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Mortality Outcomes of Patients with Chronic Kidney Disease and Chronic Obstructive Pulmonary Disease

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Abstract

Background—Chronic Obstructive Pulmonary Disease (COPD) is associated with higher mortality in the general population. We studied the associations between COPD and death among chronic kidney disease (CKD) patients along with reporting cause specific death data.

Methods—We included 56,960 patients with stage 3 and stage 4 CKD who were followed in a large health care system. Associations between COPD and all-cause mortality and various causes of death (respiratory deaths, cardiovascular deaths, malignancy related deaths and deaths due to other reasons) were studied using the Cox proportional hazards and competing risk models.

Results—Out of 56,960 CKD patients, 4.7% (n=2667) had underlying COPD. Old age, presence of diabetes, hypertension, coronary artery disease, congestive heart failure, smoking were associated with higher risk for COPD. During a median follow up of 3.7 years, 15,969 patients died. After covariate adjustment, COPD was associated with a 41% increased risk (95% CI 1.31, 1.52) for all-cause mortality, and four fold increased risk (sub-hazard ratio 4.36, 95% CI 3.54, 5.37) for respiratory related deaths. In a sensitivity analysis by defining COPD as use of relevant ICD-9 codes and medications used to treat COPD, similar results were noted.

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Conclusions—COPD is associated with higher risk for death among those with CKD and underlying lung disease accounts for significant proportion of deaths. This data highlights the need for further prospective studies to understand the underlying mechanisms and potential interventions to improve outcomes in this population.

Keywords

COPD; death; kidney disease

Background

Chronic obstructive pulmonary disease (COPD) is an important public health problem and is predicted to become the third leading cause of death(1). Chronic kidney disease (CKD) is also an emerging public health issue around the globe. The prevalence of both CKD and COPD increases with age and both these diseases are associated with atherosclerotic disease(2, 3). While the mechanisms linking CKD and COPD have not been completed elucidated, systemic inflammation and hypoxia associated with COPD could contribute to adverse outcomes in those with CKD(4).

Despite the clinical significance of these two diseases, limited numbers of studies have examined their associations. The reported prevalence of kidney disease in COPD ranges from 20–30%(5, 6). Chandra et al reported that estimated glomerular filtration rate (eGFR) and serum creatinine correlated with the severity of emphysema noted on CT scan, but not with the severity of airflow obstruction by spirometry(7). In a cohort of 3371 patients undergoing vascular surgery, CKD was noted in 27% and COPD in 39% and the prevalence of COPD increased with the reduction in eGFR. In long-term follow up, moderate and severe COPD were associated with increased mortality among those with CKD(5). However, another study found no significant association between airflow obstruction and CKD after adjusting for confounding variables(8). Importantly, studies examining the impact of COPD in those with CKD, particularly on death and causes of death are lacking. Hence, we studied the factors associated with the presence of COPD and the associations of COPD with all-cause mortality among a non-dialysis CKD population followed in a large health care system. In addition, we also report the various causes of deaths in this population.

Methods

This analysis was conducted using a pre-existing Electronic Health Record (EHR)-based CKD registry at the Cleveland Clinic. The development and validation of the EHR-based CKD registry at the Cleveland Clinic has been described in detail elsewhere(9).

Study population

Patients who met the following criteria from January 1, 2005 through December 31, 2012 and lived in the State of Ohio were included: 1) had at least one face-to-face outpatient encounter with a Cleveland Clinic health care provider and 2) had at least two or more eGFR 15–59.9 ml/min/1.73 m^2 that were at least 90 days apart (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation)(9). Patients with lung transplant

or resection, end stage renal disease needing dialysis, and renal transplant prior to CKD diagnosis were excluded. Patients outside the state of Ohio were excluded as cause-specific death data was not available.

Definitions and outcome measures

Variables—Demographic details were extracted from the EHR. Diabetes mellitus, hypertension, coronary artery disease, and other comorbidities were defined using pre-specified criteria and validated. Relevant outpatient laboratory values were obtained from the EHR. Medication details were obtained from the EHR and were validated by one of the investigators.

