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Age-related association between multimorbidity and mortality in US veterans with incident chronic kidney disease

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Abstract

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Author Contributions

NRB contributed to study design, writing, reviewing, and editing of the manuscript and was responsible for the project administration. AKK contributed to study design, writing, reviewing, and editing of the manuscript and interpretation of results. WY contributed to data access, data analysis, and reviewing of the manuscript. DC, MEP, RN, AKC, and KCN contributed to study design and reviewing of the manuscript and interpretation of results. GY was responsible for study design, data access, data analysis, and project administration and contributed to the writing, reviewing, and editing of the manuscript and interpretation of results.

Prior presentation

A preliminary part of this study was presented in abstract form (PO2414) at the Kidney Week Meeting of the American Society of Nephrology, 4–7 November 2021.

Statement of Ethics

This study protocol was reviewed, approved, and deemed exempt from patient consent by the Research and Development Committee at the Salem VA Medical Center, approval number DCD 0020.

Conflict of Interest Statement

The authors have nothing to disclose.

Disclaimer

The views expressed in this publication are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Department of the Army/Navy/Air Force, the Department of Defense, National Institutes of Health, or the United States government.

Introduction—Mortality is an important long-term indicator of the public health impact of chronic kidney disease (CKD). We investigated the role of individual comorbidities and multimorbidity on age-specific mortality risk among US veterans with new onset CKD.

Methods—The cohort included 892,005 veterans aged ≥18 with incident CKD stage 3 between January 2004 and April 2018 in the US Veterans Health Administration (VHA) system and followed until death, December 2018, or up to 10 years. Incident CKD was defined as the first time estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 m^2 for >3 months. Comorbidities were ascertained using inpatient and outpatient clinical records in the VHA system and Medicare claims. We estimated death rates for any cardiovascular disease (CVD, a composite of 6 CVD conditions) and 15 non-CVD comorbidities, and adjusted risks of death (hazard ratio [HR], 95% confidence interval [CI]) overall and by age group at CKD incidence.

Results—At CKD incidence, mean age was 72 years, 97% were male, mean eGFR was 52 ml/min/1.73 m^2, and 95% had ≥2 comorbidities (median, 4) in addition to CKD. During a median follow-up of 4.5 years, among the 16 comorbidities, CVD was associated with the highest relative risk of death in younger veterans (HR 1.96 [95% CI, 1.61–2.37] in ages 18–44 and HR 1.66 [1.63–1.70] in ages 45–64). Dementia was associated with the highest relative risk of death among older veterans (HR 1.71 [1.68–1.74] in ages 65–84 and HR 1.69 [1.65–1.73] in ages 85–100). The additive effect of multimorbidity on risk of death was stronger in younger than older veterans. Compared to having 1 or no comorbidity at CKD onset, the risk of death with ≥5 comorbidities was >7-fold higher among veterans aged 18–44 and >2-fold higher among veterans aged 85–100.

Discussion/Conclusion—The large burden of comorbidities in US veterans with newly identified CKD places them at risk of premature death. Compared with older veterans, younger veterans with multiple comorbidities, particularly with CVD, at CKD onset are at an even higher relative risk of death.

Keywords

Chronic kidney disease; cardiovascular disease; dementia; mortality; mortality risk

Introduction

The prevalence of chronic kidney disease (CKD) rises steeply with age [1,2] and commonly occurs in the setting of multiple comorbidities [3]. In a large population-based cohort study of Canadian adults, nephrology patients had the highest mean number of comorbidities, highest mean number of prescribed medications, and highest rate of death compared to those seen by primary care physicians and ten other subspecialists [4]. Multimorbidity is an important consideration in patient management [5,6] because it is associated with increased treatment burden [3] and major adverse outcomes and death [7], among other patient and health care issues.

Many patients with CKD are subject to multimorbidity, with diabetes, hypertension, and cardiovascular disease (CVD) being the most prevalent comorbidities [2]. These comorbidities can increase mortality risk and hasten progression of CKD to end-stage kidney disease (ESKD) [2,8]. Risk of death with comorbidities other than diabetes, hypertension, and CVD are however less well studied [8,9]. While several prior studies

have examined the association of comorbidities and mortality [10–12], very few recent studies have examined the relation between age and CKD diagnosis on these associations, largely due to insufficient sample size in prior studies. Furthermore, the population burden of comorbidities at the onset of CKD stage 3 is not well described because prior studies examining comorbidities used cohorts of prevalent CKD patients. Therefore, the objectives of this study are to 1) describe prevalence of various comorbidities at the time of CKD onset using a national cohort of US veterans with incident CKD stage 3; 2) evaluate associations with mortality risk of both individual comorbidities and multimorbidity identified at CKD onset; and 3) examine whether the associations differed by age group.

