Association of acute kidney injury with readmissions after hospitalization for acute exacerbation of chronic obstructive pulmonary disease: A population-based study

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Abstract

Background and Aim Little is known about the relationship between acute kidney injury (AKI) and outcomes after acute exacerbation of chronic obstructive pulmonary disease (AECOPD). We aimed to investigate associations between AKI and readmission risk after hospitalization for AECOPD. **Methods** A retrospective, population-based cohort study using State Inpatient Databases from seven U.S. states (Arkansas, California, Florida, Iowa, Nebraska, New York, and Utah) from 2010 through 2013. We identified all adults (aged ≥ 40 years) hospitalized for AECOPD during the study period. Among them, we further identified patients with a concurrent diagnosis of AKI. The outcome measures were any-cause readmissions within 30 days and 90 days after hospitalization for AECOPD. To determine associations between AKI and readmission risk, we constructed Cox proportional hazards models examining the time-to-readmission. Additionally, we also identified the primary reason of readmission. **Results** We identified 356,990 patients hospitalized for AECOPD. The median age was 71 years and 41.9% were male. Of these, 24,833 (7.0%) had a concurrent diagnosis of AKI. Overall, patients with AKI had significantly higher risk of 30-day all-cause readmission compared to those without AKI (hazard ratio 1.47; 95% CI 1.43-1.51; $P < 0.001$). Likewise, patients with AKI had significantly higher risk of 90-day all-cause readmission compared to those without AKI (hazard ratio 1.35; 95% CI 1.32-1.38; $P < 0.001$). These associations remained significant after adjustment for confounders (both, $P < 0.05$). Additionally, patients with AKI were likely to be readmitted for non-respiratory reasons including sepsis, acute renal failure, and congestive heart failure. **Conclusions** Among patients hospitalized for AECOPD, patients with AKI were at higher risk of 30-day and 90-day readmission compared to those without AKI, with non-respiratory reasons.

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major public health burden accounting for 600,000 hospitalizations in the US annually [1]. As a readmission after hospitalization for AECOPD is a common and costly event [2, 3], investigating its characters and risks are important. Acute kidney injury (AKI) is another important public health burden; the incidence of AKI has been reported to be 5% of hospitalized patients or 30% of critically ill patients [4]. These two acute conditions share similar pathobiology in development and progression, such as systemic inflammation [5]. The relationship of these two conditions are also shown in the clinical settings; in-hospital mortality rate in patients with AKI was significantly higher compared to those without AKI [6]. Despite the clinical importance, no study has investigated whether AKI is associated with the risk of readmissions after hospitalization for AECOPD. To address this knowledge gap, we investigated the association of AKI with all-cause readmissions within 30 and 90 days after hospitalization for AECOPD.

Methods

Study Design and Setting

We conducted a retrospective cohort study using large, population-based data from the Healthcare Cost and Utilization Project (HCUP) State Inpatient Database (SID) of seven geographically-dispersed US states (Arkansas, California, Florida, Iowa, Nebraska, New York, and Utah) from 2010 through 2013. The HCUP is a family of healthcare databases that are developed through a federal-state-industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ). The HCUP is the largest collection of longitudinal hospital care data in the US, with all-payer, encounter-level information. The HCUP SIDs capture all hospitalizations, regardless of source of disposition, from acute care, non-federal, general and other specialty hospitals within the participating states [7]. These seven states were selected for their high data quality, geographic distribution, and mainly because their data included unique encrypted patient identifiers that enable longitudinal follow-up of specific individuals across years. The institutional review board of Massachusetts General Hospital approved this study.

Study Population

We identified all hospitalized adult patients (age > 40 years) with a principal discharge diagnosis of COPD, as defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22, and 496, or those with a primary diagnosis of respiratory failure [codes 518.81, 518.82, 518.84, and 799.1] and a secondary diagnosis of COPD) [8, 9]. In the current analysis, we used only the first hospitalizations of the eligible patients during the study period. We also excluded patients who left the hospital against medical advice, those who died in-hospital at their index hospitalization, those who were transferred to another acute-care facility, and out-of-state residents.

