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Association of Depression and Antidepressant Use with Mortality in a Large Cohort of Patients with Nondialysis-Dependent CKD

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Summary

Background and objectives Depression is common and is associated with higher mortality in patients with ESRD or CKD (stage 5). Less information is available on earlier stages of CKD. This study aimed to determine the prevalence of depression and any association with all-cause mortality in patients with varying severity of nondialysis-dependent CKD.

Design, setting, participants, & measurements This is a retrospective study of a national cohort of 598,153 US veterans with nondialysis-dependent CKD stages 1–5 followed for a median of 4.7 years in the US Department of Veterans Affairs Health System. Diagnosis of depression was established as a result of systematic screening and administration of antidepressants. Association of depression with all-cause mortality overall and stratified by CKD stages were examined with the Kaplan–Meier method and in Cox models.

Results There were 179,441 patients (30%) with a diagnosis of depression. Over median follow-up of 4.7 years, depression was associated with significantly higher age-adjusted mortality overall (hazard ratio, 1.55; 95% confidence interval, 1.54–1.57; $P<0.001$). Sequential adjustments for sociodemographic characteristics and especially for comorbid conditions attenuated this association, which nevertheless remained significant (hazard ratio, 1.25; 95% confidence interval, 1.23–1.26).

Conclusions In this large cohort of predominantly elderly male patients with CKD, prevalence of depression and antidepressant use is high (30%) and is associated with significantly higher all-cause mortality independent of comorbid conditions.

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Introduction

Major depression is the most common psychiatric diagnosis in adults with CKD (1). This is of great importance because the presence of depression in CKD is associated with poorer outcomes such as hospitalizations, progression to dialysis, and death (2,3). In spite of these grave outcomes, depression is often unrecognized, underdiagnosed, and undertreated (4,5) in these patients because CKD patients have somatic symptoms that can mimic symptoms of depression. In a 2003 study, only 16% of depressed CKD patients were being treated with antidepressants (4).

Major depression is diagnosed by medical interview, according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM IV-TR) (6). There are several screening tools that are useful in detecting depressive symptoms and help identify patients who are at high risk for depression. Once depression is suspected by using a screening tool, it is then recommended that the presence of major depression be confirmed by thorough clinical interviewing using the DSM IV diagnostic criteria, which are regarded as the gold standard in diagnosing major depression (7–15).

Surprisingly, the limited available literature on smaller patient cohorts suggests that the presence of depression does not vary significantly with the stage of kidney disease (2,16,17). Less information is known about depression in earlier stages of CKD compared with ESRD (18,19). In this study, using a large national database, we aimed to investigate the prevalence of depression and its association with mortality in patients with all stages of nondialysis-dependent CKD. We examined whether nondialysis-dependent CKD is associated with a higher prevalence of depression and mortality, especially after adjusting for factors previously known to be predictive of depression and of mortality in CKD patients (sociodemographics and comorbidities) (20–24).

Materials and Methods

Cohort Definition and Depression Diagnosis

The creation of our CKD cohort was described previously (25). Briefly, we identified patients with

CKD using laboratory data of serum creatinine and urine microalbumin/creatinine ratio from the Veterans Affairs (VA) Decision Support System National Data Extracts Laboratory Results file (a VA-wide database containing select laboratory results obtained in the clinical setting) (26). CKD was defined as a persistent estimated GFR (eGFR) of <60 ml/min per 1.73 m^2 on at least two occasions separated by no less than 3 months and/or the presence of an elevated spot urine microalbumin/creatinine ratio on at least one occasion (for those with eGFR ≥ 60) (27). GFR was estimated from serum creatinine measurements and demographic characteristics by the Chronic Kidney Disease Epidemiology Collaboration equation (28). Formation of the cohort was done between October 1, 2004 and September 30, 2006. Laboratory and other follow-up data on patients who formed the cohort were collected from inclusion (October 1, 2004 or a later inclusion date) until end of follow-up (death or September 30, 2009). There were 598,153 patients with nondialysis-dependent CKD, available depression diagnosis, and sufficient follow-up for survival analysis.

