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Enhanced risk of traumatic brain injury in patients with chronic obstructive pulmonary disease

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ABSTRACT

This study tests our hypothesis that patients with chronic obstructive pulmonary disease (COPD) have an increased risk of traumatic brain injury (TBI).

In this nationwide retrospective cohort study, we used a subset of Taiwan's National Health Insurance Research Database, involving 1 million randomly selected beneficiaries. Patients with newly diagnosed COPD between 2000 and 2008 were identified. They were subgrouped as '$COPD_{AE+}$' (if they had severe acute exacerbation of COPD during the follow-ups) or '$COPD_{AE-}$' (if they had no acute exacerbation), and were frequency matched with randomly selected subjects without COPD (the 'non-COPD' group). Baseline differences were balanced by the inverse probability of treatment weighting based on the propensity score. For each patient, the risk of TBI during the subsequent 5 years was determined. The competing risk of death was controlled.

We identified 3734 patients in '$COPD_{AE+}$', and frequency matched them with 11,202 patients in '$COPD_{AE-}$' and 11,202 subjects in 'non-COPD'. Compared with those in 'non-COPD', patients in '$COPD_{AE+}$' and '$COPD_{AE-}$' had an increased risk of TBI: the adjusted HR for '$COPD_{AE+}$' was 1.50, 95% CI 1.31 to 1.73, and that for '$COPD_{AE-}$' was 1.21, 95% CI 1.09 to 1.34. The highest risk was observed in the '$COPD_{AE+}$' group that aged <65 (the adjusted HR was 1.92; 95% CI 1.39 to 2.64).

COPD has been linked to complications beyond the respiratory system. In this study we showed that COPD is associated with an increased risk of TBI.

Significance of this study

What is already known about this subject?

► Chronic obstructive pulmonary disease (COPD) causes such extrapulmonary complications as sarcopenia and impairments in cognitive, neuromuscular, and balancing functions. These complications predispose the patients to fall and transport-related injury, both of which are epidemiologically leading causes of traumatic brain injury (TBI).

What are the new findings?

► We showed that patients with COPD of both sex had an increased risk of TBI. The risk was highest in those who had an age of less than 65 years and at least 1 episode of severe acute exacerbation of COPD during the follow-up.

How might these results change the focus of research or clinical practice?

► Patients and caregivers of COPD need to be aware of such an increased risk of TBI, for TBI would certainly complicate the management and rehabilitation of patients with COPD. Our findings would call for further research to clarify the causal mechanism underlying the association between COPD and TBI, and to develop effective measures to decrease the risk of TBI in this population.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) continues to be a great threat in public health globally.[1] The debilitating effect of COPD is not confined to the respiratory tract, but can involve multiple organ systems. Cognitive dysfunction, musculoskeletal deconditioning, and impairments in balance and instrumental activities (referring to those activities required to sustain daily living and self-care) of the patients have been well described.[1–14] These extrapulmonary complications might predispose patients to fall accidents,[12–14] particularly those who need supplemental oxygen.[14] Previous studies also demonstrated that COPD might have potentially detrimental effects on the driving performance of the patients, including those without hypoxemia.[15–20] Moreover, many patients also suffer from acute exacerbations, which accelerate disease progression and further compromise patients' functional capacity.[1 21–25] Meanwhile, traumatic brain injury (TBI) remains another great hazard to health. Epidemiological surveys around the world consistently reported falls and transport-associated injuries as major etiologies of TBI.[26–37] Based on this background, we hypothesized that patients with COPD might be susceptible to TBI, which would cause enhanced disability in the patients and complicate subsequent care. In this study, we tested our hypothesis using a nationwide population-based database.

