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

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Key Words

Chronic obstructive pulmonary disease · Death and kidney disease · Cause-specific death · Lung disease

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 stages 3 and 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 = 2,667) had underlying COPD. Old age, presence of diabetes, hypertension, coronary artery disease, congestive heart failure, and 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% in-

creased risk (95% CI 1.31–1.52) for all-cause mortality, and fourfold increased risk (sub-hazard ratio 4.36, 95% CI 3.54–5.37) for respiratory-related deaths. In a sensitivity analysis that was performed by defining COPD as the use of relevant International Classification of Diseases-9 codes and medications used to treat COPD, similar results were noted. **Conclusions:** COPD is associated with higher risk for death among those with CKD, and an underlying lung disease accounts for significant proportion of deaths. These data highlight the need for further prospective studies to understand the underlying mechanisms and potential interventions to improve outcomes in this population.

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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 completely elucidated, systemic inflammation and hypoxia associated with COPD could contribute to adverse outcomes in those with CKD [4].

Despite the clinical significance of these 2 diseases, a limited number of studies have examined their associations. The reported prevalence of kidney disease in COPD ranges from 20 to 30% [5, 6]. Chandra et al. [7] 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. In a cohort of 3,371 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 2 or more eGFR 15–59.9 ml/min/1.73 m² that were at least 90 days apart (using the CKD 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 2 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, Ind., USA) in our laboratory. CKD was defined according to current guidelines as follows: stage 3 CKD (eGFR 30–59 ml/min/1.73 m²) and stage 4 CKD (eGFR 15–29 ml/min/1.73 m²). We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min/1.73 m²) and stage 3b (eGFR 30–44 ml/min/1.73 m²).

COPD

COPD was defined as the presence of 2 International Classification of Diseases (ICD), Ninth Revision (ICD-9) codes in any encounter type in the EHR. A modified definition of COPD and bronchiectasis as recommended by the Agency for Healthcare Research and Quality 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 abovementioned 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 ICD, 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, hyperten-

sion, hyperlipidemia, malignancy, insurance, smoking, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, BMI group, angiotensin converting enzyme/angiotensin receptor blocker (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 m².

We tested two-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 the presence of relevant ICD-9 codes plus prior prescription of COPD medications while excluding patients with COPD diagnosis and no prior prescription.

The percentage 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 (online suppl. table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000444422).

All analyses were conducted using Unix SAS version 9.4 (SAS Institute, Cary, N.C., USA), 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 m². We excluded 6,600 patients because they did not meet the specified inclusion criteria (online suppl. 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 and 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 (fig. 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 (hazard ratio 1.41 95% CI 1.31–1.52, $p < 0.05$; fig. 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. Online 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 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 interactions between COPD and race, and COPD and CKD stage were not significant.

Table 1. Characteristics of study cohort based on the presence or absence of COPD

Factor	n	Overall	No COPD (n = 54,293)	COPD (n = 2,667)	p value
Age	56,960	72.4±11.8	72.2±11.8	74.6±9.7	<0.001 ^a
Male, gender, %	56,960	43.7	43.6	46.0	0.017 ^b
African American, %	56,960	12.5	12.4	15.1	<0.001 ^b
Smoking, %	56,960				<0.001 ^b
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	54,144	29.5±6.6	29.5±6.5	29.1±7.1	<0.001 ^a
BMI group, kg/m ²	56,960				<0.001 ^b
<18.5		1.2	1.1	2.8	
18.5–24.9		22.6	22.4	26.3	
25–29.9		33.8	34.0	30.8	
30+		37.4	37.5	36.7	
Missing		4.9	5.0	3.4	
Diabetes, %	56,960	22.8	22.5	29.7	<0.001 ^b
Malignancy, %	56,960	24.4	24.2	26.8	0.003 ^b
Hypertension, %	56,960	84.5	84.0	95.2	<0.001 ^b
Hyperlipidemia, %	56,960	76.9	76.5	84.3	<0.001 ^b
Coronary artery disease, %	56,960	20.2	19.5	34.4	<0.001 ^b
Congestive heart failure, %	56,960	7.8	7.2	18.4	<0.001 ^b
Cerebrovascular disease, %	56,960	9.0	8.7	14.7	<0.001 ^b
ACE/ARB use, %	56,960	63.2	62.7	72.7	<0.001 ^b
Statins use, %	56,960	57.0	56.6	66.6	<0.001 ^b
β-Blocker use, %	56,960	57.4	57.2	62.4	<0.001 ^b
eGFR, ml/min/1.73 m ²	56,960	47.6±10.3	47.6±10.3	47.7±9.9	0.75 ^a
eGFR categories, ml/min/1.73 m ²	56,960				0.52 ^b
45–59		67.4	67.3	67.7	
30–44		24.9	24.9	25.1	
15–29		7.8	7.8	7.2	
Albumin, g/dl	46,137	4.1±0.79	4.1±0.80	4.1±0.42	0.86 ^a
Hemoglobin, mg/dl	46,963	12.8±1.8	12.8±1.8	12.7±1.9	0.012 ^a
Insurance, %	56,960				<0.001 ^b
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, %	56,960	30.0	27.1	88.5	<0.001 ^b

