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Prevalence and influence of chronic obstructive pulmonary disease on stroke outcomes in hospitalized stroke patients

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) and stroke are important causes of death. COPD patients are at higher risk of cerebral hypoxia and aspiration. Yet, relatively little is known about the prevalence of COPD among stroke patients or its impact on outcomes after an index stroke. We assess the prevalence of COPD among hospitalized stroke patients in a nationally representative sample and examine the effect of COPD with mortality risk in the hospital after a stroke.

Methods: Using the National Inpatient Sample, a nationally representative dataset of US hospital admissions between January 2004 and December 2009 (n = 48,087,002), we assessed Crude and age-adjusted COPD prevalence among stroke patients and in-hospital mortality rates by COPD status. Independent associations of COPD with in-hospital mortality following stroke were evaluated using multivariable logistic regression.

Results: 11.71% (95% CI: 11.48–11.94%) of all adult patients hospitalized for stroke had COPD. The crude and age-adjusted in-hospital mortality rates for these patients were 6.33% (95% CI: 6.14–6.53%) and 5.99% (95% CI: 4.05–7.94%), respectively. On multivariable analyses, COPD was modestly associated with overall stroke mortality (OR 1.03; 95% CI 1.01–1.06; p = 0.018). The greater risks of mortality were seen among those with intracerebral hemorrhage (OR: 1.12; 95% CI 1.03–1.20; p = 0.005) and ischemic stroke patients (OR 1.08; 95% CI 1.03–1.13, p = 0.001).

Conclusions: 12% of hospitalized stroke patients have COPD. The presence of COPD is independently associated with higher odds of dying during stroke. Prospective studies are needed to identify any modifiable risk factors contributing to this deleterious relationship.

1. Introduction

The prevalence and mortality of stroke and chronic obstructive pulmonary disease (COPD) remain high. In 2011, COPD was the third leading cause of death and the estimated crude prevalence of COPD was 6.3% (95% CI: 6.2–6.4) [1]. Likewise, the burden of stroke in the United States remains significant despite recent prevention advances notably the change from the 3rd to the 4th cause of mortality [2]. Interestingly, both conditions are closely interrelated. For example, smoking is an important risk factor for stroke and the strongest determinant of COPD. In addition, Patients with severe COPD have chronic hypoxemia at and hypercapnia that could potentially put them at greater risk of cerebral insults in the event that they have an acute stroke. Furthermore, patients with stroke and COPD are at increased risk of risk of aspiration, a leading cause of death among patients with stroke [3,4]. Given all of the aforementioned issues, it is conceivable that the prevalence of COPD might be elevated in stroke patients and that COPD may confer a higher risk of early mortality after stroke. Despite these epidemiological and pathophysiological considerations, there is scarcity of data on COPD prevalence among stroke patients and mortality risk in COPD patients after an acute stroke.

In this study, we hypothesized that COPD is highly prevalent among individuals with stroke and that COPD patients are at increased risk of death after a stroke.

2. Methods

2.1. Study population

Data were obtained from all US states that contributed to the National Inpatient Sample for adult patients, 18 years and older, admitted to US non-federal hospitals between January 2004 and December 2009 (n = 48,087,002). Briefly, the National Inpatient Sample (NIS), the largest publicly available all-payer inpatient care database in the United States. The NIS contains data from ≈8 million-de-identified hospital stays a year and approximates a 20% stratified sample of nonfederal US hospitals. The majority (≥97%) of the hospitals in the United States is nonfederal and include government hospitals operated by the city, county, and

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state, as well as hospitals operated by for-profit and nonprofit organizations. The database sampling strategy allows for extrapolation from the sample to represent all US hospitalizations nationwide, using sampling weights. The National Healthcare Cost Utilization Project of the Agency maintains the database for Healthcare Research and Quality. Detailed information on the design of the NIS is available at www.hcup-us.ahrq.gov. The study qualified for Institutional Review Board waiver.

2.2. Diagnosis of stroke and COPD

Primary discharge diagnoses of stroke were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes 430–432 and 433–436, of which a subset with co-existing COPD were defined with secondary ICD-9-CM diagnoses codes 490–492, 494, and 496.