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MATERIALS AND METHODS

Study objective, design, and population

In this study, we tested our hypothesis that patients with COPD have an increased risk of TBI. This is a retrospective cohort study using a subset of the National Health Insurance (NHI) Research Database containing comprehensive inpatient and outpatient claims of 1 million beneficiaries randomly selected from Taiwan's 23 million population between 1996 and 2013. All beneficiaries were screened for patients with COPD who were diagnosed between 2000 and 2008. A patient with COPD was defined as one who was 40 years or older, had received the diagnosis of COPD (defined as having such International Classification of Diseases, Ninth Revision, Clinically Modified (ICD-9-CM) codes as 491, 492, and 496) in at least 2 outpatient records (within 1 year apart) or 1 inpatient record, and had received COPD-specific medicinal prescriptions within 2 years that the diagnosis was made. The date when a patient met all these inclusion criteria was defined as the index date for the patient. The codes of all the available prescription medicines used to treat COPD in Taiwan during this same period of time were obtained from the official website of Taiwan's NHI Administration, Ministry of Health and Welfare.[38] Online supplementary table S1 lists the COPD-specific medicinal prescriptions that were determined according to the contemporary Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines parallel in time to our study period.[39–41] The diagnosis of TBI was specified by such ICD-9-CM codes as 800, 801, 803, 804, and 850–854, of which 852 and 853 specify hemorrhagic TBI while the others represent non-hemorrhagic TBI. A subject was identified as having an event of TBI when the subject had 1 record of emergency room visit, 1 inpatient record, or 2 outpatient records bearing TBI as a major diagnosis. We excluded patients who had already received the diagnosis of COPD or TBI before the year 2000, those who received the diagnosis of TBI earlier than the diagnosis of COPD, those who were chronically dependent on mechanical ventilation, and those without COPD-specific medicinal prescriptions. We also excluded patients who, within 1 year before and after the diagnosis of COPD, also received the diagnosis of asthma (ICD-9-CM 493) in at least 2 outpatient records or 1 inpatient record. Among all the included patients with COPD, we identified those patients who had at least 1 episode of severe acute exacerbation (defined as an emergency room visit or hospitalization with COPD as the primary diagnosis)[1 21–25] after the index date but before the occurrence of TBI or the end of follow-up to constitute the '$COPD_{AE+}$' group. Those remaining patients with COPD who had no severe acute exacerbation after the index date during follow-up constituted the '$COPD_{AE-}$' group. Subjects without COPD were randomly selected from the remaining beneficiaries to constitute the 'non-COPD' group. These 3 groups (namely '$COPD_{AE+}$', '$COPD_{AE-}$', 'non-COPD') were frequency matched in age, sex, and index date with a ratio of 1:3:3, respectively. For all included subjects, pertinent demographical data were obtained, including age, sex, living area, urbanization level, monthly income, enrollee category (containing 4 categories that served as an approximation of occupational and socioeconomic status: (1) full-time or regularly paid teachers and government employees; (2) employees of privately owned enterprises; (3) other employees or independent professionals; (4) low-income earners, unemployed pensioners, or veterans). Because COPD and TBI were both associated with multiple comorbidities, for each included subject we paid particular attention to identify the presence of coexisting morbidities. Online supplementary table S2 lists the ICD-9-CM codes of all the disease entities included in this study. For all included subjects, data for 5 years following the index date were analyzed to determine the subsequent risk of developing TBI. Death was identified for competing risk analysis. For those who had been hospitalized due to TBI, days of hospital stay were calculated. Subjects missing any of the above-mentioned data, and subjects with insufficient follow-ups, were excluded.

Statistical analysis

Data were presented as means with SD if normally distributed, and medians with IQR if otherwise. To account for the differences in baseline characteristics and comorbidities among the 3 groups ('$COPD_{AE+}$', '$COPD_{AE-}$', and 'non-COPD'), we first compared the baseline characteristics among the 3 groups using Pearson's χ^2 test for categorical variables and one-way analysis of variance for continuous variables. We then applied the method of inverse probability of treatment weighting (IPTW) based on the propensity score.[42–45] Briefly, for each patient the propensity score was calculated by constructing multivariable logistic regression models involving all the demographical characteristics and comorbidities as covariables. The IPTW for each patient was subsequently derived by the inverse of the propensity score, and then transformed to a patient-specific stabilized weight. Stabilized weights were then applied to balance the differences in baseline characteristics and in the prevalence of comorbidities among the 3 study groups, giving rise to an unbiased pseudocohort ('the IPTW cohort'). IPTW was performed separately to balance the differences among the 3 major whole groups and also those among the subgroups. We used the IPTW-balanced data for all subsequent analyses.[43 45] Kaplan-Meier analysis was conducted to determine the 5-year TBI-free survival probabilities. Cox proportional hazards regression was carried out to derive crude HRs for TBI during follow-up, while stratified Cox regression was performed to derive adjusted HRs, adjusting for such covariates as age, living area, urbanization level, monthly income, enrollee category, and comorbidities. We also controlled for the competing risk of death by constructing competing risk regression models to derive subdistribution HRs.[46] Sensitivity analysis was done, using R package 'obsSens', by setting an additional hypothetical covariable to evaluate the effect from the potentially unmeasured confounder. All statistical analyses were performed with the statistical packages SAS (V.9.4, SAS Institute) and R (V.3.2.5).

Validation of major diagnoses

The working definitions we applied in this study to define major diagnoses (COPD and TBI) were validated using the actual medical records at National Cheng Kung University Hospital (a 1200-bed tertiary medical center in southern Taiwan) between January 2008 and December 2011. For COPD, we randomly screened out 200 candidate patients

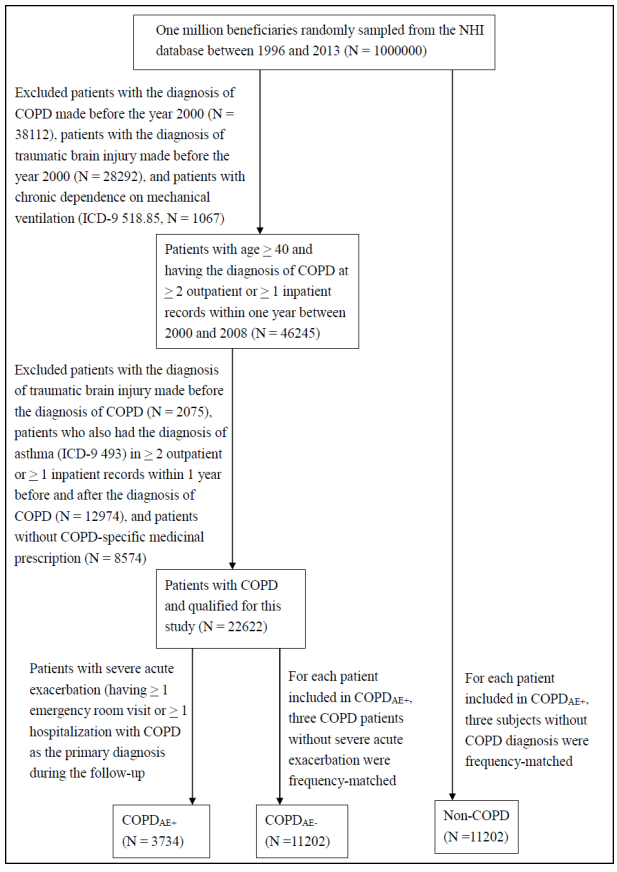


Figure 1 Flow chart of inclusion and exclusion for this study. COPD, chronic obstructive pulmonary disease; ICD-9, International Classification of Diseases, Ninth Revision; NHI, National Health Insurance.