Materials and Methods

Data sources and study population

This study includes veterans in the US Veterans Health Administration (VHA) aged ≥18 with incident CKD stage 3 between January 1, 2004 and April 30, 2018 and followed through December 31, 2018 or up to 10 years for mortality analysis. Eligible veterans had to be in the VHA for at least 2 years prior to their earliest estimated glomerular filtration rate (eGFR) value <60 mL/min/1.73 m^2 and be regular VHA users, defined as having utilized VHA care services recorded in the VHA annual utilization files for two consecutive years prior to the date of incident CKD and with two outpatient visits during these two years. Incident CKD was defined as the second of two eGFR values <60 mL/min/1.73 m^2 at least 3 months apart, occurring for the first time during the study period. eGFR was determined using the 2009 CKD Epidemiology (CKD-EPI) Collaboration equation (i.e., with the race coefficient) [13], as it was the standard for estimating GFR during the study period. To ensure our analyses had adequate representation of comorbidities at the onset of CKD stage 3, we excluded veterans (<3%) who had CKD stage 4 or 5 (eGFR <30 mL/min/1.73 m^2) when first identified or those who were being treated for ESKD as determined using the US Renal Data System (USRDS). Those with missing blood pressure (BP) measurements or missing body mass index (BMI) at baseline (<1%) were also excluded from the analysis. The cohort construction is presented in the Supplemental Figure 1. The study utilized VHA integrated electronic health records—VHA Corporate Data Warehouse (CDW), VHA Vital Status File, and VHA/CMS/USRDS Data for Research. This study was approved by the Institutional Review Boards at the University of Virginia and the Salem Veterans Affairs Medical Center.

Study variables

We used those comorbidities reported in the annual USRDS surveillance reports or the comorbidities used in the calculation of the Charlson index (a widely used composite indicator of health conditions) to focus on comorbidities most relevant to CKD [2,14]. Thus, we selected 16 comorbidities for this study: hypertension, any CVD, diabetes, anemia, depression, chronic obstructive pulmonary disease (COPD), obesity, cancer, sleep apnea, gastrointestinal (GI) bleeding disorders, alcohol abuse, drug abuse, psychoses, dementia, liver disease and HIV/AIDS. Any CVD was defined as presence of any of the following: heart failure, coronary artery disease, cardiac dysrhythmia, other cardiac diseases, cerebrovascular accident or transient ischemic attack, and peripheral vascular

disease. Presence or absence of comorbidities was ascertained using inpatient and outpatient clinical records in VHA system and Medicare claims from the Centers for Medicare and Medicaid Services (CMS) during the two years before and six months after the incident CKD date, based on the International Classification of Diseases codes, Ninth and Tenth editions (ICD-9/ICD-10) (shown in Supplemental Table 1). A single ICD code was used to indicate presence of a comorbidity. Death information was based on the VHA Vital Status File and supplemented with the VHA CDW Patient Domain [15]. These files integrate death data from multiple official sources inside and outside of the VHA.

Baseline demographic and clinical characteristics included age, sex, race/ethnicity, U.S. Census region (Northeast/Midwest/South/West/Territory) based on the veteran's residence, and eGFR at the date of incident CKD. BP, urinary albumin-to-creatinine ratio (UACR), smoking status (never/former/current), BMI, and use of renin-angiotensin-aldosterone system inhibitors (RAASi), sodium-glucose cotransporter 2 inhibitors (SGLT2i), angiotensin receptor-neprilysin inhibitor (ARNi), and mineralocorticoid receptor antagonists (MRA) were determined using two years prior to the incident date.

Statistical analyses

Unadjusted and age- and sex-standardized death rates —with the entire study population serving as the standard population—were calculated for each comorbidity (absence or presence) as the number of deaths per 1,000 person-years at risk.

Associations between each of the comorbidities at incident CKD and risk of death were examined using Cox regression models adjusted for sex, race and ethnicity, U.S. Census region, baseline age, eGFR, BMI, medication use (RAASi, ARNi and MRA as separate variables) and year of incident CKD (Model 1). Multivariable models were also used to examine associations for all comorbidities jointly, adjusting for the same baseline covariates (Model 2). Regression analyses were conducted for the entire cohort and for each age group (18–44, 45–64, 65–84, and 85–100) at CKD incidence to identify potentially age-modified associations between comorbidities and death. To understand the additive effect of multimorbidity, we grouped patients into 8 risk groups using the total number (0–1, 2, 3, 4, 5, 6, 7, and ≥8) of comorbidities present and examined the mortality risk across these categories for each age group while controlling for the same baseline covariates mentioned above. All statistical analyses were performed using SAS software 9.4.

Results

We identified a cohort of 892,005 veterans with incident CKD. Mean (± standard deviation) age at CKD incidence was 72.3 ± 9.9 years, and nearly all veterans (96.9%) were male (shown in Table 1). The race and ethnicity distribution differed by age. At baseline, mean BP was 131/72 mmHg and mean eGFR was 52 mL/min/1.73 m^2 and this was similar across age groups. Among 357,193 veterans with albumin test results, 37.5% had moderate to severely increased albuminuria (UACR ≥30 mg/g) at CKD onset; this proportion was highest (49.0%) among veterans aged 18–44. Current smoking at CKD onset was more prevalent among younger than older veterans. Mean baseline BMI overall was 29.8 kg/m^2 and was in the obesity range (BMI ≥30 kg/m^2) for veterans aged 18–64 and in the overweight range (BMI

25.0–29.9 kg/m^2) for those aged ≥65. Across age groups, the most common medications used were RAASi (range: 52.2%–73.4%) and the least used medications were SGLT2i (range: 0.04%–0.2%).