All patients who visit a primary care provider at all VA clinic sites receive a periodic step-wise systematic screen for depression prompted automatically by the electronic medical record system. The first step consists of two brief questions asked (usually) by the nurse checking the patient in, based on the previously validated Patient Health Questionnaire (PHQ)-2 (13,29–31). If the patient screens positive, this will trigger a more detailed evaluation using the PHQ-9 (12,32). A positive result on the PHQ-9 triggers a referral for a psychiatric consultation in which a formal psychiatric interview is performed. We identified patients with depression based on either the presence of depression-related *International Classification of Diseases, Ninth Revision* (ICD-9) codes in their medical records between October 1, 2004 and September 30, 2006 (n=36,936), and/or the dispensation of antidepressants during the same period (n=173,820), yielding a total of 179,441 patients with depression. We excluded 59,417 patients who received antidepressants for the first time after September 30, 2006 (the end of our evaluation period), but who had no diagnosis of depression before this date. Our final cohort consisted of 598,153 patients (n=179,441 [30%] with depression and n=418,712 [70%] without depression).

Sociodemographic Characteristics, Medication Use, and Comorbidities

Data on patients' age, sex, race, geographic location (Veteran Integrated Service Network number), and BP were obtained through the VA Corporate Data Warehouse. Information on race was complemented with data obtained from Medicare through the VA-Medicare data merge project (33). We identified exposure to antidepressants based on VA pharmacy dispensation records (34). Data on comorbidities (including the presence of depression: *296.*×) was collected from the VA Inpatient and Outpatient Medical SAS Datasets (35,36) using ICD-9 diagnostic and procedure codes and Current Procedural Terminology codes recorded during the October 1, 2004 to September 30, 2006 time period. These databases contain up to 12 diagnostic and/or procedure codes for every inpatient, long-term care, and outpatient VA encounter, and also for many non-VA encounters. Prevalent cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, or myocardial infarction, or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We calculated the Charlson comorbidity index using the Deyo modification for administrative datasets, without including kidney disease (37).

Laboratory Characteristics

Data on laboratory variables were collected from October 1, 2004 through September 30, 2009 by using the VA Decision Support System National Data Extracts Laboratory Results file (26). To minimize random variability, all available laboratory values were grouped by calendar quarters, and their quarterly averaged values were used in analyses.

Statistical Analyses

Descriptive analyses were performed by using means ± SDs, medians (interquartile ranges), and proportions as appropriate; skewed variables were log-transformed. Due to the extremely large sample size, traditional statistical testing of differences in baseline characteristics was statistically significant for most variables; hence, the significance of differences was established based on what we deemed to be biologically meaningful differences, rather than statistical significance. Data points were missing for race (0.1%), marital status (3.1%), and insurance status (6.2%). There were 550,677 patients (92% of the total study population) with complete data available for multivariable analyses. Missing values were not imputed.

The start of the follow-up period was the date of the eGFR used to define CKD. Patients were followed until death or until the date of the last health care or administrative encounter, as documented in the VA Vital Status Files. The VA Vital Status Files are a registry containing dates of death or last medical/administrative encounter from all available sources in the VA system, including the Beneficiary Identification Records Locator Subsystem, the patient treatment file, Medicare, and the Social Security Administration. The sensitivity and specificity of the Vital Status Files using the National Death Index as the gold standard were shown to be very high (98.3% and 99.8%, respectively) (38). The association of depression with all-cause mortality was examined by using the Kaplan–Meier method and the log-rank test. The proportionality assumption was tested using plots of log(-log[survival rate]) against log(survival time), and by comparing predicted and actual survival curves. The effect of potential confounders was examined in Cox models. Variables were included in multivariable models if they could be considered confounders (39) based on theoretical considerations and after examination of baseline associations with depression status. Associations were examined sequentially in models with incremental multivariable adjustments as follows: model 1, age; model 2, age, sex, race, marital status, insurance status, and geographic location; model 3, variables included in model 2 plus comorbid conditions (diabetes, hypertension, cardiovascular disease, CHF, cerebrovascular disease, liver disease, chronic lung disease and Charlson comorbidity index); and model 4, variables included in model