by applying the same working definitions to those we used in this present study (ICD-9-CM codes, age, and the prescription of COPD-specific medication). The diagnoses of these candidate patients were then validated by confirming (through an extensive review of the medical records) the documentation of compatible symptoms, that the diagnosis was made by board-certified pulmonologist, the documentation of GOLD-defined obstructive ventilatory deficit on spirometry, and preferably a positive history of smoking. For TBI, we randomly screened out 200 candidate patients by applying the same working definitions (ICD-9-CM disease codes) as we used in this present study. The diagnoses of these candidate patients were then validated by confirming a documented history of head trauma, the prescription of pertinent managements, and preferably data from brain imaging studies. Positive predictive values (PPV) of the working definitions were 94% (95% CI 89% to 97%) for COPD and 94% (95% CI 90% to 97%) for TBI.

RESULTS

Figure 1 illustrates the flow chart of inclusion and exclusion for this study. From 1 million randomly selected beneficiaries, we identified 3734 patients who had COPD and severe acute exacerbation during follow-up ('$COPD_{AE+}$'), and frequency matched them with 11,202 patients with COPD without acute exacerbation ('$COPD_{AE-}$') and 11,202 non-COPD subjects ('non-COPD'). Table 1 displays the baseline characteristics of these 3 groups. Of the included subjects, 65% were male and more than 70% aged ≥65 years. Compared with non-COPD subjects, patients with COPD had a higher prevalence of all the selected comorbidities (many of which were also associated with TBI). However, the application of IPTW based on the propensity score effectively balanced those baseline intergroup differences in the prevalence of comorbidities (table 1).

During the 5-year period after the index date, 312 (8.4%), 742 (6.6%), and 588 (5.3%) patients in '$COPD_{AE+}$', '$COPD_{AE-}$', and 'non-COPD' developed TBI, respectively. Patients with COPD, regardless of having severe acute exacerbation or not, consistently exhibited elevated crude and adjusted HRs for TBI relative to non-COPD subjects: the adjusted HRs for patients with COPD as a whole, and for patients in '$COPD_{AE+}$' and '$COPD_{AE-}$' subgroups, were 1.28 (95% CI 1.16 to 1.41), 1.50 (95% CI 1.31 to 1.73), and 1.21 (95% CI 1.09 to 1.34), respectively. After controlling for the risk of death, multivariable competing risk regression models yielded concordant findings: for patients with COPD as a whole, and for patients in '$COPD_{AE+}$' and '$COPD_{AE-}$' subgroups, the subdistribution HRs for TBI were 1.13 (95% CI 1.02 to 1.23), 1.27 (95% CI 1.11 to 1.46) and 1.08 (95% CI 0.97 to 1.20), respectively. When a comparison was made specifically between the 2 subgroups of patients with COPD, we found that patients in '$COPD_{AE+}$' also had a slightly but significantly higher risk of TBI than those in '$COPD_{AE-}$' (the adjusted HR was 1.25; 95% CI 1.09 to 1.43), even after controlling for the risk of death (table 2). Kaplan-Meier analyses revealed the worst TBI-free survival in the group '$COPD_{AE+}$', which was followed by '$COPD_{AE-}$'; non-COPD subjects exhibited the highest probability of TBI-free survival (figure 2).

Further stratifying analysis based on age revealed that patients with COPD (particularly those having severe acute exacerbation), either with advanced (≥65) or with younger (≥40 and <65) ages, consistently exhibited increased crude, adjusted, and subdistribution HRs for TBI as compared with non-COPD subjects of the same ranges of age. Moreover, although the study cohort was predominated by patients aged ≥65 years, it was those patients with COPD aged <65 years (regardless of having acute exacerbation or not) that exhibited the highest risk of TBI: the adjusted HRs for TBI for patients with COPD as a whole and for patients in '$COPD_{AE+}$' and '$COPD_{AE-}$' subgroups were 1.73 (95% CI 1.37 to 2.18), 1.92 (95% CI 1.39 to 2.64), and 1.67 (95% CI 1.31 to 2.13) for patients aged <65 years, and 1.23 (95% CI 1.10 to 1.37), 1.52 (95% CI 1.30 to 1.77), and 1.14 (95% CI 1.01 to 1.28) for patients aged ≥65 years, respectively (table 2). When the comparison was made between the 2 subgroups of patients with COPD ('$COPD_{AE+}$' vs '$COPD_{AE-}$'), those patients in '$COPD_{AE+}$', regardless of age, exhibited an increased risk of TBI as compared with those in '$COPD_{AE-}$' (table 2).