Comorbidities at CKD incidence

Among the 892,005 veterans in the study population, based on 16 comorbidities (any CVD and 15 non-CVD comorbidities), hypertension (91.5%), CVD (74.9%), and diabetes (50.0%) were the three most common comorbidities at CKD incidence (shown in Table 1). Overall, of the six CVD comorbidities studied, 230,133 (25.8%) veterans had heart failure and 660,900 (74.1%) had atherosclerotic CVD, based on any of the other five CVD comorbidities (coronary artery disease, cardiac dysrhythmia, other cardiac diseases, cerebrovascular accident or transient ischemic attack, and peripheral vascular disease). Nearly all (96.9%) veterans with heart failure also had atherosclerotic CVD and 33.8% of those with atherosclerotic CVD had heart failure. Coronary artery disease was the most prevalent CVD (49.7%). Other frequent comorbidities included anemia (36.3%), depression (34.8%), COPD (34.0%), and obesity (31.2%). Depression was very prevalent among younger veterans, affecting 62.9% of veterans aged 18–44 and 53.3% of veterans aged 45–64.

At the time of CKD incidence, 95% of veterans experienced at least 2 comorbidities in addition to CKD. The median number of comorbidities at CKD incidence was four (interquartile range: 3–6) overall and this was similar across age groups (shown in Supplemental Table 2). Multimorbidity patterns also differed by age. For example, among those with 2 concurrent comorbidities, hypertension and depression co-occurred most frequently in ages 18–44, as compared to hypertension and CVD in older groups. Among veterans with three or more comorbidities, hypertension, CVD, and diabetes were the three most frequent co-occurring comorbidities in the overall cohort (38.7%), in veterans aged 45–64 (36.3%), and in those aged 65–84 (40.5%). On the other hand, the most frequent three co-occurring comorbidities were hypertension, CVD, and depression (22.2%) among veterans aged 18–44 and hypertension, CVD, and anemia (43.9%) among those aged ≥85.

Risk of death associated with comorbidities

Over a median follow-up of 4.5 years (interquartile range, 2.3–8.0 years), 325,560 veterans with incident CKD died from any cause. The highest age- and sex-standardized death rates were observed for dementia (160.8 deaths/1,000 person-years with dementia vs 68.0 without) and for psychoses (127.3 deaths/1,000 person-years with psychoses vs 68.4 without) (shown in Table 2). In Model 1, when assessing each comorbidity adjusting for age, sex, race and ethnicity, U.S. Census region, eGFR at CKD onset, BMI, RAASi use, ARNi use, MRA use, and incident year, increased risk of death ranged from 10% for obesity to more than 2-fold for dementia or heart failure relative to veterans without these comorbidities (shown in Table 2). The age-specific associations of individual comorbidities with mortality are presented in the Supplemental Figure 2.

In Model 2, when all comorbidities were considered together adjusting for the same covariates, dementia (hazard ratio [HR], 1.70, 95% CI, 1.68–1.72), COPD (HR, 1.53, 95%

CI, 1.52–1.54), and any CVD (HR, 1.50, 95% CI, 1.48–1.51) were the leading comorbidities associated with at least a 50% increased relative risk of death (shown in Table 2). However, these associations varied by age. Individual comorbidities were generally associated with greater risk in the youngest age group, although these estimates had the greatest uncertainty due to fewer veterans with comorbidities in this age group. Among veterans aged 18–44, the comorbidities associated with the greater risk of death were dementia (HR 3.09 [95%CI 1.57–6.08]), CVD (HR 1.96 [1.61–2.37]), diabetes (HR 1.83 [1.52–2.21]), anemia (HR 1.70 [1.41–2.05]), and cancer (HR 1.58 [1.22–2.05]). Among veterans aged 45–64, five comorbidities were associated with a 45% to 66% increased risk of death: CVD, cancer, COPD, diabetes, and anemia. For older veterans in both the 65–84 and 85–100 age groups, the comorbidities associated with the greater risk of death were similar and included dementia, COPD, CVD, and psychosis, associated with a 31% to 71% increased risk of death (shown in Fig. 1).

After multivariable adjustment, the association between increasing multimorbidity and risk of death was seen in all age groups but was stronger in younger than in older groups (shown in Table 3). Compared to their age counterparts with 0–1 comorbidity, the risk of death when having ≥5 comorbidities was >7-fold higher in veterans aged 18–44 in contrast to >2-fold higher in those aged 85–100.