Table 1. Baseline characteristics of individuals in the entire cohort, stratified by the presence or absence of depression

	Depression (*n*=179,441)	No Depression (*n*=418,712)
Age (yr)	71.3±10.8	75.1±8.9
Race		
White	156,141 (88)	363,448 (88)
Black	15,329 (9)	39,438 (10)
Hispanic	2386 (1)	5050 (1)
Other	2621 (2)	5957 (2)
Sex (male)	171,696 (96)	409,811 (98)
Marital status		
Married	104,243 (60)	269,708 (66)
Single	9464 (5)	18,394 (5)
Divorced	34,730 (20)	55,834 (14)
Widowed	24,347 (14)	63,010 (15)
Health insurance (yes)	109,069 (66)	301,388 (76)
Diabetes mellitus	87,507 (49)	169,484 (40)
Hypertension	153,705 (86)	359,180 (86)
Atherosclerotic cardiovascular disease	81,174 (45)	173,155 (41)
Congestive heart failure	33,659 (19)	52,966 (13)
Cerebrovascular disease	34,253 (19)	53,969 (13)
Chronic lung disease	53,946 (30)	83,055 (20)
Liver disease	2062 (1.2)	2278 (0.5)
Comorbidity index	4 (3–5)	3 (2–4)
Systolic BP (mmHg)	133±18	136±18
Diastolic BP (mmHg)	72±11	72±11
Estimated GFR (ml/min per 1.73 m^2)	51.3±15.6	49.6±13.3
Serum sodium (mEq/L)	139±3	140±3
Serum albumin (g/dl)	3.9±0.5	4.0±0.4
Total cholesterol (mg/dl)	172±42	169±38
Serum calcium (mg/dl)	9.3±0.5	9.3±0.5
Serum bicarbonate (mEq/L)	27.2±3.1	27.3±3.0
Blood hemoglobin (g/dl)	13.7±1.8	13.9±1.7
Blood white blood cell count (1000/mm^3)	7.6±4.1	7.3±4.1

Data are presented as mean ± SD, *n* (% of total), or median (interquartile range). All differences were significant at $P<0.001$ level except for hypertension ($P=0.20$).

3 plus eGFR. To examine effect modification, the association of depression with mortality was examined separately in subgroups of patients categorized by key covariates. eGFR was categorized according to the Kidney Disease Outcomes Quality Initiative classification, further subdividing stage 3 into stages 3A (eGFR 45–59) and 3B (eGFR 30–44). Due to the low number of patients with a diagnosis of depression in patients with stage 5 CKD (eGFR <15), this group was not examined separately in subgroup analyses. Statistical analyses were performed using STATA MP software (version 11; STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VA Medical Center.

Results

The mean age of the cohort at baseline was 73.9±9.7 years; 88% and 9% of patients were white and black, respectively; and the mean eGFR was 50.1±14.0 ml/min per 1.73 m^2. The prevalence of depression was 30% (*n*=179,411). Depression was more common in patients with stage 1 CKD (*n*=6978; 47%) than in patients with CKD stages 2 (*n*=10,634; 37%), 3A (*n*=109,023; 29%), 3B (*n*=41,775; 29%), 4 (*n*=9842; 30%), and 5 (*n*=1189; 30%). Baseline characteristics in patients categorized by their baseline depression status are shown in Tables 1 and 2. Patients with depression were younger, were more likely to be divorced and to not have insurance, and had higher prevalence of comorbid conditions, especially diabetes mellitus, chronic lung disease, and liver disease. Of 179,441 patients with depression, 31,315 (17.5%) had both an ICD-9 diagnosis and used an antidepressant; 142,505 (79.4%) used an antidepressant but had no ICD-9 diagnosis noted; and 5621 (3.1%) had an ICD-9 diagnosis but used no antidepressants.

A novel finding is the more robust association of depression with mortality in patients with less severe CKD (CKD stage 3A versus 3B and 4 when using only eGFR, or CKD stage 1 versus 2 when using microalbuminuria and eGFR to define severity of disease) and with fewer comorbidities.

