <0.05), with an adjusted hazard ratio (HR) of 1.17 (95% confidence interval [CI], 1.08–1.26, $P<0.001$) and 1.19 (95% CI, 1.12–1.26, $P<0.001$) within 2-year and 6-year follow-ups, respectively. Patients with COPD using steroids were at a marginally higher risk of recurrent PUB than those who did not use steroids. Multivariate stratified analysis revealed similar results in many subgroups.

Conclusions: The risk of recurrent PUB is higher in patients with COPD than in patients without COPD.

1. Introduction

Peptic ulcer bleeding (PUB) is a major healthcare problem [1] with substantial economic effects [2]. Although the prevalence and incidence of peptic ulcer disease have declined [3], PUB remains a serious complication, typically resulting in admission to a hospital with a global mortality rate ranging from 5% to 10% [4,5].

Rebleeding is recognized as a major adverse prognostic factor that potentially contributes to morbidity and mortality [6–8]. Predictors of recurrent PUB include the initial clinical presentations of patients, underlying comorbidities, and whether peptic ulcers have low- or high-risk stigmata [6,8–10]. Identifying the major risk factors for recurrent PUB within a vulnerable population is critical because it would enable clinicians to more accurately identify patients who are at higher risk of morbidity and mortality as well as provide gastroprotective management in a cost-effective manner.

Most studies on recurrent PUB have focused on early or short-term rebleeding risk [10–12], and few studies have discussed long-term rebleeding risk. Two previous studies conducted using the Taiwan National Health Insurance Research Database (NHIRD) have shown that patients with liver cirrhosis or those undergoing hemodialysis were at a high risk of short-term and long-term recurrent PUB [13,14]. These findings are in agreement with previous reports by Rockall et al. and Blatchford et al. [6,15].

Patients with chronic obstructive pulmonary disease (COPD), a common disease with implications on global health [16], are also at a higher risk of developing peptic ulcer disease [17,18]. In addition, COPD has poor outcomes in patients with complications from peptic ulcer-related diseases, such as bleeding and perforation [19]. Moreover,

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a recent large population-based cohort study from Taiwan revealed that patients with COPD are at a higher risk of PUB [20]. To date, evidence of whether COPD increases the risk of recurrent PUB is scarce. Recently, a few studies with small sample sizes have determined that patients with COPD exhibit a higher early risk of recurrent PUB within 30 days after the index PUB event [21,22]. Therefore, in this large population-based cohort study, we examined the risk of recurrent PUB in patients with and without COPD.

2. Methods

2.1. Database

Established in 1995, the National Health Insurance (NHI) program in Taiwan provides comprehensive medical care to nearly all 23.74 million Taiwan residents [23]. The NHI research database, the NHIRD, is one of the largest administrative healthcare databases in the world. It contains information regarding disease diagnosis coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) as well as the treatment procedures, dates of service, and medical costs of beneficiaries, and the names of nearly 20,000 prescription drugs that they have used. Furthermore, basic demographic information regarding the beneficiaries and beneficiary- and provider-encrypted identifiers are included in the NHIRD. To verify the accuracy of the diagnoses and rationale for treatments, the NHIA routinely samples a portion of NHI claims. Furthermore, hospitals and clinics are penalized if they provide unnecessary medical treatment to patients.

In this study, NHIRD data collected between 2000 and 2011 were used, and the data set was maintained by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Executive Yuan, Taiwan. The original identification number for each patient was encrypted for privacy. This cohort data set consisted of deidentified secondary data released to the public for research purposes. This study was approved by the Joint Institutional Review Board of Taipei Medical University.

2.2. Study population

We first identified patients who were initially admitted to the hospital between January 1, 2002 and December 31, 2009 with a primary diagnosis of PUB and who had an endoscopic examination during the same hospitalization. Patients diagnosed with PUB in the years 2000–2001 and 2010–2011 were not included. The former criterion was applied because we used a 2-year period to confirm that PUB occurred recently. The latter criterion ensured that PUB recurrence could be tracked for each patient for a 2-year period. The admission date for PUB was treated as the index date. We excluded patients who were under 18 years, those who had undergone gastric or duodenal surgery or a vagotomy, and those who had gastric cancer during the study period. The third exclusion criterion was applied because differentiating peptic ulcers from gastric cancer mimicking gastric ulcers is difficult.