^a t test; ^b chi-square.

Discussion

In this study of stages 3 and 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, the presence of COPD was associated with higher risk of all-cause mortality and importantly, COPD was associated with fourfold 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 bron-

Table 2. Factors associated with COPD in those with CKD

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

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

Fig. 1. Survival among those with and without COPD in CKD. **Fig. 2.** Associations of various causes of death in those with COPD and CKD.

Table 3. Associations of COPD with mortality in CKD (sensitivity analyses)

	n	Adjusted HR and SHR (95% CI)*
<i>Model 1</i> (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)
<i>Model 2</i> (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)

HR = Hazard ratio; SHR = sub-hazard ratio.

* 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.

** HRs presented were pooled using MI analyze from 5 multiple imputed datasets.

Table 4. Effect modification of COPD on mortality based on age and gender

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

HR = Hazard ratio.

* 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, β -blocker use, statin use, albumin, hemoglobin and COPD medication use.

** Not presented due to very low number of patients with COPD HRs presented were pooled using MIanalyze from 5 multiple imputed datasets.

chitis, 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 show 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 overweight (not being obese) was associated with lower risk of having COPD. This might reflect the severity of the illness, that is, 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]. Long-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 [10] 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. 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 a significant proportion of deaths in CKD and we report fourfold higher risk for respiratory deaths among those with COPD and CKD. Using data collected in NHANES 2007–2010, Agarwal et al. [2] reported higher prevalence of self-reported cardiovascular disease in subjects with COPD than in those without COPD. 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 the 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 is unclear and require further studies.

In addition to 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 stages 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 confirming 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 did not 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, which 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]. The 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 did not 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 stages 3 and 4 CKD population. The 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.

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Disclosure Statement

The authors have no financial interests relevant to the contents of this manuscript.