Despite that our cohort had a male predominance, stratifying analysis revealed that both male and female patients with COPD exhibited elevated crude, adjusted, and subdistribution HRs for TBI as compared with non-COPD subjects, particularly those having severe acute exacerbation. When comparing between '$COPD_{AE+}$' and '$COPD_{AE-}$',

Table 1 Baseline demographic characteristics and comorbidities among the 3 patient groups (before and after balancing by the inverse probability of treatment weighting (IPTW) based on the propensity scores)

	Full cohort				IPTW cohort			
Characteristic	$COPD_{AE+}$* (%) n=3734	$COPD_{AE-}$† (%) n=11,202	Non-COPD‡ (%) n=11,202	P value	$COPD_{AE+}$* (%)	$COPD_{AE-}$† (%)	Non-COPD‡ (%)	P value
Whole group mean age±SD (y)	71.0±11.8	68.7±11.5	66.2±12.4	<0.01	67.9±12.3	68.0±11.8	68.0±11.8	0.738
Male	65.3	65.3	65.3	1.000	65.6	65.2	65.7	0.802
Living area				<0.01				0.819
Northern Taiwan	35.9	42.0	46.0		42.1	42.8	42.7	
Central Taiwan	28.6	26.4	22.3		24.6	25.0	25.2	
Southern Taiwan	30.9	28.5	28.0		29.9	28.6	28.5	
East and offshore	4.1	3.1	3.7		3.3	3.6	3.6	
Urbanization level				<0.01				0.923
1 (most urbanized)	23.5	27.4	31.7		28.6	28.5	28.6	
2	21.6	24.2	25.4		24.0	24.6	24.2	
3 (rural)	54.9	48.4	42.9		47.4	46.9	47.2	
Enrollee category				<0.01				0.956
1	9.1	11.9	13.1		11.8	12.2	12.2	
2	22.7	24.0	32.0		27.0	27.0	26.8	
3	50.6	49.0	42.5		47.4	46.5	46.7	
4	17.6	15.1	12.5		13.8	14.4	14.3	
Monthly income				<0.01				0.989
NT$≤15,840	42.0	37.7	38.6		38.2	38.6	38.3	
NT$15,840–NT$25,000	50.5	48.8	43.9		47.3	47.0	47.2	
NT$≥25,001	7.5	13.5	17.5		14.5	14.4	14.5	
Comorbidities								
Epilepsy	3.8	2.2	0.6	<0.01	1.8	1.8	2.0	0.687
Sleep apnea	1.3	1.0	0.3	<0.01	0.7	0.7	0.9	0.708
Ischemic stroke/TIA	21.5	15.5	8.2	<0.01	13.7	13.4	14.3	0.330
Dementia	12.6	7.7	2.8	<0.01	6.5	6.3	7.0	0.444
Alzheimer's disease	4.0	2.3	0.9	<0.01	2.0	2.0	2.5	0.404
Parkinson's disease	6.0	3.7	1.7	<0.01	3.4	3.2	3.7	0.407
Alcoholic mental disorder	0.3	0.2	0.1	0.04	0.2	0.2	0.2	0.852
Drug-related mental disorders	0.3	0.1	0.1	0.01	0.2	0.1	0.3	0.778
ASVD	40.7	34.8	18.3	<0.01	28.3	28.8	29.5	0.388
DM	30.7	29.3	19.6	<0.01	25.6	25.6	26.2	0.698
Chronic hepatitis	10.5	14.4	9.0	<0.01	11.3	11.7	11.8	0.735
CKD	8.7	6.3	3.3	<0.01	5.7	5.4	5.9	0.506

Continued

Table 1 Continued

Characteristic	Full cohort				IPTW cohort			
	$COPD_{AE+}$* (%) n=3734	$COPD_{AE-}$† (%) n=11,202	Non-COPD‡ (%) n=11,202	P value	$COPD_{AE+}$* (%)	$COPD_{AE-}$† (%)	Non-COPD‡ (%)	P value
Obesity	0.6	0.6	0.3	<0.01	0.5	0.5	0.5	0.980
Hyperlipidemia	19.3	27.2	19.4	<0.01	23.0	23.1	23.9	0.471

Data are presented as percentages, except for 'whole group mean age' presented as mean±SD.
*Patients having COPD and ≥1 severe acute exacerbation during follow-up.
†Patients with COPD but without severe acute exacerbation during follow-up.
‡Patients without COPD.
ASVD, atherosclerotic vascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; NT$, new Taiwanese dollars; TIA, transient ischemic attack.

patients of both sexes in '$COPD_{AE+}$' had a higher risk of TBI than those in '$COPD_{AE-}$' (table 3).