Mortality

A total of 172,614 patients died (mortality rate, 67.8/1000 patient-years; 95% confidence interval [95% CI], 67.4–68.1) during a median follow-up of 4.7 years (Figure 1). Depression was significantly associated with higher age-adjusted

Table 2. Distribution of prevalence of CKD stages by depression category

Depression			No Depression		
Stage	Frequency	%	Stage	Frequency	%
1	6978	3.89	1	7983	1.91
2	10,634	5.93	2	17,833	4.26
3A	109,023	60.76	3A	263,217	62.86
3B	41,775	23.28	3B	103,524	24.72
4	9842	5.48	4	23,353	5.58
5	1189	0.66	5	2802	0.67
Total	179,441	100.00	Total	418,712	100.00

Estimated GFR categorized according to the Kidney Disease Outcomes Quality Initiative classification, with further subdivision of stage 3 into stages 3A (estimated GFR 45–59 ml/min per 1.73 m^2) and 3B (estimated GFR 30–44 ml/min per 1.73 m^2).

mortality overall (Figure 2). The age-adjusted hazard ratio (HR) associated with a diagnosis of depression was 1.55 (95% CI, 1.54–1.57; $P<0.001$). Sequential adjustments for sociodemographic characteristics, and especially for comorbid conditions, attenuated this association, which remained significant nevertheless (fully adjusted HR associated with depression, 1.25; 95% CI, 1.23–1.26; $P<0.001$) (Table 3). Figure 2 shows the fully adjusted mortality HRs and 95% CIs associated with depression in various prespecified subgroups of patients. Table 4 shows HRs and 95% CIs of mortality associated with depression defined as presence of an ICD-9 code, the use of antidepressant medications, or both.

Depression remained associated with significantly higher mortality even after multivariable adjustment in all subgroups, albeit quantitatively more substantial associations were observed in patients with a lower Charlson comorbidity score, with insurance coverage, with no lung disease, and in patients with less severe CKD (Table 3 and Figure 2). Mortality associated with depression was highest when the diagnosis was made solely based on the administration of an antidepressant, lowest when the diagnosis was based solely on the presence of an ICD-9 code, and in-between when it was based on the concomitant presence of both an ICD-9 code and the administration of an antidepressant (Table 4).

Discussion

In this large national data set of predominantly elderly patients with CKD, we have described, to the best of our knowledge for the first time, the prevalence of depression and of its association with mortality across all stages of CKD. Our results also suggest that depression is associated with increased mortality even after adjustment for measured confounders. The prevalence of depression and its

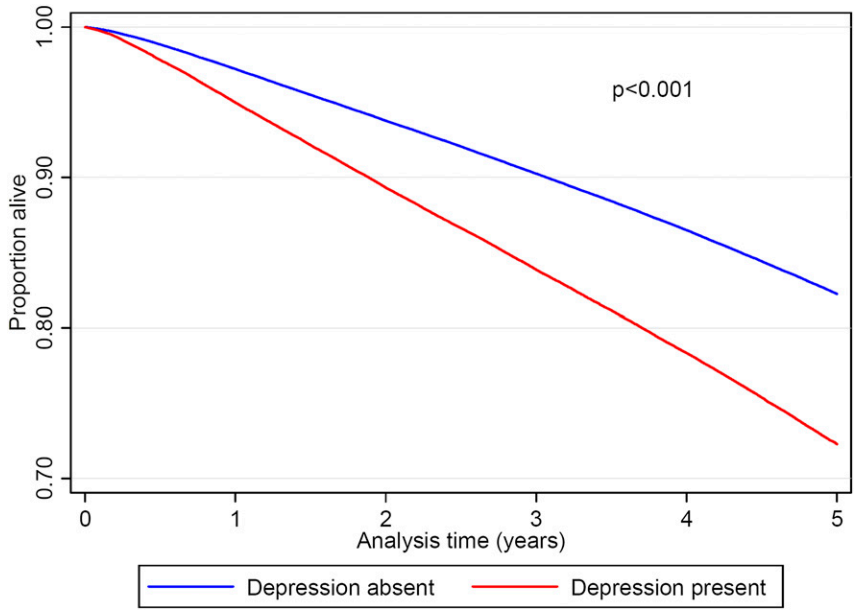

Figure 1. | **Age-adjusted Kaplan–Meier survival curves in patients with and without a diagnosis of depression**. Comparison was made by log-rank test for equality of survival function.