Renal function—We applied the CKD-EPI equation to patients who had two outpatient serum creatinine levels between January 1, 2005 and December 31, 2012 to calculate eGFR. All creatinine measurements were performed by the modified kinetic Jaffe reaction, using a Hitachi D 2400 Modular Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) in our laboratory. CKD was defined according to current guidelines as follows: stage 3 CKD (eGFR 30–59 ml/min/1.73 m^2) and stage 4 CKD (eGFR 15–29 ml/min/1.73 m^2). We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min/1.73 m^2) and stage 3b (eGFR 30–44 ml/min/1.73 m^2).

COPD—COPD was defined as presence of two ICD 9 codes in any encounter type in the EHR. A modified definition of chronic obstructive pulmonary disease and bronchiectasis as recommended by the Agency for Healthcare Research and Quality (AHRQ) was used and included the following ICD 9 codes:, 491, 491.0, 491.1, 491.2, 491.20, 491.21, 491.22, 491.8, 491.9, 492, 492.0, 492.8, 494, 494.0, 494.1, 496. In a sensitivity analysis, we also defined COPD as the use of above-mentioned ICD-9 codes plus the use of relevant medications used to manage COPD.

Mortality—The primary outcome of interest, all-cause mortality, was ascertained from our EHR and linkage of the CKD registry with the Ohio Department of Health mortality data. We censored patients on December 2012. For cause-specific death analysis, we used the Ohio Department of Health mortality data. The underlying cause of death was coded according to the *International Classification of Diseases*, Tenth Revision (ICD-10). We grouped the underlying causes of death as per the National Center for Health Statistics for each coding system, except for some changes as outlined below. We classified deaths into the following 4 major categories: a) cardiovascular deaths, b) malignancy, c) respiratory, and d) other deaths. We defined cardiovascular deaths as deaths due to diseases of the heart, essential hypertension, cerebrovascular disease, atherosclerosis, or other diseases of the circulatory system (ICD-10 codes I00–I78). Respiratory deaths were defined using the ICD-10 codes J40–J47.

Statistical analysis

We compared baseline characteristics between patients with and without COPD using Chi-square and t-tests for categorical and continuous variables, respectively. We used a logistic regression model to evaluate the factors associated with having COPD. We included the

following variables: age, race, gender, BMI group, eGFR, diabetes, malignancy, coronary artery disease, congestive heart failure, hypertension and smoking while adjusting for year of entry into the registry. We used a Kaplan-Meier curve and the log-rank test to evaluate the relationship between COPD and mortality. We also used unadjusted and adjusted Cox proportional hazards models to evaluate the relationship between COPD and all-cause mortality and competing risks regression analysis to evaluate the relationship between COPD and various causes of death. The mortality models were adjusted for age, gender, race, CKD stage, diabetes, hypertension, hyperlipidemia, malignancy, insurance, smoking, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, BMI group, ACE/ARB use, beta blocker use, and statin use, albumin, hemoglobin and current prescription of COPD medications. Inception point for survival analysis was the date of the second eGFR<60 ml/min/1.73 m^2.

We tested 2-way interactions between CKD and age, race, gender and CKD stage on overall mortality. Because there were some patients with COPD and no prior prescription of COPD medications, we also did a sensitivity analysis defining COPD as presence of relevant ICD-9 codes plus prior prescription of COPD medications while excluding patients with COPD diagnosis and no prior prescription.

Percent of missing information among patients was as follows: 3% insurance information, 15% smoking status, 5% BMI, 19% albumin, and 18% hemoglobin. We used multiple imputations (SAS proc MI) with the Markov Chain Monte Carlo method and a single chain to impute 5 datasets with complete continuous and binary covariate data in a first step, and then in a second step we imputed insurance group on each of the 5 datasets using discriminant function analysis. All logistic and Cox models were performed on each of the 5 imputed datasets, and parameter estimates were combined using SAS MIanalyze. To evaluate the effect of using multiple imputations, we fit the logistic, cox, and competing risks models on complete cases only. We also tabulated the leading causes of death in those with and without COPD (Table S1).