2.3. Statistical analysis

We computed crude and age-adjusted prevalence of stroke and stroke subtypes in the whole database as well as prevalence of COPD prevalence among stroke patients overall and stroke patients in each subtype. Crude and age-adjusted in-hospital mortality rates were also calculated. Independent associations of COPD with in-hospital mortality following stroke were evaluated using multivariable logistic regression. The following were included as co-variates in the logistic regression analyses: 1) Age [18–44 years (reference), 45–64 years, 65–84 years, >85 years], 2) Gender [Male (reference), Female], 3) Race/Ethnicity [White Non-Hispanic (reference), Black Non-Hispanic, Hispanic, Others], 4) Residential zip code median income divided in quartiles with the highest quartile as reference, 5) Admission day [Weekday (reference), Weekend], 6) Source of admission [Routine (reference), Emergency department, Other Hospital, Other Health facility/Law enforcement], 7) Hospital size [Large (reference), Medium, Small], 8) Hospital location/teaching hospital status [Urban Teaching (reference), Urban non-Teaching, Rural], 9) Hospital census region [West (reference), Northeast, Midwest, South], 10) Primary payer [Medicare/Medicaid (reference), Private Insurance, Self-pay, No charge], and 11) Charlson co-morbidity index (CCI) grouped into 3 categories: 0 (reference), 1, and ≥2. CCI is a weighted score of 17 conditions including congestive heart failure, myocardial infarction, chronic pulmonary disease, cerebrovascular disease, dementia, diabetes without complications, mild liver disease, peptic ulcer disease, peripheral vascular disease, and connective tissue disease (weight 1); hemiplegia or paraplegia, diabetes with complications, malignancy, renal disease (weight 2); moderate or severe liver disease (weight 3); metastatic solid tumor and HIV/AIDS (weight 6) [5].

We also tested for statistically significant interactions between COPD and age, gender, or race/ethnicity. Appropriate survey weights were applied in estimating the population-based rates, odds ratios (OR), and confidence intervals (CI). Statistical hypotheses were tested with $p < 0.05$ as the level of statistical significance.

3. Results

We identified 33,053,263 NIS participants ≥18 years of whom overall 2.65% (unadjusted) (95% CI: 2.61%–2.70%) were hospitalized for acute stroke. Ischemic strokes, hemorrhagic strokes, sub-arachnoid hemorrhages, and intra-cerebral hemorrhages were present in 2.29% (2.25%–2.33%), 0.37% (0.35%–0.38%), 0.08% (0.072%–0.085%), and 0.20% (0.19%–0.21%) of participants respectively.

3.1. Overall and stroke subtypes specific COPD prevalence

Overall, the unadjusted prevalence (95% CI) of COPD among stroke patients was 11.71% (11.48%–11.94%). Corresponding figures for patients with ischemic stroke, hemorrhagic stroke, sub-arachnoid hemorrhage, and intracerebral hemorrhage were 12.16% (95% CI: 11.48%–11.94%), 8.87% (8.59%–9.16%), 7.47% (6.99%–7.95%), and 9.13% (8.82%–9.43%) respectively; Table 1.

3.2. Stroke mortality among stroke patients with COPD vs. without COPD

Concerning frequency of mortality, overall there was no difference between COPD and non-COPD stroke participants (unadjusted mortality rate 6.3%; 95% CI: 6.1%–6.5% vs. 6.1%, 95% CI: 6.0%–6.3%). Similarly, no difference in mortality rates was detected for intracerebral hemorrhage between COPD and non-COPD participants. However, frequency of mortality was significantly higher in COPD patients than non-COPD patients with hemorrhagic stroke combined (unadjusted mortality rate 25.4%; 95% CI: 24.5–26.3%, vs. 23.95%, 95% CI 23.5–24.4%), Subarachnoid hemorrhage (unadjusted mortality rate 26.9-%; 95% CI 24.8–28.9% vs. 22.2%, 95% CI 21.4–23.0%), and ischemic stroke (unadjusted mortality rate 4.11%; 95% CI 3.96–4.3% vs. 3.2%, 95% CI 3.1–3.3%). When analysis was restricted to ischemic stroke patients who received r-tPA, the excess mortality in COPD patient was no more apparent; Table 2.