References

- 1 Mannino DM, Buist AS: Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;370:765–773.
- 2 Agarwal S, Rokadia H, Senn T, Menon V: Burden of cardiovascular disease in chronic obstructive pulmonary disease. *Am J Prev Med* 2014;47:105–114.
- 3 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–1305.
- 4 Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al: Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clin J Am Soc Nephrol* 2012;7:1938–1946.
- 5 van Gestel YR, Chonchol M, Hoeks SE, Welten GM, Stam H, Mertens FW, et al: Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients. *Nephrol Dial Transplant* 2009;24:2763–2767.
- 6 Incalzi RA, Corsonello A, Pedone C, Battaglia S, Paglino G, Bellia V, et al: Chronic renal failure: a neglected comorbidity of COPD. *Chest* 2010;137:831–837.
- 7 Chandra D, Stamm JA, Palevsky PM, Leader JK, Fuhrman CR, Zhang Y, et al: The relationship between pulmonary emphysema and kidney function in smokers. *Chest* 2012;142:655–662.
- 8 Funakoshi Y, Omori H, Mihara S, Onoue A, Ogata Y, Aizawa H, et al: C-reactive protein levels, airflow obstruction, and chronic kidney disease. *Environ Health Prev Med* 2012;17:18–26.
- 9 Navaneethan SD, Jolly SE, Schold JD, Arrigain S, Saupe W, Sharp J, et al: Development and validation of an electronic health record-based chronic kidney disease registry. *Clin J Am Soc Nephrol* 2011;6:40–49.
- 10 Ford ES: Urinary albumin-creatinine ratio, estimated glomerular filtration rate, and all-cause mortality among US adults with obstructive lung function. *Chest* 2015;147:56–67.
- 11 Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, et al: Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015;148:971–985.
- 12 Abramson MJ, Schattner RL, Sulaiman ND, Del Colle EA, Aroni R, Thien F: Accuracy of asthma and COPD diagnosis in Australian general practice: a mixed methods study. *Prim Care Respir J* 2012;21:167–173.
- 13 Afonso AS, Verhamme KM, Sturkenboom MC, Brusselle GG: COPD in the general population: prevalence, incidence and survival. *Respir Med* 2011;105:1872–1884.
- 14 Leivseth L, Brumpton BM, Nilsen TI, Mai XM, Johnsen R, Langhammer A: GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT study, Norway. *Thorax* 2013;68:914–921.
- 15 Miniati M, Monti S, Pavlickova I, Bottai M: Survival in COPD: impact of lung dysfunction and comorbidities. *Medicine (Baltimore)* 2014;93:e76.
- 16 Pływaczewski R, Maciejewski J, Bednarek M, Zieliński J, Górecka D, Śliwiński P: Causes of deaths in COPD patients in primary care setting – a 6-year follow-up. *Pneumonol Alergol Pol* 2015;83:193–202.
- 17 Lahousse L, Niemeijer MN, van den Berg ME, Rijnbeek PR, Joos GF, Hofman A, et al: Chronic obstructive pulmonary disease and sudden cardiac death: the Rotterdam study. *Eur Heart J* 2015;36:1754–1761.
- 18 Chou CY, Wang SM, Liang CC, Chang CT, Liu JH, Wang IK, et al: Risk of pneumonia among patients with chronic kidney disease in outpatient and inpatient settings: a nationwide population-based study. *Medicine (Baltimore)* 2014;93:e174.
- 19 Dalrymple LS, Go AS: Epidemiology of acute infections among patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2008;3:1487–1493.
- 20 Sethi S, Murphy TF: Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:2355–2365.
- 21 McDonald HI, Thomas SL, Millett ER, Nitsch D: CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using electronic health records. *Am J Kidney Dis* 2015;66:60–68.
- 22 Navaneethan SD, Roy J, Tao K, Brecklin CS, Chen J, Deo R, et al: Prevalence, predictors, and outcomes of pulmonary hypertension in CKD. *J Am Soc Nephrol* 2015;pii: ASN.2014111111.
- 23 Loprinzi PD, Walker JF, Lee H: Association between physical activity and inflammatory markers among U.S. adults with chronic obstructive pulmonary disease. *Am J Health Promot* 2014;29:81–88.
- 24 Magnussen H, Watz H: Systemic inflammation in chronic obstructive pulmonary disease and asthma: relation with comorbidities. *Proc Am Thorac Soc* 2009;6:648–651.
- 25 Navaneethan SD, Schold JD, Kirwan JP, Arrigain S, Jolly SE, Poggio ED, et al: Metabolic syndrome, ESRD, and death in CKD. *Clin J Am Soc Nephrol* 2013;8:945–952.
- 26 Mannino DM, Higuchi K, Yu TC, Zhou H, Li Y, Tian H, et al: Economic burden of COPD in the presence of comorbidities. *Chest* 2015;148:138–150.
- 27 Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, et al: Validation of chronic obstructive pulmonary disease recording in the clinical practice research data-link (CPRD-GOLD). *BMJ Open* 2014;4:e005540.
- 28 Molnar MZ, Mucsi I, Novak M, Szabo Z, Freire AX, Huch KM, et al: Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax* 2015;70:888–895.
- 29 Cooke CR, Joo MJ, Anderson SM, Lee TA, Udris EM, Johnson E, et al: The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv Res* 2011;11:37.
- 30 Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Nally JV Jr: Cause-specific deaths in non-dialysis-dependent CKD. *J Am Soc Nephrol* 2015;26:2512–2520.
- 31 Gibson PG, McDonald VM: Asthma-COPD overlap 2015: now we are six. *Thorax* 2015;70:683–691.