All analyses were conducted using Unix SAS version 9.4 (SAS Institute, Cary, NC), and graphs were created using R 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria). The CKD registry and this study were approved by the Cleveland Clinic Institutional Review Board.

Results

Baseline patient characteristics

Between January 1, 2005 and December 31 2012, 63,560 patients were included in our CKD registry with eGFR 15–59 ml/min/1.73 m^2. We excluded 6,600 patients because they did not meet the specified inclusion criteria (Fig S1). The clinical characteristics of the patients with and without COPD are presented in Table 1. Patients with COPD were older and had a higher proportion of comorbid conditions such as diabetes, hyperlipidemia, coronary artery disease, and congestive heart failure (Table 1).

Factors associated with COPD

In the multivariable logistic regression model, older age, African American race, diabetes, coronary artery disease, congestive heart failure, hypertension and smoking were associated with statistically significantly higher odds of having COPD (Table 2).

COPD and all-cause mortality

With a median follow up of 3.7 years, there were 15,969 deaths. The Kaplan-Meier analysis (Figure 1) showed significant differences in all-cause mortality for CKD patients with and without COPD. After adjusting for age, gender, race, CKD stage, diabetes, hypertension, hyperlipidemia, malignancy, insurance, smoking, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, BMI group, ACE/ARB use, beta blocker use, and statin use, albumin, hemoglobin and current prescription of COPD medications, COPD was associated with significantly higher hazards of mortality (HR 1.41 95% CI 1.31, 1.52, $P< 0.05$) (Figure 2).

Causes of death

Causes of death details were available from the Ohio Department of Health mortality data for 15,761 patients. We excluded the small number (n=208) of patients whose deaths were only found in our EHR from all cause-specific mortality analyses. Supplemental Table 1 shows the causes of death overall and by COPD. Figure 2 shows the associations between various causes of death in those with COPD and highlights that the underlying respiratory diseases poses a higher sub-hazard than other causes.

Sensitivity analysis

Complete case analysis—Results similar to primary analyses were noted in a sensitivity analysis restricting to those with complete details (Table 3).

COPD defined as use of ICD-9 codes and bronchodilators—The sensitivity analysis defining COPD as those with ICD-9 diagnoses codes along with the use of COPD medication, while excluding from analysis patients with ICD-9 diagnosis codes and no medications, yielded similar results (Table 3).

Interactions

The interaction between COPD and age on overall mortality was significant (P = 0.001) indicating that the hazard associated with COPD is stronger among younger patients. The interaction between COPD and gender on overall mortality was also significant indicating that the hazard associated with COPD is significant for both genders but stronger among females (Table 4). The interaction between COPD and race, and COPD and CKD stage were not significant.

Discussion

In this study of stage 3 and stage 4 CKD patients who are followed in a large health care system, COPD (defined using ICD-9 codes) was prevalent in 5.3% of CKD population. Old age and multiple comorbid conditions were associated with higher odds of COPD. Even

though modest, presence of COPD was associated with higher risk of all-cause mortality and importantly, COPD was associated with four-fold higher risk of respiratory related deaths in CKD population. The observed associations were more pronounced in younger CKD patients and among females with CKD.

Previous studies have examined the prevalence of CKD in COPD but population studies examining the prevalence of COPD in CKD population are lacking(10). Our prevalence estimate is probably an underestimation given the lack of spirometry data. It is important to note that even in general population, COPD is underdiagnosed with about 63% of adults showing evidence of impaired lung function but do not carry a diagnosis of lung disease such as asthma, chronic bronchitis, or emphysema(11, 12). Further studies using NHANES and other national representative databases are warranted to understand the prevalence of COPD in CKD.