Discussion/Conclusion

At CKD stage 3 onset, 95% of US veterans experienced at least 2 comorbidities in addition to CKD. Regardless of age, the most frequent comorbidities at the time of incident CKD were hypertension, CVD, and diabetes. Other comorbidities such as cancer, anemia, and depression varied by age, the latter being most prevalent among young veterans. Overall, after accounting for other comorbidities, the comorbidities associated with the highest adjusted relative risk of death were dementia, COPD, and any CVD. Among all the comorbidities examined (excluding dementia in ages 18–44 because of very few dementia cases), the relative risk of death with CVD was highest for veterans aged 18–64, while the relative risk of death with dementia was highest for veterans aged ≥65. Furthermore, the relative risk of death with more comorbidities, compared to fewer comorbidities, was much greater among younger than older veterans.

Our findings showing comorbidity as a likely major driver of mortality are consistent with a retrospective population-based cohort study of adults with CKD (eGFR <60 ml/min per 1.73 m^2 or the presence of albuminuria) in Canada who were followed from 2003 to 2011 [9]. The median number of comorbidities was lower in the Canadian study than in our study. However, consistent with our findings, they reported that mental health conditions, COPD, and cancer, in addition to diabetes and heart failure, were associated with poor outcomes in people with CKD. Similarly, using an incident CKD cohort of veterans from 2005 to 2008, Bowling et al reported higher risks of adverse health outcomes, including death, in patients with a higher number of chronic conditions [7]. Using more contemporary VHA data, we expanded Bowling's study by conducting an in-depth analysis of the association of multimorbidity and mortality stratified by age groups.

Of the six CVD comorbidities studied at the time of CKD incidence, the association with relative risk of death was greatest for heart failure, particularly for younger veterans, and emphasizes the importance of maximizing guideline-directed medical therapy in a multidisciplinary approach in younger CKD patients with heart failure [16,17]. Consistent with our finding, among Medicare patients aged ≥66 with a diagnostic code of CKD, those with incident heart failure had a lower survival rate compared with those with other incident CVD conditions [2]. In community-based cohort studies, CKD was associated with an increased risk of heart failure similar to the risk of coronary heart disease and greater than the risk of stroke [18]. Furthermore, a prospective study by Bibbins-Domingo and colleagues reported that, among participants who were aged 18–30 at baseline, CKD along with hypertension, obesity, and systolic dysfunction were important early heart failure risk factors [19].

While the majority of comorbidities conveyed a greater risk of mortality at younger compared to older age groups, some comorbidities, such as depression and psychosis, showed the opposite trend. Although it is not possible to empirically evaluate why these results were observed, we can speculate as to potential explanations. For example, depression may be less likely to be treated among older compared to younger adults [20], resulting in worse outcomes. Moreover, psychosis in older adults may include more cases that are secondary to underlying conditions prevalent in late life and known to have a strong mortality risk, such as neurodegenerative disorders [21]. As for those comorbidities conveying a greater mortality risk at younger ages, the etiology of some comorbidities can differ depending on age of onset. For example, early-onset Alzheimer's disease has a stronger genetic component than late-onset Alzheimer's disease, with the former more strongly associated with mortality [22]. Alternatively, comorbidities may be undercaptured among older adults [7], as screening or diagnosis of certain conditions may not be given priority if patients already have other more severe comorbidities.

Our findings highlight the importance of reducing the risk of CVD complications in veterans with CKD. In our study, urinary albumin measurements were available in 40% of veterans with new-onset CKD, consistent with previous reports showing marked underutilization of urine albumin testing in Medicare beneficiaries, veterans, primary care settings, and commercially insured adults [1,2,23,24]. The presence of albuminuria in CKD patients with or without diabetes increases the risk of incident CVD and mortality [25] and may indicate the need for earlier intervention or even a referral to a nephrologist if albuminuria is severely increased [25,26]. For patients with CKD, diabetes, and albuminuria, or for patients with CKD and severely increased albuminuria, the use of RAASi is recommended [26,27]. RAASi reduce albuminuria in addition to lowering blood pressure and have been shown the reduce the risk of CKD progression and CVD outcomes in people with diabetic CKD [28,29]. However, from 2005 to 2010, the percentage filling at least one prescription for RAASi declined significantly from 58.5% to 43.4% in the veteran population with CKD (eGFR < 60 mL/min/1.73 m^2) and from 71.9% to 54.9% in the veteran population with diabetes and CKD [1].

Other treatments such as SGLT2 inhibitors have been shown to reduce the risk of kidney or cardiovascular death in people with CKD and type 2 diabetes [30,31]. In the Dapagliflozin

and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, dapagliflozin reduced the risk of kidney failure or cardiovascular death in CKD patients with or without type 2 diabetes, independently of a history of heart failure [32]. However, this class of drugs is currently very underused among patients with diabetes and CKD [33]. Increased use of SGLT2 inhibitors in people with type 2 diabetes and CKD [34] is likely to impact future trends in CVD and ESKD incidence and mortality.