We further classified TBI into non-hemorrhagic and hemorrhagic subtypes. Patients with COPD, whether having acute exacerbation or not, had significantly increased risk of non-hemorrhagic TBI as compared with non-COPD subjects, with the adjusted HRs being 1.30 (95% CI 1.17 to 1.45), 1.61 (95% CI 1.39 to 1.88), and 1.20 (95% CI 1.07 to 1.35) for all patients with COPD, patients in '$COPD_{AE+}$', and patients in '$COPD_{AE-}$', respectively. For hemorrhagic TBI, although all the CIs of HRs did not reach statistical significance, the point estimates show several interesting trends. Patients in '$COPD_{AE-}$' exhibited a trend of increased risk as compared with non-COPD subjects: the adjusted HR was 1.22 (95% CI 0.96 to 1.56) for '$COPD_{AE-}$'. Patients in '$COPD_{AE+}$', on the other hand, seemed to exhibit a trend of lower risk of hemorrhagic TBI. When comparing the 2 groups of patients with COPD, we found that patients in '$COPD_{AE+}$' still exhibited a significantly increased risk of non-hemorrhagic TBI, but a trend of decreased risk of hemorrhagic TBI, as compared with '$COPD_{AE-}$'. Multivariable competing risk regression models (controlling for the risk of death) also yielded concordant findings (table 4).

For those patients who developed TBI during follow-up, 111 (35.6%), 250 (33.7%), and 189 (34.4%) patients in '$COPD_{AE+}$', '$COPD_{AE-}$', and 'non-COPD' were hospitalized due to TBI, respectively. We found no significant difference in the length of hospital stay among the 3 groups (online supplementary table S3 and figure S1). Sensitivity analysis showed that even when a hypothetical unmeasured confounder was present, COPD (either with or without severe acute exacerbation) was mostly a significant risk factor for TBI at 5 years of follow-up, which further supported the robustness of our findings (online supplementary figure S2a,b).

DISCUSSION

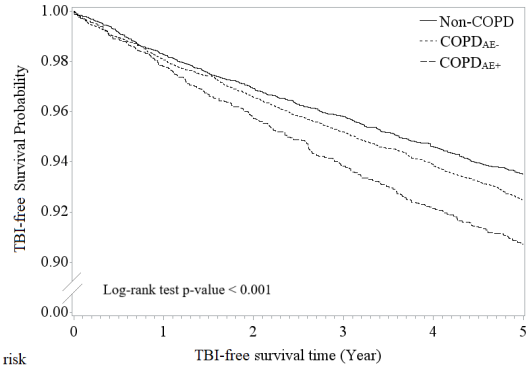
COPD is associated with extrapulmonary complications. In this present study, after controlling for the competing risk of death and the differences in baseline characteristics and comorbidities, we show that patients with COPD have an increased risk of TBI, regardless of the differences in sex, age, and the history of acute exacerbation of COPD.

Worldwide epidemiological studies have repeatedly reported fall and transport-related injury as 2 major etiologies of TBI.[26–37] Specifically, in elderly patients fall accounts for most TBI, whereas in younger adults traffic accidents are the leading cause.[30] Cognitive dysfunction and weakness of the extremities (particularly lower extremities) have been repeatedly reported as risk factors for fall in elderly patients.[47–50] The prevalence of COPD increases with advancing age (this was also observed in our study cohort where > 70% of patients aged ≥65). Besides, cognitive dysfunction and cachexia (causing sarcopenia and weakness) are well-recognized complications of COPD. Moreover, previous studies have well demonstrated an impairment in balance among patients with COPD, which predisposed these patients to fall.[12–14] Therefore, it is likely that an association exists between COPD and fall, and also between COPD and fall-induced TBI. The findings of our present study support for such an association.

Table 2 HRs for traumatic brain injury at 5 years of follow-up for all the included patients and for the subgroups of age

	Groups of patients with COPD versus patients without COPD				$COPD_{AE+}$ versus $COPD_{AE-}$	
Patient groups	**$COPDAll_{patients}$**	**$COPD_{AE+}$**	**$COPD_{AE-}$**	**Non-COPD**	**$COPD_{AE+}$**	**$COPD_{AE-}$**
All patients (n)	14,936	3734	11,202	11,202	3734	11,202
Death, n (%)*	4099 (27.4)	1476 (39.5)	2623 (23.4)	1361 (12.2)	1476 (39.5)	2623 (23.4)
TBI, n (%)	1054 (7.06)	312 (8.4)	742 (6.6)	588 (5.3)	312 (8.4)	742 (6.6)
cHR (95% CI)	1.23 (1.11 to 1.35)	1.45 (1.26 to 1.66)	1.16 (1.04 to 1.29)	1	1.25 (1.09 to 1.43)	1
aHR (95% CI)	1.28 (1.16 to 1.41)†	1.50 (1.31 to 1.73)†	1.21 (1.09 to 1.34)†	1	1.25 (1.09 to 1.43)†	1
CRR (95% CI)	1.13 (1.02 to 1.23)†	1.27 (1.11 to 1.46)†	1.08 (0.97 to 1.20)†	1	1.18 (1.03 to 1.36)†	1
40≤Age<65 (n)	4064	1016	3048	3048	1016	3048
IPTW-balanced mean age±SD (y)	51.9±7.2	52.0±7.1‡	51.9±7.2‡	52.2±7.5‡	52.0±7.1‡	51.9±7.2‡
Death, n (%)*	399 (9.8)	194 (19.1)	205 (6.7)	91 (3.0)	194 (19.1)	205 (6.7)
TBI, n (%)	241 (5.93)	72 (7.1)	169 (5.5)	98 (3.2)	72 (7.1)	169 (5.5)
cHR (95% CI)	1.72 (1.36 to 2.16)	1.90 (1.38 to 2.62)	1.66 (1.30 to 2.12)	1	1.15 (0.85 to 1.55)	1
aHR (95% CI)	1.73 (1.37 to 2.18)†	1.92 (1.39 to 2.64)†	1.67 (1.31 to 2.13)†	1	1.15 (0.85 to 1.55)†	1
CRR (95% CI)	1.68 (1.33 to 2.12)†	1.80 (1.30 to 2.48)†	1.64 (1.28 to 2.10)†	1	1.09 (0.81 to 1.47)†	1
65≤Age (n)	10,872	2718	8154	8154	2718	8154
IPTW-balanced mean age±SD (y)	74.0+6.6	74.1±6.6§	74.0±6.6§	74.0±6.9§	74.1±6.6§	74.0±6.6§
Death, n (%)*	3700 (34.0)	1282 (47.2)	2418 (29.7)	1270 (15.6)	1282 (47.2)	2418 (29.7)
TBI, n (%)	813 (7.48)	240 (8.8)	573 (7.0)	490 (6.0)	240 (8.8)	573 (7.0)
cHR (95% CI)	1.20 (1.08 to 1.34)	1.49 (1.27 to 1.73)	1.12 (0.99 to 1.27)	1	1.33 (1.14 to 1.55)	1
aHR (95% CI)	1.23 (1.10 to 1.37)†	1.52 (1.30 to 1.77)†	1.14 (1.01 to 1.28)†	1	1.33 (1.14 to 1.55)†	1
CRR (95% CI)	1.07 (0.96 to 1.19)†	1.27 (1.08 to 1.48)†	1.00 (0.89 to 1.13)†	1	1.26 (1.08 to 1.48)†	1