Several factors were associated with COPD. As noted in the general population, old age and multiple comorbid conditions were associated with COPD(1, 13). Akin to kidney function, lung function is often at its peak in young adults and starts to decline with aging and as such, we noted higher odds of COPD as age increased. Based on the World Health Organization data, 73% of COPD related deaths are related to smoking and our data shows similar higher odds of COPD in CKD patients with smoking history. We also noted that being underweight was associated with higher risk of having COPD and being over-weight (not being obese) was associated with lower risk of having COPD. This might reflect the severity of the illness, i.e., those with COPD and CKD being more prone for malnourished state. Various other factors such as infections, indoor and outdoor air pollutants and genetic factors have been described with COPD in the general population but we lacked these details as our study population is from a clinical setting and EHR of which these data are not routinely available(1).

COPD is associated with increased overall mortality in the general population(14, 15). Longer-term studies have shown that the mortality rates (age-adjusted) differed substantially between COPD patients and non-COPD patients highlighting the mortality burden from COPD. Main causes of death in COPD included cardiovascular deaths and underlying lung diseases which accounted for about 75% of deaths(16). Ford and colleagues using NHANES (1988–1994) data reported that higher urinary albumin excretion and lower eGFR were associated with all-cause mortality among adults with obstructive lung function(10). But whether the presence of COPD in CKD is associated with higher risk of death has not been examined before. More importantly, non-cardiovascular diseases account for significant proportion of deaths in CKD and we report four fold higher risk for respiratory deaths among those with COPD and CKD. Using data collected in NHANES 2007–2010, Agarwal et al., reported higher prevalence of self-reported cardiovascular disease in subjects with COPD than in those without COPD(2). Further, among those without previous cardiovascular disease, the risk of future cardiovascular disease was significantly higher in the COPD group than in the non-COPD group. It has also been noted that COPD is associated with an increased risk for sudden cardiac death(17). Whether such increased risk for sudden cardiac death exists among those with COPD and CKD is unclear and merits further studies.

What might explain the higher hazards for overall and respiratory deaths in a CKD population? Higher infection related deaths, particularly with pneumonia have been reported in the CKD population and thus the additional presence of COPD could further increase risk for pneumonia or other infection due to immunosuppression from long-term use of COPD medications explaining the noted observations(18–21). Also, COPD is a known contributor to pulmonary hypertension and could contribute to adverse outcomes in CKD(22). Further, COPD by itself is associated with inflammation and is also accompanied by other chronic diseases (including CKD) that are also associated with systemic inflammation(23, 24). Physical inactivity and metabolic syndrome are associated with both COPD and CKD(23, 25). An inverse association between physical activity level and inflammation were noted in those with COPD. These factors could contribute to the excess mortality risk in those with COPD and CKD and warrant further investigation. We noted higher hazards for death in younger population with COPD. It appears that with aging, the effect of COPD on outcomes become less relevant in those with CKD. Even though females were not at higher odds of having COPD in CKD, its presence has more pronounced effects than in males. Mechanisms for such discrepant impact in unclear and require further studies.

Apart from mortality, morbidity and costs associated with care of patients with COPD and CKD are staggering. Data from a large claims database (Truven Health MarketScan Commercial Claims and Encounters and the MarketScan Medicare Supplemental Databases) showed that COPD- or asthma-related total health-care costs were greatest among patients with COPD and asthma and CKD ($41,288 for the first year after the diagnosis of CKD). Our results add to the existing literature about the mortality burden among this population and argue for further studies to elucidate the important clinical factors associated with COPD among those with CKD(26).

This study has several strengths. It is comprised of a large diverse clinical population of stage 3 and 4 CKD patients enhancing the generalizability of our results. Furthermore availability of both all-cause mortality and cause specific death details in a population with CKD and COPD is novel. Additionally, we conducted several key sensitivity analyses and our results remained the same speaking to the robustness of the findings. Nevertheless as an observational study using a clinical population there are important limitations. We included patients who are followed in our health system for various clinical conditions and hence whether these data can be applicable to less sicker community-based CKD population is unknown. We did not have spirometry data and previous studies have showed the limited utility of ICD-9 codes to define COPD and other lung diseases for such epidemiological investigations but (27, 28). It is suggested that the use of multiple diagnostic codes for COPD and pharmacy data for medications can improve the ability to appropriately identify COPD patients(29). However, even though we didn’t have pharmacy data, we did a sensitivity analyses by defining COPD as those who had the ICD-9 codes and were on relevant medications and found similar results.