For veterans aged ≥65 with incident CKD, having dementia (vs not) was associated with the highest risk of death. Having dementia was also associated with the highest risk of death among veterans aged 18–44, but this finding may be unreliable given the very wide confidence interval of the HR because of the small number veterans with dementia in this age group. Hiramatsu and colleagues, after adjusting for a wide range of comorbidities, reported incident diagnosis of dementia in a cohort of CKD patients seen in a primary care setting in England from 2004 to 2014 [35]. The association between CKD and incident dementia was stronger soon after patients were identified as having CKD and attenuated but still statistically significant after six months; a strong association between worsening CKD and all-cause mortality was also found [36].

Based on the fully adjusted models, obesity, hypertension, and sleep apnea appeared to have a protective effect on survival. This is consistent with the survival paradox in people with CKD and particularly in dialysis populations where hypertension and obesity have been associated with better survival [36,37]. The association between sleep apnea and improved survival in people with CKD is less clear although obesity has been shown to be an important risk factor for sleep apnea [38].

This is the first analysis of a US large-scale incident CKD cohort for a detailed examination of age-related associations between comorbidities at CKD onset and risk of death. With the incident cohort, follow-up for mortality started from a common entry point in CKD development for all individuals, which can minimize the confounding effect related to disease duration at entry (a common, major confounder in prevalent cohort studies). Furthermore, our analysis of a US large-scale incident CKD cohort resulted in a detailed documentation of prevalence of various comorbidities, both concordant and discordant (i.e., sharing or not sharing a common pathophysiological pathway with CKD) at the time of CKD incidence [3]. However, we did not assess other potential comorbidities such as asthma, thyroid disease, rheumatoid arthritis, inflammatory bowel disease, and chronic pain. Despite our large study cohort, our findings are limited to the veteran population and may not be generalizable to the US population, especially to women, who made up only 3% of the study population. Other limitations include the potential for residual confounding and selection bias from the observational nature of the study. In particular, regular VHA patients in the younger age groups may not be representative of the overall younger veteran population. Lastly, the use of a single ICD code to ascertain comorbidities in both VHA and Medicare claims data may have high sensitivity but low specificity.

Patients with newly identified CKD have a large burden of comorbidities that place them at higher relative risk of death. Increased awareness of all comorbidities, including dementia, depression, COPD, and cancer, occurring in people with newly identified CKD could

assist clinicians in targeting interventions and improving case management. Moreover, multi-disciplinary and specialty care teams to address mental health conditions, COPD, and cancer, among other comorbidities, in people with newly diagnosed CKD, could play a vital role in patient care and management and attenuation of CKD progression and its complications [39].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

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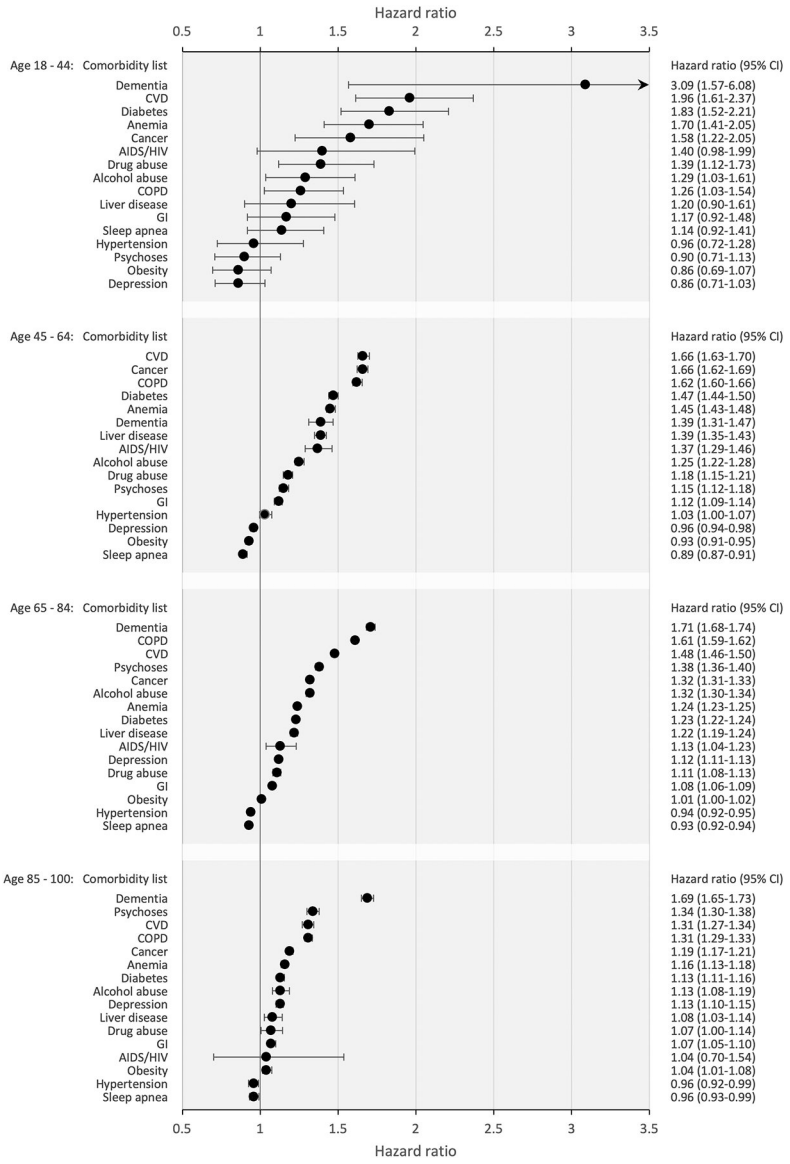

Fig. 1.