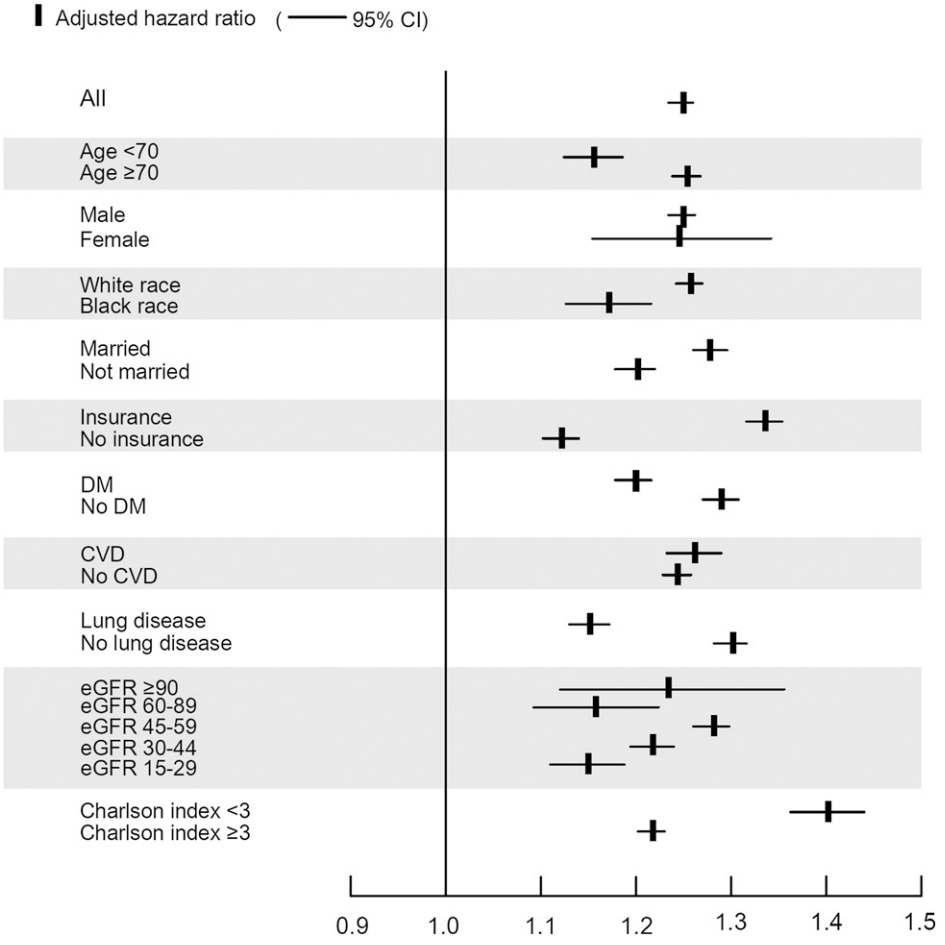

Figure 2. | Forest plot showing all-cause mortality hazard ratios (95% confidence intervals) associated with depression in several pre-specified subgroups of patients. All models were adjusted for age, sex, race, marital and insurance status, geographic location, diabetes mellitus, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, liver disease, chronic lung disease, the Charlson comorbidity index, estimated GFR, serum sodium, albumin, calcium, bicarbonate, hemoglobin, and white blood cell count. 95% CI, 95% confidence interval; DM, diabetes mellitus; CVD, cerebrovascular disease; eGFR, estimated GFR.