We acknowledge that it is a single-center study limiting its potential for external validity, but such associations in a large CKD cohort have not been reported previously. We lacked comprehensive data for some variables, but performed multiple imputations and complete case analysis to address the missingness issue and overall our findings remained the same.

We obtained cause-specific death data from the State of Ohio Department of Health mortality files. The National Death Index obtains data from individual States and several studies have reported using these data and are considered reliable. For previous studies, we recently performed a validation study for those who died within our hospital system and this analysis confirmed the reliability of death certificate derived data(30). Overlap syndrome of asthma and COPD has been consistently reported in studies with an estimated prevalence of 20% in patients with obstructive airways diseases(31). We didn't have spirometry data to distinguish this syndrome.

In summary, several demographic and clinical factors such as diabetes, heart failure, and hypertension were associated with COPD in stage 3 and stage 4 CKD population. Presence of COPD was associated with higher mortality in this population after accounting for other significant risk factors. Deaths due to respiratory disease accounted for a higher mortality burden among those with COPD and CKD. Additional studies to estimate the prevalence of COPD in CKD population using spirometry data to better characterize the lung disease and see if associations differ are needed. Fundamentally, additional research is needed to elucidate the mechanisms that link COPD and CKD that could then lead to important targeted therapy at improving the outcomes of those with COPD and CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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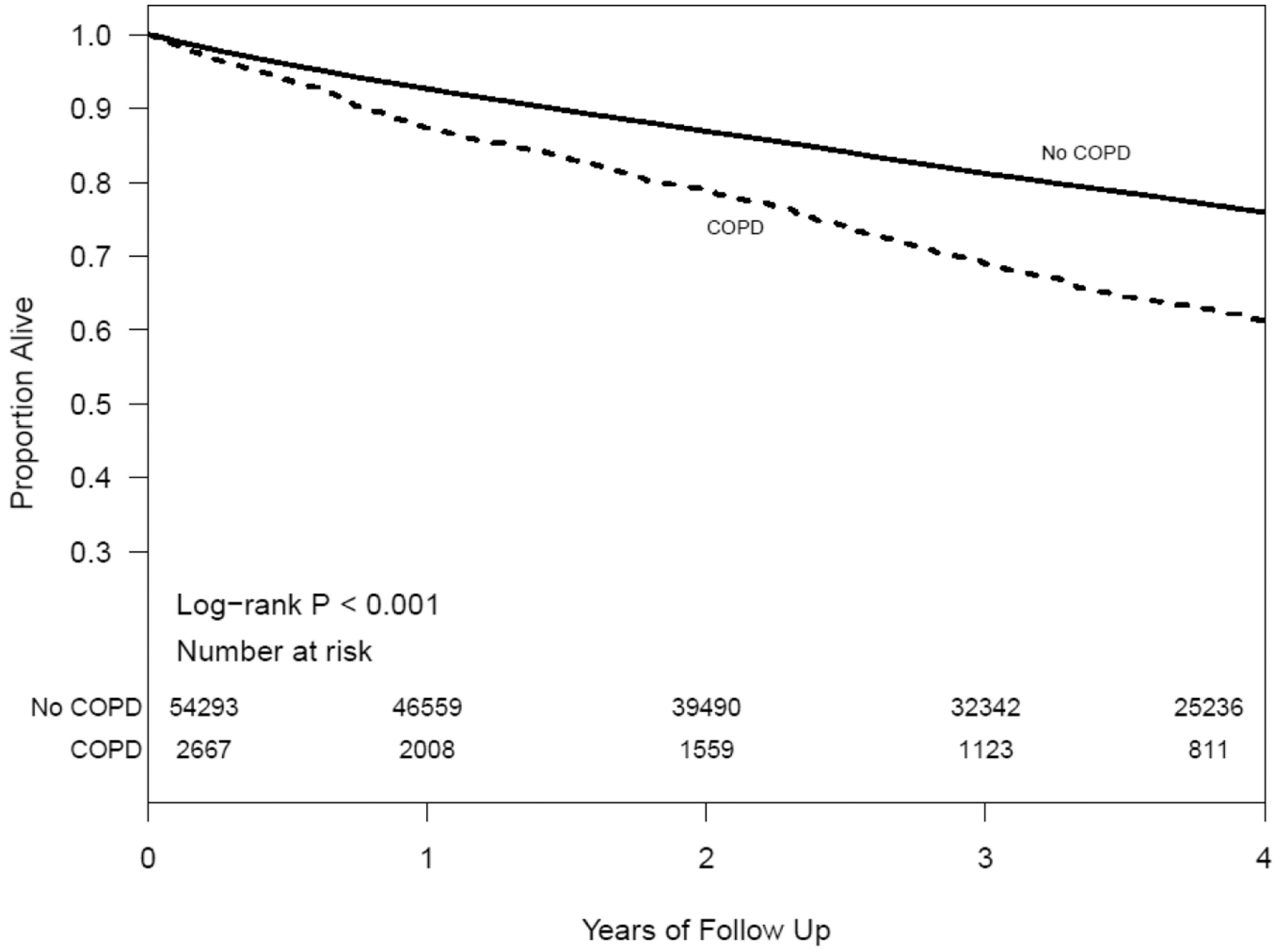