Multivariable associations of comorbidities at chronic kidney disease incidence and mortality among US veterans aged ≥18 years, by age group.[a]

CI=confidence interval; COPD=chronic obstructive pulmonary disorder; CVD=cardiovascular disease; GI=gastrointestinal bleeding disorders; HIV/AIDS=human immunodeficiency virus/acquired immunodeficiency syndrome.

[a] The multivariable associations were examined separately for each age group. All comorbidities were included in the model, controlling for additional variation of age within the age group, sex, race and ethnicity, estimated glomerular filtration rate at chronic kidney disease incidence, body mass index, RAASi use, ARNi use, MRA use, U.S. Census region, and incident year. CVD included coronary artery disease, cardiac dysrhythmia, other cardiac disease, peripheral vascular disease, cerebrovascular accident/transient ischemic attack, or heart failure.

Table 1.

Demographic and clinical characteristics, and prevalence of comorbidities in US veterans aged ≥18 years at chronic kidney disease incidence, overall and by age group, January 1, 2004 to April 30, 2018.

Characteristic	Overall	Age 18–44	Age 45–64	Age 65–84	Age 85–100
Patients, n	892,005	4,687	202,617	595,539	89,162
Mean age at CKD onset, years (SD)	72.3 (9.9)	40.6 (4.1)	59.5 (4.4)	74.5 (5.7)	88.4 (2.7)
Male, n (%)	864,080 (96.9)	3,816 (81.4)	187,796 (92.7)	585,461 (98.3)	87,007 (97.6)
Race and ethnicity, n (%)[a]					
White	714,511 (80.1)	2,552 (54.4)	136,783 (67.5)	497,543 (83.5)	77,633 (87.1)
Black	113,327 (12.7)	1,601 (34.2)	47,491 (23.4)	58,317 (9.8)	5,918 (6.6)
Hispanic	37,299 (4.2)	287 (6.1)	9,729 (4.8)	23,588 (4.0)	3,695 (4.1)
Other[b]	26,868 (3.0)	247 (5.3)	8,614 (4.3)	16,091 (2.7)	1,916 (2.1)
eGFR, mL/min/1.73 m^2	52.0 (6.6)	52.3 (6.9)	52.1 (6.7)	52.1 (6.5)	50.9 (7.1)
Mean systolic BP, mmHg (SD)	131.3 (18.4)	130.8 (20.3)	130.6 (19.4)	131.5 (18.0)	131.8 (18.6)
Mean diastolic BP, mmHg (SD)	72.4 (11.4)	81.7 (13.6)	76.6 (11.9)	71.5 (10.8)	68.6 (10.5)
UACR, n (%)[c]					
<30 mg/g	223,102 (62.5)	756 (50.9)	50,730 (58.6)	154,500 (63.8)	17,116 (63.0)
30–299 mg/g	104,566 (29.3)	383 (25.8)	24,654 (28.5)	70,661 (29.2)	8,868 (32.6)
≥300 mg/g	29,525 (8.3)	345 (23.2)	11,177 (12.9)	16,821 (7.0)	1,182 (4.4)
Smoking, n (%)[d]					
Never	200,529 (22.9)	1,370 (29.6)	39,957 (19.9)	134,628 (23.0)	24,574 (28.1)
Former	487,525 (55.6)	1,755 (37.9)	88,812 (44.3)	341,188 (58.4)	55,770 (63.9)
Current	188,873 (21.5)	1,506 (32.5)	71,542 (35.7)	108,838 (18.6)	6,987 (8.0)
Mean BMI, kg/m^2 (SD)	29.8 (6.0)	31.8 (6.8)	31.7 (6.9)	29.6 (5.6)	26.6 (4.2)
Medications, n (%)[e]					
RAASi	624,850 (70.0)	2,447 (52.2)	148,664 (73.4)	422,613 (71.0)	51,126 (57.3)
SGLT2i	1,805 (0.2)	3 (0.1)	474 (0.2)	1,292 (0.2)	36 (0.04)
ARNi	34,322 (3.8)	143 (3.1)	7,120 (3.5)	23,756 (4.0)	3,303 (3.7)
MRA	67,523 (7.6)	401 (8.6)	20,969 (10.3)	41,420 (7.0)	4,733 (5.3)
Census region, n (%)					
Northeast	133,998 (15.0)	397 (8.5)	21,072 (10.4)	93,226 (15.6)	19,303 (21.7)
Midwest	215,394 (24.2)	963 (20.5)	45,922 (22.7)	146,466 (24.6)	22,043 (24.7)
South	381,097 (42.7)	2,469 (52.7)	96,932 (47.8)	249,481 (41.9)	32,215 (36.1)
West	151,592 (17.0)	829 (17.7)	37,453 (18.5)	99,362 (16.7)	13,948 (15.6)
U.S. Territory	9,924 (1.1)	29 (0.6)	1,238 (0.6)	7,004 (1.2)	1,653 (1.9)
Comorbidity, n (%)[e]					
Hypertension	815,945 (91.5)	3,174 (67.7)	179,807 (88.7)	551,228 (92.6)	81,736 (91.7)
Any CVD[f]	667,967 (74.9)	1,977 (42.2)	126,092 (62.2)	462,338 (77.6)	77,560 (87.0)