3.3. Multiple logistic regression analysis of the risk of death in stroke patients by COPD status

In univariate logistic regression analysis, COPD was a predictor of stroke mortality in the entire cohort (OR 1.03, 95% CI: 1.01–1.06), ischemic stroke (1.30, 95% CI: 1.26–1.35), hemorrhagic stroke combined (1.08, 95% CI: 1.03–1.13), and subarachnoid hemorrhage (1.29, 95% CI: 1.16–1.42) but not among intracerebral hemorrhage patients (1.03, 95% CI: 0.98–1.09). As shown in Table 3, after multivariate adjustment, the association between stroke mortality and COPD persisted for stroke overall (OR 1.06, 95% CI: 1.02–1.08) and ischemic stroke (1.08, 95% CI: 1.03–1.13) while it became significant for intracerebral hemorrhage (OR 1.12, 95% CI: 1.03–1.20). There were no statistically significant interactions between COPD and age, gender, or race/ethnicity.

4. Discussion

In this study totaling over a million stroke admissions during a 5-year period, we observed that: 1) approximately 1 out of 9 hospitalized

Table 1
Stroke prevalence and COPD Prevalence.

Variables	Stroke prevalence		COPD prevalence	
	Crude survey-weighted rate % (95% CI) n (unweighted total): 33,053,263	Age-adjusted survey-weighted rate % (95% CI) N (weighted total): 162,610,833	Crude survey-weighted rate % (95% CI) n (unweighted total): 1,061,177	Age-adjusted survey-weighted rate % (95% CI) N (weighted total): 5,214,559.46
All strokes	2.65 (2.61, 2.70)	1.70 (1.63, 1.79)	11.71 (11.48, 11.94)	5.68 (5.52, 5.84)
Ischemic strokes	2.29 (2.25, 2.33)	1.39 (1.37, 1.41)	12.16 (11.93–12.31)	5.91 (5.74–6.08)
All hemorrhagic strokes	0.37 (0.35, 0.38)	0.27 (0.26, 0.29)	8.87 (8.59–9.16)	4.52 (4.31–7.73)
Sub-arachnoid hemorrhages	0.08 (0.07, 0.09)	0.08 (0.073, 0.088)	7.47 (6.99–7.95)	4.69 (4.34–5.04)
Intra-cerebral hemorrhages	0.20 (0.19, 0.21)	0.13 (0.13, 0.140)	9.13 (8.82–9.43)	4.49 (4.26–4.72)

Table 2
Unadjusted and adjusted stroke mortality by COPD status.

Variables	COPD		Non-COPD	
	Unadjusted mortality rate % (95% CI)	Age-adjusted mortality rate % (95% CI)	Unadjusted mortality rate % (95% CI)	Age-adjusted mortality rate % (95% CI)
All stroke	6.33 (6.14–6.53)	5.99 (4.05–7.94)	6.14 (5.95–6.30)	5.80 (5.57–6.04)
Ischemic strokes	4.11 (3.96–4.26)	2.32 (1.81–2.83)	3.18 (3.10–3.27)	2.06 (1.92–2.21)
Ischemic stroke with tPA	11.3% (9.61%–12.99%)	6.01 (3.55–8.48)	10.75 (10.07–11.44)	6.94 (5.83–8.05)
All hemorrhagic strokes	25.41 (24.57–26.25)	18.92 (15.79–22.06)	23.95 (23.50–24.41)	18.55 (18.02–19.09)
Sub-arachnoid hemorrhages	26.86 (24.84–28.87)	14.94 (12.90–17.03)	22.18 (21.37–23.00)	17.98 (17.21–17.75)
Intra-cerebral hemorrhages	28.62 (27.53–29.71)	21.25 (16.78–25.73)	27.92 (27.44–28.41)	22.31 (21.55–23.07)

patients with stroke have COPD, 2) mortality rate was higher in COPD patients than in non-COPD patients with ischemic stroke and subarachnoid hemorrhage, and 3) COPD was an independent predictor of mortality after stroke. Given a shared risk factor (which accounts for up to 25% of all strokes and is found in twice as many COPD vs non-COPD patients) [6,7] smoking, it stands to reason that both stroke and COPD would co-exist in certain individuals. However, the rate of COPD among stroke patients has not previously been reported. To the best of our knowledge, this study is the first to specifically provide COPD prevalence estimates among stroke patients in general and for each stroke subtypes. Furthermore, we used a large nationally representative sample of hospitalized patients therefore increasing the generalizability of our findings to the hospitalized US population. In one nationwide population-based cohort of approximately 7 million Swedish residents integrating data from the Prescribed Drug-, Patient-, Cause of Death-, Income-, Educational- and Emigration Registers, the prevalence of COPD among the 132,291 ischemic stroke participants was 3.27% (95% CI: 3.17–3.36). No data were provided for hemorrhagic stroke or stroke overall [8]. The prevalence provided in the Swedish cohort is lower than that reported in the current study even after adjusting for age. This difference is likely the reflection of the differential design as the Swedish study was population-based while our sample comprised only hospital admissions.