Measurements

The SID contain information on the patient characteristics, including demographics (age, sex, and race/ethnicity), primary insurance type (payer), quartiles for estimated household income, patient residence, ICD-9-CM diagnosis and procedure codes, patient comorbidities (29 Elixhauser comorbidity measures and arrhythmia), hospital course (e.g., hospital length-of-stay, in-hospital death), and disposition.

Primary Exposure

The primary exposure was AKI at the index hospitalization for AECOPD, as defined by the ICD-9-CM diagnostic codes of 584.5, 584.6, 584.7, 584.8, and 584.9 in any diagnostic fields [10, 11, 12].

Outcome Measures

The outcome measures were readmission attributable to any cause within 30 and 90 days of discharge from the index hospitalization for AECOPD. The secondary outcome measure was the primary discharge diagnosis of the readmission. To make data presentation and interpretation more meaningful, we consolidated the principal discharge diagnoses (> 14,000 ICD-9-CM diagnosis codes) into 285 mutually exclusive diagnostic categories by using the AHRQ-defined Clinical Classifications Software (CCS) [13].

Statistical Analysis

First, we compared the patient characteristics between patients with and without OSA by using Wilcoxon rank sum test or chi-squared test, as appropriate. We also compared Kaplan-Meier curves between the two groups with the use of the log-rank test. Next, we modeled the time-to-readmission by fitting Cox proportional hazards models with generalized estimating equations accounting for patient clustering within hospitals. The time-to-readmission for each patient was defined as the period from the discharge to when the first readmission occurred within the 30-day and 90-day follow-up periods. Patients who did not have an outcome were censored at 30 days (or 90 days) from discharge. We fitted Cox proportional hazards model with adjustment for potential confounders, such as age, sex, race/ethnicity, primary insurance, quartiles for median household income, residential status, length-of-stay at the index hospitalization, hospital state, and 28 Elixhauser comorbidities (except renal failure) as well as arrhythmia. [14, 15]). Furthermore, as sensitivity analyses, we repeated the analysis with stratifications by age category (40–64 years and > 65 years) and sex. All analyses used STATA 14.0 (STATA Corp, College Station, TX). All P values were two-tailed, with $P < 0.05$ considered statistically significant.

Results

We identified 356,990 patients hospitalized for AECOPD in the seven states. Overall, the median age was 71 years, 41.9% were male, and 73.9% were non-Hispanic white; 7.0% had diagnosis of AKI. Patient characteristics differed between patients with and without AKI (Table 1). Overall, 58,076 (16.3%) patients had at least one readmission within 30 days after their index hospitalization, and 112,917 (31.6%) had at least one readmission within 90 days after their index hospitalization. The Kaplan-Meier survival curves demonstrated a significant difference in the risk of all-cause 30-day and 90-day readmission between patients with and without AKI ($P < 0.001$, Fig. 1 and Supplemental Fig. 1). In the unadjusted Cox proportional hazards model, patients with AKI had a significantly higher risk of 30-day readmission compared to those without AKI (hazard ratio [HR] 1.47; 95%CI 1.43–1.51; $P < 0.001$; Table 2). In the adjusted model, the significant association persisted (HR 1.07; 95%CI 1.04–1.11; $P < 0.001$). Likewise, with regard to all-cause 90-day readmission, patients with AKI had a significantly higher risk of 90-day readmission compared to those without AKI (hazard ratio [HR] 1.35; 95%CI 1.32–1.38; $P < 0.001$; Table 3). The significant association persisted after adjustment for possible confounders (HR 1.03; 95%CI 1.00–1.05; $P = 0.04$). With stratifications by age, sex, these significant associations persisted after adjustment for possible confounders in aged ≥ 65 years and women (both, $P < 0.05$, Tables 2 and 3). Among patients without AKI, the most frequent primary cause for readmission was COPD, followed by pneumonia, respiratory failure, and asthma; Table 4). By contrast, patients with AKI were more likely readmitted due to non-respiratory diseases (e.g., acute renal failure, congestive heart failure).