Figure 1.
Survival among those with and without COPD in CKD

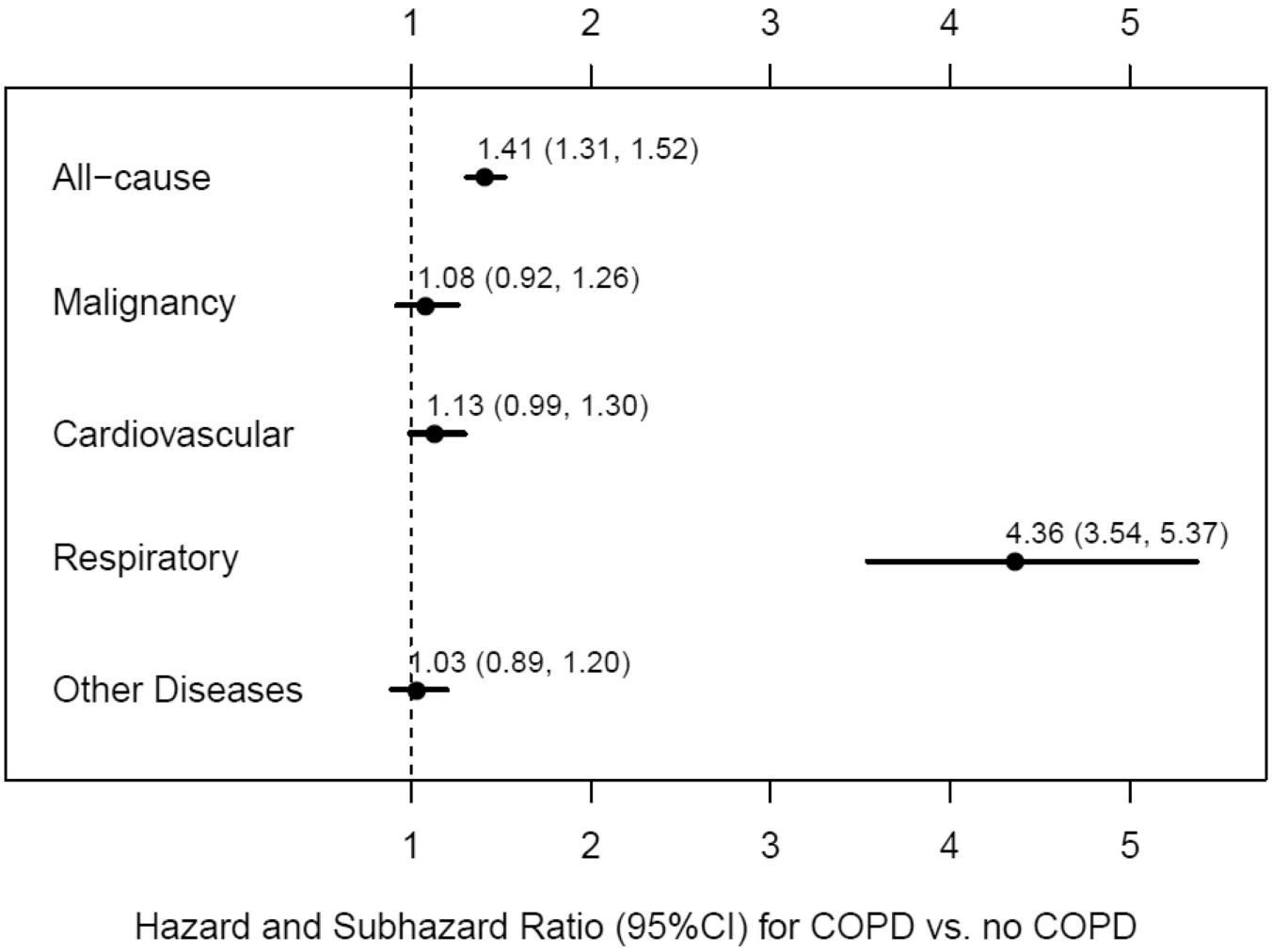

Figure 2.
Associations of various causes of death in those with COPD and CKD

Table 1

Characteristics of study cohort based on the presence or absence of COPD

Factor	N	Overall	No COPD (N=54293)	COPD (N=2667)	p-value
Age	56960	72.4±11.8	72.2±11.8	74.6±9.7	<0.001[a]
Male gender,%	56960	43.7	43.6	46.0	0.017[c]
African American, %	56960	12.5	12.4	15.1	<0.001[c]
Smoking,%	56960				<0.001[c]
No		77.9	77.8	79.8	
Yes		7.0	6.5	16.8	
Missing		15.1	15.7	3.4	
BMI (kg/m^2)	54144	29.5±6.6	29.5±6.5	29.1±7.1	<0.001[a]
BMI group	56960				<0.001[c]
<18.5 kg/m^2		1.2	1.1	2.8	
18.5–24.9 kg/m^2		22.6	22.4	26.3	
25–29.9 kg/m^2		33.8	34.0	30.8	
30+ kg/m^2		37.4	37.5	36.7	
Missing		4.9	5.0	3.4	
Diabetes, %	56960	22.8	22.5	29.7	<0.001[c]
Malignancy, %	56960	24.4	24.2	26.8	0.003[c]
Hypertension, %	56960	84.5	84.0	95.2	<0.001[c]
Hyperlipidemia, %	56960	76.9	76.5	84.3	<0.001[c]
Coronary artery disease, %	56960	20.2	19.5	34.4	<0.001[c]
Congestive heart failure, %	56960	7.8	7.2	18.4	<0.001[c]
Cerebrovascular disease, %	56960	9.0	8.7	14.7	<0.001[c]
ACEI/ARB use, %	56960	63.2	62.7	72.7	<0.001[c]
Statins use, %	56960	57.0	56.6	66.6	<0.001[c]
Beta Blocker use, %	56960	57.4	57.2	62.4	<0.001[c]
eGFR (ml/min/1.73 m^2)	56960	47.6±10.3	47.6±10.3	47.7±9.9	0.75[a]