Table 3. All-cause mortality hazard ratios (95% confidence intervals) associated with depression overall and in subgroups of patients categorized by their baseline level of eGFR[a]

	n	Model 1	Model 2	Model 3	Model 4
All	598,153	1.55 (1.54–1.57)	1.46 (1.44–1.47)	1.24 (1.23–1.25)	1.25 (1.23–1.26)
CKD stage 1 (eGFR ≥90)	14,961	1.48 (1.36–1.61)	1.47 (1.34–1.62)	1.23 (1.12–1.36)	
CKD stage 2 (eGFR 60–89)	28,467	1.55 (1.47–1.63)	1.41 (1.33–1.49)	1.16 (1.09–1.22)	
CKD stage 3A (eGFR 45–59)	372,240	1.63 (1.61–1.65)	1.52 (1.50–1.54)	1.28 (1.26–1.30)	
CKD stage 3B (eGFR 30–44)	145,299	1.48 (1.46–1.51)	1.40 (1.37–1.43)	1.22 (1.19–1.24)	
CKD stage 4 (eGFR 15–29)	33,195	1.33 (1.29–1.37)	1.28 (1.23–1.32)	1.15 (1.11–1.19)	

Model 1 adjusted for age. Model 2 adjusted for age, sex, race, marital and insurance status, and geographic location. Model 3 adjusted for model 2 variables plus diabetes mellitus, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, liver disease, chronic lung disease, and Charlson comorbidity index. Model 4 adjusted for Model 3 variables plus eGFR (for the overall group only). eGFR, estimated GFR (ml/min per 1.73 m^2).

[a]The group with eGFR <15 ml/min per 1.73 m^2 had too few patients with depression for reliable estimates.

association with mortality may be affected by the severity of the underlying disease states. It is possible that the lower mortality seen in patients with only a diagnostic code of depression was due to the lesser severity of depression in this group of patients possibly treated by other means and not requiring medications (*e.g.*, psychotherapy). The reason why patients with antidepressant use but no ICD-9 code noted for depression had the highest mortality is

Table 4. Hazard ratios (95% confidence intervals) of mortality associated with depression defined as presence of an ICD-9 code, the administration of antidepressant medications, or both

	n	Model 1	Model 2	Model 3	Model 4
ICD-9 code only	5621	1.30 (1.23–1.37)	1.15 (1.08–1.21)	1.07 (1.01–1.13)	1.07 (1.01–1.13)
Antidepressant use only	142,505	1.58 (1.56–1.60)	1.49 (1.48–1.51)	1.27 (1.26–1.28)	1.28 (1.26–1.29)
Both ICD-9 code and antidepressant use	31,315	1.31 (1.28–1.34)	1.30 (1.18–1.44)	1.11 (1.08–1.13)	1.12 (1.09–1.15)

Model 1 adjusted for age. Model 2 adjusted for age, sex, race, marital and insurance status, and geographic location. Model 3 adjusted for model 2 variables plus diabetes mellitus, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, liver disease, chronic lung disease, and Charlson comorbidity index. Model 4 adjusted for model 3 variables plus estimated GFR. ICD-9, *International Classification of Diseases, Ninth Revision*.

unclear, but may be because patients in this category could have received antidepressants for indications other than depression, with the high mortality reflecting the presence of these other indications (*e.g.*, peripheral neuropathy related to diabetes or neuropathic pain) or that the use of antidepressants is associated with an attributable risk of mortality.

Depression remained associated with significantly higher mortality even after multivariable adjustment in all subgroups, albeit quantitatively more substantial associations were observed in older, in married and in white patients, in patients with a lower Charlson comorbidity score, in those with insurance coverage, with no diabetes or lung disease, and in patients with less severe CKD (Table 3 and Figure 2) ($P<0.001$ for all interaction terms except $P=0.002$ for the interaction term for race).

The overall prevalence of depression in our study population was 30%. This is similar to what was previously reported in CKD patients. Hedayati *et al.* reported a prevalence of major depression to be 21% in the CKD population (17). Andrade *et al.* reported an even higher prevalence of 38% of CKD patients when other depressive syndromes such as dysthymia were considered (40). Knowing that each VA patient is screened for depression, we believe our data to be accurate within the limitations that are inherent in such observational studies using large electronic databases (41,42). In a study by Foster *et al.*, using the same Veterans Health Administration systematic screens for major depressive disorder as this study in 574 male veterans treat primary care settings in the VA health care system, 13% ($n=73$) screened positive for depression and 33% of those patients were eventually diagnosed with depression, an extrapolated prevalence of 4.2% (43). This variability in the prevalence data among different studies could be due to the methods used in screening for depression, or to differences in the screened patient populations. It is noteworthy that in our cohort only a minority of patients was diagnosed with depression based on medical record entries of ICD-9 codes, with most of them diagnosed based on their prescribed use of antidepressant medications.