Discussion

In this population-based study of 356,990 patients hospitalized for AECOPD in the seven U.S. states, we found that patients with AKI had a 50% higher risk of all-cause readmissions during 30 days after their

index hospitalization compared to those without AKI. This significant association persisted after the sequential adjustment for potential confounders.

Limited epidemiological literature has indicated the association of acute kidney disease with COPD [16]. A retrospective cohort study using electronic medical records in Taiwan showed that COPD is associated with a higher risk of development of AKI [16]. Furthermore, among patients hospitalized for AECOPD, those with AKI had approximately 2-fold higher mortality rate within six months compared to those without AKI [6]. Our findings based on the large population-based data corroborate these prior studies, and expand them by demonstrating the longitudinal association of AKI with a higher risk of all-cause readmission after hospitalization for AECOPD.

The underlying mechanisms of the observed association of AKI with the higher risk of readmission after hospitalization for AECOPD warrant clarification. In the present study, a part of the association was attributable to the differences in patient-level socio-demographic factors, hospital length-of-stay and comorbidity between the two populations. However, despite the rigorous adjustment, AKI remained an independent predictor for readmission in patients hospitalized for AECOPD. This finding suggests that there are other factors predisposing patients with AKI to worse disease control. One possible mechanism is impaired immunity following AKI [17, 18]. Clinical studies have showed that AKI is a risk factor of subsequent infection (e.g., incident active tuberculosis infection [19] or sepsis [20]). Indeed, the most frequent primary cause of readmission was sepsis in our cohort. Furthermore, AKI-related systemic inflammation [5] or volume overload [21] may contribute the poorer morbidity after hospitalization for AECOPD. These potential mechanisms may contribute to worse disease control and greater healthcare utilization in patients with concurrent AECOPD and AKI and merit further investigation.

Our study has several potential limitations. First, as we used administrative datasets, there may be misclassifications, such as misdiagnosis of COPD and AKI. Nevertheless, the ICD-9-CM codes for COPD are widely used [8, 9], and the HCUP data are rigorously tested and considered accurate [13, 22, 23, 24]. Additionally, while the literature showed that the ICD-9-CM codes for AKI had a high specificity but a low sensitivity [25], assuming that underdiagnoses or misclassifications in exposure (AKI) occurred equally regardless of the outcomes, the results would have biased our estimates toward the null. Second, SIDs do not capture information on out-of-hospital deaths. However, we accounted for in-hospital deaths in the analysis. Third, as with any observational study, the association of AKI with readmission does not prove causality and might be confounded by unmeasured factors (e.g., access to ambulatory healthcare, patient's health behavior). Lastly, the studied data are not a random sample of all people with AECOPD in the US. However, the seven geographically-dispersed states represent approximately 27% of the US population, thereby supporting the generalizability of our inferences.

Conclusions

In the large population-based database of 356,990 patients hospitalized for AECOPD across seven US states, we found that patients with AKI had a significantly higher risk of all-cause readmissions during 30

and 90 days after their index hospitalization, compared to those without AKI. For clinicians, our findings underscore the importance of prevention of AKI and post-discharge care in this population. For researchers, our findings should facilitate further investigations into the mechanisms underlying the COPD-AKI link to develop novel preventive and therapeutic interventions in this population at high-risk for healthcare utilization.

Declarations

Ethical approval and consent to participate

The institutional review board of Massachusetts General Hospital approved this study and the requirement for informed consent was waived.

Availability of data and materials

HCUP's Nationwide and State-Specific Databases are available for purchase from the online HCUP distributor.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AH, TG, and KH conceived the study. AH and TG analyzed the data. AH drafted the manuscript. KH supervised the conduct of the study. Finally, all authors contributed substantially to its revision and all authors had access to data.