2.3. COPD cohort and matched controls

Among the patients with PUB, we defined patients with COPD as those who had at least two diagnostic claims for COPD 1 year prior to and 6 months after the index PUB event. We did not include patients with the first diagnosis of COPD more than 6 months after the index PUB event because of the difficulty in examining the association between COPD and recurrent PUB by using a retrospective cohort study design even though COPD is a chronic illness. Furthermore, this study primarily focused on patients with COPD; therefore, we additionally excluded those who also had asthma. Furthermore, patients with acute respiratory failure (ARF) might also have COPD, but this could potentially introduce a bias if ARF is associated with an increased risk of peptic ulcer formation and bleeding. Therefore, we also excluded patients with ARF.

The globally accepted method for identifying the severity of COPD is based on the guideline of the current global initiative for chronic obstructive lung disease (GOLD). According to the guideline, four categories of COPD patients were created on the basis of the patients' symptoms and the risk of exacerbation. Unfortunately, data on spirometric classification were unavailable for this study. Therefore, we used the following broad categories to classify the COPD patients for proxy measurement of the severity of COPD: (1) using inhaled or oral β_2-agonists only and (2) using inhaled or oral glucocorticoids (including regimens combining β_2-agonists).

The non-COPD cohort comprised patients who were not diagnosed with COPD, asthma, or ARF throughout the study period. Because the baseline characteristics of patients with COPD might differ from those of the patients without COPD, we applied propensity score matching (PSM) to select a group of patients that had very similar characteristics to those of patients with COPD but differed in COPD status. The propensity score was calculated using a combination of a patient's age, sex, use of ulcerogenic medication (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], acetylsalicylic acid, steroids, clopidogrel, ticlopidine, and warfarin), and the presence of *Helicobacter pylori* infection and other comorbidities (e.g., coronary artery disease, hypertension, diabetes mellitus, heart failure, and chronic kidney disease). The Charlson comorbidity index was also inlcuded as a measure of the homogeneity and severity of the clinical conditions associated with the probability of patients having or not having COPD. The ICD-9-CM codes for disease diagnostic coding are presented in Supplementary Table 1. The PSM is commonly used in observational studies to reduce sample selection bias [24,25]. After PSM, the baseline demographics and medical characteristics (including gastroprotective and ulcerogenic medication) between the two groups (COPD and non-COPD) were comparable (Table 1).

Both patients with COPD and matched control patients who received eradication therapy for *H. pylori* after the index PUB event were defined as having *H. pylori*-associated peptic ulcers. *H. pylori* eradication therapy was defined as treatment involving proton pump inhibitors or H_2 receptor antagonists, with clarithromycin or metronidazole, with amoxicillin or tetracycline, with or without bismuth, and other regimens (details on all eligible *H. pylori* eradication regimens are available in other reports) [13,14,26]. We used H_2 receptor antagonists to define patients with *H. pylori* eradication therapy because the prescription of proton pump inhibitors was permitted for patients with *H. pylori* infection after October 1, 2003.

2.4. Main outcome measure

The primary endpoint was hospitalization for recurrent PUB during the follow-up period. Recurrent PUB was identified according to the patient having a discharge record with a primary diagnosis of PUB and an endoscopic examination after the index PUB event during the study period. Patients who were readmitted or transferred to another hospital within 3 days after the index PUB event were considered to receive a part of the same treatment course as that of the index hospitalization. Furthermore, we analyzed only the first episode of rebleeding for patients who had more than one episode of recurrent PUB.

2.5. Statistical analysis

The standardized difference was used to compare the mean of continuous and binary variables between the COPD and control groups. The standardized difference is a method that has been suggested to measure the similarity of baseline characteristics in propensity score-matched samples [25,27,28]. It represents the difference in means between two groups in units of standard deviation. Unlike significance testing where the convention that a *P* value of less than 0.05 denotes statistical significance, some authors have suggested that standardized differences of less than 0.10 likely denote a negligible imbalance between case patients and their matched controls [25].