*Number of deaths during follow-up before the development of TBI (not a major outcome, but for competing risk adjustment).
†Values were derived from stratified Cox regression.
‡The p value is 0.331 for intergroup comparison.
§The p value is 0.536 for intergroup comparison.
aHR, adjusted HR; cHR, crude HR;COPD, chronic obstructive pulmonary disease; $COPD_{AE+}$, patients having COPD and ≥1 severe acute exacerbation during follow-up; $COPD_{AE-}$, patients with COPD but without severe acute exacerbation during follow-up; CRR, competing risk regression (values are subdistribution HR, controlling for the competing risk of death); IPTW, inverse probability of treatment weighting (based on the propensity scores);non-COPD, patients without COPD; TBI, traumatic brain injury.



Number at risk						
$COPD_{AE+}$	3716	3192	2893	2660	2431	2212
$COPD_{AE-}$	11177	9809	9220	8725	8333	7927
Non-COPD	11328	10746	10223	9728	9267	8856

Figure 2 Kaplan-Meier curves of traumatic brain injury (TBI)-free survival rates for the 3 groups of patients (log-rank test p<0.001; numbers at risk of the inverse probability of treatment weighting (IPTW) cohort are listed below the plot). COPD, chronic obstructive pulmonary disease; $COPD_{AE+}$, patients having COPD and ≥1 severe acute exacerbation during follow-up; $COPD_{AE-}$, patients having COPD and no severe acute exacerbation during follow-up; non-COPD, patients without COPD.

Details about the etiology of individual TBI were unavailable from the NHI Research Database. However, it was possible that in addition to fall, a great proportion of the TBIs of our patients might be transport related. This rationale is based on the international and local epidemiological data. Chiu *et al*[35 36] and Lin *et al*[37] surveyed the epidemiological characteristics of TBI in Taiwan between 1988 and 2002 and reported that traffic accidents (particularly those relating to riding scooters) accounted for more than 60% of TBI over this long period of time. As described in the Materials and Methods section, we have validated the working definitions for the major diagnoses for this study using the clinical data of randomly selected 200 patients with COPD and 200 patients with TBI from our hospital. Analysis of the data of these 200 patients for validating the TBI diagnostic definition also identified transport-related injury, in addition to fall, as a major cause of TBI particularly in those aged 40–64 (online supplementary table S4). Previous studies have shown that patients with COPD, even those with mild disease and without hypoxemia, exhibited impairment in their driving performance.[15–20] Orth *et al* reported that patients with COPD (with GOLD-defined moderate or severe airflow obstruction but without hypoxemia or hypercapnea) caused more accidents in simulated driving situations than controls.[18] Interestingly, we observed an even higher risk of TBI in those patients with COPD aged <65 years than those aged ≥65 years. Epidemiologically, transport-related injury is more likely than fall to be the cause of TBI among patients of younger age groups.[26–37] It is possible that both fall and transport-related injury are important causes of TBI in patients with COPD. Nevertheless, further study is warranted to clarify whether there is a direct link between COPD and TBI due to transport-related injury.

Regardless of sex and age strata, patients in '$COPD_{AE+}$' consistently exhibited a slightly higher risk of TBI than those in '$COPD_{AE-}$'. This finding is possibly a reflection of the deleterious impacts of severe acute exacerbations of COPD on the physical and functional performances of the patients.[21 22] However, due to the lack of patient-specific data from the NHI Research Database on changes in ambulatory capacities and functional status following an acute exacerbation of COPD, it is still not possible at this moment, apart from identifying an association, to draw a definite conclusion on the causal relationship between acute exacerbation and the TBI risk. Another interesting finding from our study is that, when compared with patients in '$COPD_{AE-}$', those in '$COPD_{AE+}$' had an increased risk of non-hemorrhagic TBI, but showed a trend toward a reduced risk of hemorrhagic TBI. A possible explanation for this finding is that patients in '$COPD_{AE+}$' might suffer from compromised activity levels (either temporary or prolonged) after the exacerbation event, and might be somehow 'protected' from those physically demanding activities that would potentially cause severe hemorrhagic TBI. Nevertheless, further research is necessary to ascertain whether this explanation is valid.