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Factor	N	Overall	No COPD (N=54293)	COPD (N=2667)	p-value
eGFR categories	56960				0.52[c]
45–59 ml/min/1.73 m^2		67.4	67.3	67.7	
30–44 ml/min/1.73 m^2		24.9	24.9	25.1	
15–29 ml/min/1.73 m^2		7.8	7.8	7.2	
Albumin (g/dL)	46137	4.1±0.79	4.1±0.80	4.1±0.42	0.86[a]
Hemoglobin (mg/dl)	46963	12.8±1.8	12.8±1.8	12.7±1.9	0.012[a]
Insurance, %	56960				<0.001[c]
Medicaid		0.72	0.70	1.2	
Medicare		78.7	78.4	84.6	
Missing		3.0	3.1	2.2	
Other		17.5	17.8	12.0	
Bronchodilator use, %	56960	30.0	27.1	88.5	<0.001[c]

[a] t-test;

[c] Chi-square

Table 2

Factors associated with COPD in those with CKD

Effect	OR (95% CI)
Age (per 10 years increase)	1.26 (1.21, 1.31)
African American	1.14 (1.01, 1.27)
Female	1.04 (0.95, 1.13)
BMI (Ref: 18.5–24.9 kg/m^2)	
25–29.9 kg/m^2	0.80 (0.72, 0.89)
≥30 kg/m^2	0.90 (0.81, 1.00)
<18.5 kg/m^2	1.81 (1.38, 2.37)
CKD stage (Ref: 45–59 ml/min/1.73 m^2)	
eGFR 30–44 ml/min/1.73 m^2	0.97 (0.89, 1.07)
eGFR 15–29 ml/min/1.73 m^2	0.86 (0.73, 1.01)
Diabetes	1.19 (1.08, 1.30)
Malignancy	1.10 (1.00, 1.20)
Coronary artery disease	1.64 (1.49, 1.79)
Congestive heart failure	2.30 (2.06, 2.57)
Hypertension	3.02 (2.51, 3.63)
Smoking status	
Yes vs No	2.94 (2.61, 3.30)

*Adjusted for year of entry into the registry. Odds ratios shown were pooled using MIanalyze from 5 datasets created using multiple imputation.

Table 3

Associations of COPD with mortality in CKD (sensitivity analyses)

	N	Adjusted HR and SHR (95%CI)*
Model 1* (Complete case analysis)		
All-cause	33,631	1.37 (1.25, 1.49)
Respiratory death SHR	33,503	4.54 (3.45, 5.99)
Malignancy death SHR	33,503	1.03 (0.86, 1.24)
Cardiovascular death SHR	33,503	1.18 (1.001, 1.40)
Other causes SHR	33,503	0.96 (0.80, 1.15)
Model 2* (COPD defined ICD-9 codes and use of bronchodilators)		
All-cause	56,653	1.47 (1.36, 1.59)
Respiratory death SHR	56,447	4.51 (3.61, 5.63)
Malignancy death SHR	56,447	1.09 (0.92, 1.29)
Cardiovascular death SHR	56,447	1.14 (0.99, 1.32)
Other causes SHR	56,447	1.06 (0.90, 1.24)

*Model includes age, gender, race, CKD stage, diabetes, hypertension, hyperlipidemia, malignancy, insurance, smoking, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, BMI group, ACE/ARB use, beta blocker use, and statin use, albumin, hemoglobin and current prescription of COPD medications

Table 4

Effect modification of COPD on mortality based on age and gender

	Adjusted HR (95%CI)
Age	
18–44 years	**
45–60 years	2.12 (1.64, 2.75)
61–70 years	1.62 (1.37, 1.91)
71–80 years	1.35 (1.21, 1.51)
>81 years	1.28 (1.15, 1.43)
Gender	
Male	1.29 (1.17, 1.42)
Female	1.55 (1.41, 1.71)

* Model includes age, gender, race, CKD stage, diabetes, hypertension, hyperlipidemia, malignancy, insurance, smoking, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, BMI group, ACE/ARB use, beta blocker use, statin use, albumin, hemoglobin and COPD medication use

** Not presented due to very low number of patients with COPD

Hazard ratios presented were pooled using MIanalyze from 5 multiply imputed datasets.