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Tables

Table 1. Characteristics of patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease by acute kidney injury

	AKI	Non-AKI	
	n=24,833	n=332,157	P value
Characteristics	(7.0%)	(93.0%)	
Age (year), median (IQR)	76 (67-83)	70 (60-80)	<0.001
Male	12,605 (50.8)	136,949 (41.2)	<0.001
Race/ethnicity			<0.001
Non-Hispanic white	17,375 (72.3)	237,741 (74.0)	
Non-Hispanic black	2,848 (11.9)	34,030 (10.6)	
Hispanic	2,593 (10.8)	35,333 (11.0)	
Others	1,217 (5.1)	14,034 (4.5)	
Primary health insurance			<0.001
Medicare	20,089 (81.4)	233,472 (70.3)	
Medicaid	1,817 (7.4)	36,878 (11.1)	
Private	1,682 (6.8)	38,944 (11.7)	
Others	1,093 (4.4)	22,698 (6.9)	
Median household income quartile			<0.001
1 (lowest)	7,216 (29.7)	103,211 (31.9)	
2	6,230 (25.6)	89,605 (27.7)	
3	5,931 (24.4)	76,312 (23.6)	
4 (highest)	4,927 (20.3)	54,794 (16.9)	
Patient residence			<0.001
Metropolitan	22,529 (90.8)	288,858 (87.0)	
Non-metropolitan	2,304 (9.2)	43,299 (13.0)	
Selected comorbidities*			
Congestive heart failure	11,326 (45.6)	78,120 (23.5)	<0.001
Depression	3,348 (13.5)	52,482 (15.8)	<0.001
Diabetes	10,415 (41.9)	93,904 (28.3)	<0.001
Hypertension	20,125 (81.0)	219,396 (66.1)	<0.001
Obesity	5,048 (20.3)	50,795 (15.3)	<0.001
Peripheral artery disease	2,967 (11.9)	24,961 (7.5%)	<0.001
Hospital length-of-stay			<0.001
<3 days	3,599 (14.5)	97,877 (29.5)	
3-4 days	7,223 (29.1)	117,624 (35.4)	
5-6 days	5,407 (21.8)	60,523 (18.2)	
≥7 days	8,604 (34.6)	56,133 (16.9)	
Hospital state			<0.001

Arkansas	1,695 (6.8)	15,644 (4.7)
California	4,561 (18.4)	63,913 (19.2)
Florida	10,295 (41.5)	135,717 (40.9)
Iowa	764 (3.1)	11,825 (3.6)
Nebraska	536 (2.2)	7,252 (2.2)
New York	6,667 (26.8)	93,863 (28.3)
Utah	315 (1.3)	3,943 (1.2)

Abbreviations: AKI, acute kidney injury; IQR, interquartile range

Data are shown as n (%) unless otherwise specified

* Selected from 29 Elixhauser comorbidity measures and arrhythmia

Table 2. Hazard ratio for all-cause readmission during 30-day periods after index hospitalization for acute exacerbation of chronic obstructive sleep apnea, according to acute kidney injury, overall and stratified by age category and sex

		30-day readmission rate		Unadjusted model		Adjusted model*	
		AKI (n=24,833)	Non-AKI (n=332,157)	HR (95% CI)	P-value	HR (95% CI)	P-value
Overall (n=356,990)		22.4%	15.8%	1.47 (1.43- 1.51)	<0.001	1.07 (1.04- 1.11)	<0.001
Age category							
40-64 (n=122,362)	years	20.9%	14.0%	1.52 (1.43- 1.63)	<0.001	1.03 (0.96- 1.10)	0.45
≥65 (n=234,628)	years	22.7%	16.8%	1.41 (1.36- 1.45)	<0.001	1.09 (1.05- 1.13)	<0.001
Sex†							
Men (n=149,333)		22.0%	16.7%	1.36 (1.30- 1.41)	<0.001	1.03 (0.99- 1.08)	0.14
Women (n=207,436)		22.7%	15.2%	1.56 (1.50- 1.62)	<0.001	1.12 (1.07- 1.17)	<0.001