In our opinion, this present study has several strengths. First, this study investigates a novel topic relating to the

Table 3 HRs for traumatic brain injury at 5 years of follow-up for the included patients after being subgrouped by sex

	Groups of patients with COPD versus patients without COPD				$COPD_{AE+}$ versus $COPD_{AE-}$	
Patient groups	**COPD All patients**	**$COPD_{AE+}$**	**$COPD_{AE-}$**	**Non-COPD**	**$COPD_{AE+}$**	**$COPD_{AE-}$**
All patients (n)	14,936	3734	11,202	11,202	3734	11,202
Male (n)	9748	2437	7311	7311	2437	7311
TBI, n (%)	690 (7.08)	213 (8.7)	477 (6.5)	372 (5.1)	213 (8.7)	477 (6.5)
cHR (95% CI)	1.25 (1.11 to 1.41)	1.51 (1.27 to 1.79)	1.17 (1.02 to 1.33)	1	1.29 (1.09 to 1.53)	1
aHR (95% CI)	1.31 (1.16 to 1.48)*	1.57 (1.32 to 1.87)*	1.23 (1.08 to 1.40)*	1	1.28 (1.08 to 1.52)*	1
CRR (95% CI)	1.14 (1.01 to 1.29)*	1.32 (1.11 to 1.57)*	1.08 (0.95 to 1.24)*	1	1.22 (1.03 to 1.45)*	1
Female (n)	5188	1297	3891	3891	1297	3891
TBI, n (%)	364 ((7.03)	99 (7.6)	265 (6.8)	216 (5.6)	99 (7.6)	265 (6.8)
cHR (95% CI)	1.20 (1.02 to 1.42)	1.36 (1.08 to 1.73)	1.15 (0.97 to 1.37)	1	1.19 (0.94 to 1.50)	1
aHR (95% CI)	1.23 (1.04 to 1.44)*	1.39 (1.10 to 1.77)*	1.17 (0.98 to 1.40)*	1	1.19 (0.94 to 1.50)*	1
CRR (95% CI)	1.10 (0.93 to 1.30)*	1.20 (0.94 to 1.52)*	1.07 (0.90 to 1.28)*	1	1.12 (0.89 to 1.42)*	1

*Values were derived from stratified Cox regression.
aHR, adjusted HR; cHR, crude HR;COPD, chronic obstructive pulmonary disease; $COPD_{AE-}$, patients with COPD but without severe acute exacerbation during follow-up; $COPD_{AE+}$, patients having COPD and ≥1 severe acute exacerbation during follow-up; CRR, competing risk regression (values are subdistribution HR, controlling the competing risk of death);non-COPD, patients without COPD; TBI, traumatic brain injury.

Table 4 HRs for traumatic brain injury (TBI) at 5 years of follow-up for the included patients after being stratified by the subtypes of TBI (hemorrhagic or non-hemorrhagic)

	Groups of patients with COPD versus patients without COPD				$COPD_{AE+}$ versus $COPD_{AE-}$	
Patient groups	$COPD_{All\ patients}$	$COPD_{AE+}$	$COPD_{AE-}$	Non-COPD	$COPD_{AE+}$	$COPD_{AE-}$
All patients (n)	14,936	3734	11,202	11,202	3734	11,202
hTBI, n (%)	174 (1.24)	41 (1.2)	133 (1.3)	94 (0.9)	41 (1.2)	133 (1.3)
cHR (95% CI)	1.07 (0.85 to 1.35)	0.90 (0.61 to 1.33)	1.12 (0.88 to 1.43)	1	0.81 (0.55 to 1.18)	1
aHR (95% CI)	1.17 (0.93 to 1.47)*	0.98 (0.67 to 1.44)*	1.22 (0.96 to 1.56)*	1	0.80 (0.55 to 1.18)*	1
CRR (95% CI)	1.00 (0.80 to 1.26)*	0.81 (0.55 to 1.19)*	1.07 (0.84 to 1.36)*	1	0.76 (0.52 to 1.12)*	1
nhTBI, n (%)	880 (5.96)	271 (7.3)	609 (5.5)	494 (4.5)	271 (7.3)	609 (5.5)
cHR (95% CI)	1.26 (1.13 to 1.40)	1.57 (1.35 to 1.82)	1.16 (1.04 to 1.31)	1	1.34 (1.16 to 1.56)	1
aHR (95% CI)	1.30 (1.17 to 1.45)*	1.61 (1.39 to 1.88)*	1.20 (1.07 to 1.35)*	1	1.34 (1.16 to 1.56)*	1
CRR (95% CI)	1.18 (1.06 to 1.33)*	1.37 (1.18 to 1.59)*	1.08 (0.96 to 1.21)*	1	1.27 (1.10 to 1.47)*	1