While COPD is an independent risk of mortality in the general population [9,10], the association between COPD status and mortality in stroke patients has not been extensively studied. Several studies have demonstrated an increased mortality risk in stroke patients with impaired lung function as measured by the baseline force expiratory volume in one second, FEV-1 [11,12,13,14], but the sample sizes were smaller than in the current study and estimates were not provided by stroke subtypes. The current study has largely confirmed the positive association between mortality and COPD. In addition, we have demonstrated that such an association was mostly significant in patients with ischemic strokes and those with subarachnoid hemorrhage.

Of note, COPD did not seem to increase the risk of death in the subgroup of ischemic stroke patients treated with r-tPA. Clots with porous network are more susceptible to fibrinolysis, yet smoking a major risk factor for COPD induce faster clot formation and resistance to fibrinolysis [15]. Furthermore, plasma pro-coagulant markers including tissue plasminogen activator-plasminogen activator inhibitor are increased in COPD patients independent of their smoking status [16]. Therefore, rather than a putative pathophysiological mechanism, the observed "protective" effect of r-tPA may reflects the presence of residual confounders. In fact, current smokers are younger than non- and former-smokers and may therefore have baseline favorable profile.

Many interconnected factors may explain the increased mortality risk among patients with COPD. First, patients with COPD have associated comorbid conditions [17] that have been associated with increased mortality in stroke patients including depression [18,19,20], and kidney disease [21]. Second, patients with stroke are at increased risk of dysphagia, aspiration, and pneumonia all of which are worsened by the COPD status [22], third patients with severe COPD are hypoxemic and hypercapnic at baseline which may increase their susceptibility to brain injury and increase their risk of death, finally COPD especially during exacerbation is associated with pulmonary inflammation which can lead to systemic inflammation and increased oxidative stress leading to unstable plaques and prothrombotic events all of which could be associated with higher stroke burden [23,24].

This study has limitations. First, this was a retrospective analysis of an administrative dataset representing only 20% of all inpatient admissions; as such, there is potential for selection bias. Second, there may have been coding errors, but given the large size of the dataset, errors were unlikely to be systematic. Third, information regarding stroke severity was lacking; however, we adjusted for CCI, an index of comorbid disease severity that may reflect overall illness severity and recovery capacity. Fourth, detailed patient-level data, such as biomarkers, medical history, FEV-1, and medications, were not available for our analysis. Fifth, this is an observational study and thus causality could not be established between COPD and mortality. More specifically, it was not possible to demonstrate the mechanistic role of smoking in increased mortality among COPD patients. Finally, in this inpatient sample, we were unable to capture stroke deaths outside the hospital. Despite the aforementioned caveats, our study's major strengths include the use of data from >1700 hospitals specifically chosen to be representative of US community hospitals, the large sample size, the clinician-based diagnosis, and the inclusion of all adults and insurance payers.

In conclusion, COPD is frequent in hospitalized stroke patients and is associated with an increase in the risk of in-hospital death across all stroke patients and by each major stroke type. Further studies are required to establish a causality link between COPD and mortality after stroke.

Table 3
Logistic regression of the risk of death during stroke hospitalization in COPD vs. non-COPD patients.

Variables	Unadjusted odds ratio	Adjusted odds ratio[a]
All stroke	1.03 (1.01–1.06)	1.06 (1.02–1.08)
Ischemic strokes	1.30 (1.26–1.35)	1.08 (1.03–1.13)
Ischemic stroke with tPA	1.06 (0.89–1.25)	0.97 (0.76–1.23)
All hemorrhagic strokes	1.08 (1.03–1.13)	1.06 (1.00–1.13)
Sub-arachnoid hemorrhages	1.29 (1.16–1.42)	0.98 (0.85–1.13)
Intra-cerebral hemorrhages	1.03 (0.98–1.09)	1.12 (1.03–1.20)

[a] Adjusted for age, gender, race/ethnicity, residential zip code median income, admission day, source of admission, hospital size, hospital location/teaching hospital status, Charlson co-morbidity index (CCI), primary payer, and hospital census region.

Disclosures

None.

Conflict of interest

The authors declare that there are no conflicts of interest.

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