Abbreviations: AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval

* Cox proportional hazards model adjusting for age, sex, race/ethnicity, insurance status, estimated household income, residential status, hospital length-of-stay, hospital state, and

Elixhauser comorbidity measures and arrhythmia with generalized estimating equations to account for patient clustering within hospitals

‡ 221 patients with missingness on sex data

Table 3. Hazard ratio for all-cause readmission during 90-day periods after index hospitalization for acute exacerbation of chronic obstructive sleep apnea, according to acute kidney injury, overall and stratified by age category and sex

		90-day Readmission rate		Unadjusted model		Adjusted model*	
		AKI (n=24,833)	Non-AKI (n=332,157)	HR (95% CI)	P-value	HR (95% CI)	P-value
Overall (n=356,990)		39.7%	31.0%	1.35 (1.32-1.38)	<0.001	1.03 (1.00-1.05)	0.04
Age category							
40-64 (n=122,362)	years	37.6%	27.8%	1.43 (1.36-1.50)	<0.001	1.00 (0.95-1.06)	0.86
≥65 (n=234,628)	years	40.2%	32.8%	1.29 (1.26-1.32)	<0.001	1.03 (1.00-1.06)	0.03
Sex†							
Men (n=149,333)		38.9%	32.2%	1.26 (1.22-1.29)	<0.001	0.99 (0.96-1.03)	0.59
Women (n=207,436)		40.5%	30.2%	1.43 (1.39-1.48)	<0.001	1.06 (1.02-1.09)	0.001

Abbreviations: AKI, acute kidney injury; HR, hazard ratio; CI, confidence interval

* Cox proportional hazards model adjusting age, sex, race/ethnicity, insurance status, estimated household income, residential status, hospital length-of-stay, hospital state, and Elixhauser comorbidity measures and arrhythmia with generalized estimating equations to account for patient clustering within hospitals

† 221 patients with missingness on sex data

Table 4. The ten most frequent principal diagnoses of readmissions in patient hospitalized for acute exacerbation of chronic obstructive pulmonary disease, overall and stratified by acute kidney injury

Without AKI (n=50,984)		With AKI (n=8,151)	
Primary diagnosis*	n (%)	Primary diagnosis*	n (%)
COPD and bronchiectasis	12,954 (25.4)	Septicemia	1,176 (14.4)
Pneumonia	3,947 (7.7)	Acute renal failure	963 (11.8)
Respiratory failure	3,571 (7.0)	COPD and bronchiectasis	944 (11.6)
Asthma	3,255 (6.4)	Congestive heart failure	713 (8.8)
Congestive heart failure	3,019 (5.9)	Respiratory failure	623 (7.6)
Septicemia	1,806 (3.5)	Pneumonia	579 (7.1)
Cardiac dysrhythmia	1,395 (2.7)	Asthma	204 (2.5)
Nonspecific chest pain	921 (1.8)	Acute myocardial infarction	166 (2.0)
Aspiration pneumonitis	683 (1.3)	Nonspecific chest pain	166 (2.0)
Fluid and electrolyte disorders	666 (1.3)	Intestinal infection	158 (1.9)

*The primary diagnoses (>14,000 ICD-9-CM diagnosis codes) consolidated into 285 mutually exclusive diagnostic categories by using the AHRQ-defined *Clinical Classifications Software*.

Figures

Figure 1

Kaplan-Meier survival estimates of all-cause readmission risk during 30-day period after the index hospitalization for acute exacerbation of chronic obstructive pulmonary disease. Patients with acute kidney injury (AKI) had a significantly higher risk of all-cause readmission during 30-day period after the index hospitalization, compared to those without AKI (Plog-rank <0.001).

Figure 2

Kaplan-Meier survival estimates of all-cause readmission risk during 90-day period after the index hospitalization for acute exacerbation of chronic obstructive pulmonary disease Patients with acute kidney injury (AKI) had a significantly higher risk of all-cause readmission during 90-day period after the index hospitalization, compared to those without AKI (Plog-rank <0.001).