Characteristic	Overall	Age 18–44	Age 45–64	Age 65–84	Age 85–100
Coronary artery disease	443,223 (49.7)	825 (17.6)	75,771 (37.4)	313,915 (52.7)	52,712 (59.1)
Cardiac dysrhythmia	352,527 (39.5)	727 (15.5)	51,025 (25.2)	248,976 (41.8)	51,799 (58.1)
Other cardiac disease	347,766 (39.0)	948 (20.2)	54,683 (27.0)	245,007 (41.1)	47,128 (52.9)
PVD	294,185 (33.0)	503 (10.7)	45,137 (22.3)	209,475 (35.2)	39,070 (43.8)
CVA/TIA	231,669 (26.0)	301 (6.4)	32,879 (16.2)	165,312 (27.8)	33,177 (37.2)
Heart failure	230,133 (25.8)	539 (11.5)	41,100 (20.3)	156,464 (26.3)	32,030 (35.9)
Diabetes	445,773 (50.0)	1,333 (28.4)	108,381 (53.5)	302,212 (50.7)	33,847 (38.0)
Anemia	323,958 (36.3)	1,253 (26.7)	60,086 (29.7)	218,228 (36.6)	44,391 (49.8)
Depression	310,689 (34.8)	2,948 (62.9)	107,916 (53.3)	177,147 (29.7)	22,678 (25.4)
COPD	303,021 (34.0)	793 (16.9)	59,766 (29.5)	210,115 (35.3)	32,347 (36.3)
Obesity	278,089 (31.2)	1,900 (40.5)	85,168 (42.0)	180,101 (30.2)	10,920 (12.2)
Cancer	227,386 (25.5)	369 (7.9)	32,206 (15.9)	163,962 (27.5)	30,849 (34.6)
Sleep apnea	174,580 (19.6)	1,302 (27.8)	51,784 (25.6)	113,279 (19.0)	8,215 (9.2)
GI bleeding disorders	124,466 (14.0)	443 (9.5)	25,769 (12.7)	84,217 (14.1)	14,037 (15.7)
Alcohol abuse	93,320 (10.5)	998 (21.3)	40,630 (20.1)	48,954 (8.2)	2,738 (3.1)
Psychoses	67,926 (7.6)	682 (14.6)	23,413 (11.6)	36,390 (6.1)	7,441 (8.3)
Drug abuse	58,229 (6.5)	993 (21.2)	32,835 (16.2)	23,024 (3.9)	1,377 (1.5)
Dementia	49,837 (5.6)	18 (0.4)	2,969 (1.5)	32,101 (5.4)	14,749 (16.5)
Liver Disease	47,403 (5.3)	298 (6.4)	17,410 (8.6)	27,549 (4.6)	2,146 (2.4)
HIV/AIDS	5,706 (0.6)	202 (4.3)	3,553 (1.8)	1,903 (0.3)	48 (0.1)

ARNi=angiotensin receptor-neprilysin inhibitor; BMI=body mass index; BP=blood pressure; COPD=chronic obstructive pulmonary disorder; CVA/TIA=cerebrovascular accident/transient ischemic attack; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; GI=gastrointestinal; HIV/AIDS=human immunodeficiency virus/acquired immunodeficiency syndrome; MRA=mineralocorticoid receptor antagonists; PVD=peripheral vascular disease; RAASi=renin-angiotensin-aldosterone system inhibitors; SD=standard deviation; SGLT2i=sodium-glucose cotransporter 2 inhibitors; UACR=urinary albumin-to-creatinine ratio.

[a] Racial groups included persons of non-Hispanic origin; Hispanic persons may be of any race.

[b] Other included American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, or multiple or other races.

[c] Available on 357,193 (40%) of patients.

[d] Available on 98% of patients.

[e] Prevalence represents column percentages and may not add up to 100, as categories are not mutually exclusive.

[f] Coronary artery disease, cardiac dysrhythmia, other cardiac disease, PVD, CVA/TIA, or heart failure.

Table 2.

Crude and age-sex standardized death rates and risk of death for comorbidities at chronic kidney disease incidence among US veterans aged ≥18 years.