Certain predisposing factors are associated with an increased risk of depression in patients with CKD. In previously published data as well as in our study, depressed patients with CKD tended to be younger, Caucasian, and female (16,17,44,45). Our patient population was older and predominantly male, and had a significant comorbidity burden, which, perhaps not unexpectedly, correlated significantly with the presence of depression and was a significant confounder in the association of depression with mortality.

Previous data showed that CKD patients with major depression are twice as likely to die or to be hospitalized (3). The finding of a more robust association of depression with mortality in patients with less severe CKD (CKD stage 3A versus 3B and 4 when using only eGFR, or CKD stage 1 versus 2 when using microalbuminuria and eGFR to define severity of disease) and with fewer comorbidities is noted. This could be because depression may have different underlying causes in these patients, or because the downstream effects of depression may be different in sicker versus healthier patients, or a combination of these. In sicker patients, depression may be more likely a result of their more severe comorbidities as opposed to healthier patients in whom different etiologic factors may be more important. It is thus possible that the effects of these could overshadow the effect of depression on mortality in patients with more severe comorbidities, whereas an independent effect of depression on survival may be easier to observe in healthier patients. This observation may have implications for future research and for therapeutic interventions.

The data also raise a challenging possibility that the use of antidepressants themselves may be a contributing source to the higher mortality in the depressed group. Another similar possibility is that psychotherapy, practiced by psychiatrists or others, is more beneficial, and the patients seen by psychiatrists are the ones more likely to have a record of the appropriate ICD-9 diagnoses. These are intriguing questions that will hopefully be answered by further studies.

Our study is notable for its large sample size, its nationally representative nature, and the fact that depression screens are preformed system-wide according to a uniform protocol in all VA facilities. Our study also has a number of limitations that have to be considered when interpreting our results. Due to the observational nature of our study, we can infer only associations, and not causality, from our results. Some limitations may also affect generalizability of our results. Only a minority of patients were diagnosed with depression based on medical record entries of ICD-9 codes, with most of them diagnosed based on their prescribed use of antidepressant medications. This would

seem to suggest that despite the widespread screening, the diagnosis is possibly not being recorded consistently and would raise the possibility of missing many cases of depression not treated with medication despite the screening. In addition, some antidepressants may have been prescribed for diagnoses other than depression. Our patients were mainly men; hence, it is unclear if the same conclusions apply to women. The quantitative differences seen in patients with different severity of comorbid conditions could have been the result of underdiagnosis of comorbidities in some patients. However, this did not affect our overall findings because depression was qualitatively associated with higher mortality in all examined subgroups. Differences in findings between CKD stages 1 and 2 and 3–5 may have been the result of selection bias, because the availability of microalbuminuria measurement needed for the diagnosis of CKD stages 1 and 2 is limited. To mitigate selection bias related to unavailability of urine microalbumin measurements, we used a less stringent definition of CKD stages 1 and 2 by accepting a single increased value of microalbuminuria to define the disease state, as opposed to the presence of repeated elevations as recommended by the National Kidney Foundation (27), which makes it possible that some patients in this group did not have true CKD. However, this would have biased our results toward zero and cannot explain either the higher prevalence or the high mortality associated with depression in this group. Our patients were all veterans, whose depression may have unique characteristics related to their military service; hence, not all of our findings may apply to nonveteran patients with CKD.

In summary, in this national study of predominantly male and elderly patients, an association of depression with higher mortality was found at all stages of CKD. Prospective studies will be needed to determine if systematic screening for depression is beneficial in this patient population and, more importantly, if treatment of depression (and what modality) is beneficial in patients with all stages of CKD. These comments refer specifically to duration of survival and it is entirely possible, perhaps even likely, that beneficial effects beyond survival time (*e.g.*, patient effects, sense of well being, and successful work and social interactions) are desirable beneficial effects beyond survival time.

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Disclosures

None.

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