*Values were derived from stratified Cox regression.
aHR, adjusted HR; cHR, crude HR;COPD, chronic obstructive pulmonary disease; $COPD_{AE-}$, patients with COPD but without severe acute exacerbation during follow-up; $COPD_{AE+}$, patients having COPD and ≥1 severe acute exacerbation during follow-up; CRR, competing risk regression (values are subdistribution HR, controlling the competing risk of death); hTBI, hemorrhagic traumatic brain injury; nhTBI, non-hemorrhagic traumatic brain injury; non-COPD, patients without COPD.

complication of COPD and the care and safety of patients with COPD. Second, findings from this study have important clinical implications. Considering its often long-lasting and devastating consequences,[31] TBI would certainly complicate the management and rehabilitation of patients with COPD. Patients and caregivers must therefore be aware of such an increased risk of TBI. Moreover, the NHI of Taiwan is a mandatory program, covering >96% population in 2000 and consistently >99% since 2002.[51 52] The use of the NHI Research Database in this study provided with a random study population of the nationwide scale, which minimized potential selection and referral biases.

Nevertheless, there are limitations to this present study. First, such patient-specific data as spirometric measurements, symptomatic and disease severity, radiographic images, and differential counts of blood cells were unavailable from the NHI Research Database and could not be incorporated to ascertain the diagnosis of COPD. It is possible that those patients with mild COPD who had been managed with only symptomatic treatments (such as antitussive and mucolytic agents) or observation might have been excluded from this study. Besides, despite that we strove to improve the accuracy of the COPD diagnosis by strictly defining our inclusion and exclusion criteria, the overdiagnosis of COPD and the misdiagnosis or miscoding of asthma as COPD in real-world clinical settings still remained possible. However, the accuracy of identifying patients with COPD from the NHI Research Database using working definitions that were similar to those we applied in this study has been validated previously.[52 53] Moreover, by performing an independent validation work as was mentioned previously, we demonstrated very high PPVs of our working definitions for COPD as well as for TBI. Therefore, the diagnosis of COPD, and also of TBI, in this present study should be reliable. One issue that must be particularly mentioned is that by strictly excluding those subjects who also received the diagnosis of asthma during the follow-ups, we could enhance the accuracy of the COPD diagnosis, but we might have also excluded patients with asthma-COPD overlap (ACO) who seem to have an increased risk of severe acute exacerbations.[54 55] Further research would help clarify whether patients with ACO and patients in '$COPD_{AE+}$' share a similar risk profile for TBI. Second, the definition we use to identify acute exacerbation of COPD, despite its frequent application in previous studies,[24 25 52] has potential drawbacks. It might have classified those patients with mild or moderate exacerbation (managed by adjusting the medication without emergency visit or hospitalization) into '$COPD_{AE-}$'. Besides, those patients whose acute exacerbation was secondary to a specific etiology (like pneumonia, ICD-9-CM codes 480–486), or whose exacerbation led to respiratory failure (ICD-9-CM code 518.81), and therefore received a different primary diagnosis than COPD for that hospitalization or emergency room visit, would also be excluded from the study.[24 25] Although our strict definition decreased the number of candidates for '$COPD_{AE+}$', we believe it is a necessary step to avoid misclassifying acute events unrelated to COPD into this group. Third, both COPD and TBI are associated with comorbidities. Although in this study we undertook multiple statistical methods to minimize the potentially confounding effects from comorbidities as possible (namely using IPTW based on propensity

score to balance intergroup differences in comorbidities, adjusting for all the identified comorbidities in multivariate regression analyses, and controlling for the competing risk of death), it remains possible that certain unidentified comorbidities or confounders might have played potential roles accounting for our major findings. However, based on the results of sensitivity analyses (online supplementary figure S2a,b), COPD (either with or without acute exacerbation) remained mostly as a risk factor for TBI even in the presence of a hypothetical unidentified confounder. Therefore, in our opinion, the confounding effect from an unidentified comorbidity (if any) should be small. Fourth, due to the lack of data on the detailed etiologies of TBI and on the serial changes in physical, cognitive, functional, and even behavioral performances of the included patients from the NHI Research Database, it is not possible to establish a definite mechanistic and causal relationship between COPD and TBI. Further investigation is necessary to elucidate the mechanism underlying the association that we found between COPD and the elevated risk of TBI, and also to clarify whether patients with COPD tend to have certain risk-prone behaviors that contribute to the observed increase in the risk of TBI. Fifth, the findings of this study were derived from the clinical data of Taiwan's population, and additional research in other regions studying different ethnic groups would be necessary to confirm whether the increased risk of TBI in patients with COPD is universally observed.

CONCLUSIONS

In this study, we show that patients with COPD of both sexes have an increased risk of TBI. The risk is higher in those patients with COPD aged <65 years than those aged ≥65 years, and also in those patients with COPD who had severe acute exacerbation during follow-up than in those who did not. The findings of our present study add TBI to the list of COPD-associated comorbidities, and raise the need for further research to investigate the underlying mechanism and to determine preventive measures.

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Contributors Conceptualization: THH, CZC, SHL. Methodology: THH, SHL. Software: SHL. Validation: THH, CZC, SHL. Data sorting and analysis: THH, SHL, CZC, HIK, HPE. Writing—original draft preparation: THH. Writing—review and editing: CZC, SHL. Supervision: SHL. Project administration: THH, SHL. Funding acquisition: THH, SHL.

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