Comorbidity	Crude death rate (per 1000 person-years)		Age-sex standardized death rate (per 1000 person-years)		HR (95% CI) from Model 1[a]	HR (95% CI) from Model 2[b]
	Presence	Absence	Presence	Absence		
Dementia	193.5	67.3	160.8	68.0	2.22 (2.19–2.24)	1.70 (1.68–1.72)
COPD	106.6	56.9	104.8	57.5	1.77 (1.76–1.78)	1.53 (1.52–1.54)
Any CVD	85.5	36.4	82.9	41.0	1.84 (1.82–1.86)	1.50 (1.48–1.51)
Heart failure	132.1	55.5	126.7	56.5	2.07 (2.06–2.09)	
PVD	105.2	57.7	100.2	59.6	1.54 (1.53–1.56)	
Cardiac dysrhythmia	103.2	54.6	96.6	57.6	1.49 (1.48–1.50)	
Coronary artery disease	92.3	53.7	88.8	56.4	1.43 (1.41–1.44)	
CVA/TIA	105.6	61.2	99.1	63.0	1.43 (1.42–1.44)	
Other cardiac disease	98.1	58.0	93.1	60.5	1.38 (1.37–1.39)	
Psychoses	113.7	68.8	127.3	68.4	1.90 (1.88–1.92)	1.33 (1.31–1.35)
HIV/AIDS	62.3	71.9	77.3	71.8	1.47 (1.40–1.54)	1.33 (1.27–1.40)
Cancer	103.2	62.4	97.7	64.1	1.42 (1.41–1.43)	1.32 (1.31–1.33)
Alcohol abuse	85.9	70.4	100.6	69.1	1.68 (1.66–1.69)	1.30 (1.28–1.32)
Liver disease	109.2	70.1	115.1	69.8	1.73 (1.71–1.76)	1.29 (1.27–1.31)
Anemia	104.6	56.2	100.3	58.0	1.57 (1.56–1.58)	1.26 (1.25–1.27)
Diabetes	78.2	65.8	80.4	63.8	1.32 (1.31–1.33)	1.23 (1.22–1.24)
Drug abuse	76.6	71.5	97.7	70.4	1.67 (1.65–1.70)	1.19 (1.17–1.20)
Depression	75.0	70.3	84.5	67.0	1.40 (1.39–1.41)	1.11 (1.10–1.11)
GI bleeding disorders	101.2	67.3	99.3	67.6	1.37 (1.35–1.38)	1.08 (1.07–1.09)
Obesity	60.8	76.6	67.5	73.4	1.10 (1.09–1.11)	0.99 (0.98–1.00)
Hypertension	73.5	53.6	73.2	57.1	1.15 (1.13–1.17)	0.95 (0.93–0.96)
Sleep apnea	67.2	72.8	73.6	71.5	1.16 (1.15–1.17)	0.92 (0.92–0.93)

CI=confidence interval; COPD=chronic obstructive pulmonary disorder; CVA/TIA=cerebrovascular accident/transient ischemic attack; CVD=cardiovascular disease; GI=gastrointestinal; HR=hazard ratio; HIV/AIDS=human immunodeficiency virus/acquired immunodeficiency syndrome; PVD=peripheral vascular disease.

[a]Model 1 includes each comorbidity (presence vs absence), one at a time, along with age, sex, race and ethnicity, estimated glomerular filtration rate at chronic kidney disease incidence, body mass index, each medication use at baseline (renin-angiotensin-aldosterone system inhibitors, angiotensin receptor-neprilysin inhibitor, and mineralocorticoid receptor antagonists), U.S. Census region (Northeast/Midwest/South/West/U.S. territory), and incident year. All were statistically significant ($p<0.05$).

[b]Model 2 includes all comorbidities together, along with the same covariates as above. All were statistically significant ($p<0.05$) except for obesity ($p=0.076$).

Table 3.

Risk of death across multimorbidity categories at chronic kidney disease incidence among US veterans aged ≥18 years, by age group.

Number of comorbidities at CKD incidence	Percent of veterans in each category	Hazard ratio (95% CI)			
		Age 18–44	Age 45–64	Age 65–84	Age 85–100
0–1	5.2	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2	11.8	2.63 (1.31–5.29)	1.70 (1.57–1.85)	1.40 (1.35–1.44)	1.17 (1.11–1.23)
3	18.0	3.65 (1.88–7.11)	2.49 (2.30–2.69)	1.83 (1.78–1.88)	1.43 (1.36–1.50)
4	19.3	5.62 (2.92–10.83)	3.29 (3.04–3.55)	2.32 (2.25–2.38)	1.69 (1.61–1.78)
5	16.7	7.58 (3.94–14.58)	4.25 (3.93–4.58)	2.89 (2.80–2.97)	2.06 (1.96–2.16)
6	12.4	9.47 (4.89–18.34)	5.23 (4.85–5.66)	3.56 (3.46–3.67)	2.42 (2.30–2.55)
7	8.1	11.49 (5.88–22.45)	6.54 (6.05–7.07)	4.41 (4.28–4.54)	2.92 (2.77–3.08)
≥8	8.5	12.93 (6.66–25.11)	9.07 (8.40–9.80)	6.04 (5.86–6.22)	3.78 (3.57–3.99)

CI=confidence interval; CKD=chronic kidney disease.