Age Affects Outcomes in Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is common among the elderly. However, little is known about how the clinical implications of CKD vary with age. We examined the age-specific incidence of death, treated end-stage renal disease (ESRD), and change in estimated glomerular filtration rate (eGFR) among 209,622 US veterans with CKD stages 3 to 5 followed for a mean of 3.2 years. Patients aged 75 years or older at baseline comprised 47% of the overall cohort and accounted for 28% of the 9227 cases of ESRD that occurred during follow-up. Among patients of all ages, rates of both death and ESRD were inversely related to eGFR at baseline. However, among those with comparable levels of eGFR, older patients had higher rates of death and lower rates of ESRD than younger patients. Consequently, the level of eGFR below which the risk of ESRD exceeded the risk of death varied by age, ranging from 45 ml/min per 1.73 m^2 for 18 to 44 year old patients to 15 ml/min per 1.73 m^2 for 65 to 84 year old patients. Among those 85 years or older, the risk of death always exceeded the risk of ESRD in this cohort. Among patients with eGFR levels $<$45 ml/min per 1.73 m^2 at baseline, older patients were less likely than their younger counterparts to experience an annual decline in eGFR of $>$3 ml/min per 1.73 m^2. In conclusion, age is a major effect modifier among patients with an eGFR of $<$60 ml/min per 1.73 m^2, challenging us to move beyond a uniform stage-based approach to managing CKD.

J Am Soc Nephrol 18: 2758–2765, 2007. doi: 10.1681/ASN.2007040422

Chronic kidney disease (CKD) is common in the elderly,[1,2] leading some professional organizations to recommend routine age-based screening for CKD in the primary care setting[3]; however, relatively little is known about the clinical course of CKD in older individuals. Most previous studies of CKD and current recommendations for its management have not distinguished between patients of different ages, and efforts to identify risk factors for progression of CKD have generally focused on patient characteristics other than age.[4–17]

We hypothesized that the frequency of clinically significant outcomes among patients who meet National Kidney Foundation criteria for stages 3 to 5 CKD would differ substantially across age groups. We tested this hypothesis among a national cohort

Received April 6, 2007. Accepted July 9, 2007.

Published online ahead of print. Publication date available at www.jasn.org.

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of 209,622 patients who were receiving care in the Department of Veterans Affairs.

RESULTS

The study cohort consisted of 209,622 patients who met criteria for stages 3 to 5 CKD. The mean age for the cohort was 73 yr (SD ± 9), and 47% ($n = 99,060$) of cohort members were ≥75 yr. Race was white in 86%, black in 11%, other in 0.9%, and unknown in 2.2%. Three percent ($n = 6842$) of cohort members were women. From the youngest to the oldest age group, the percentage of black and female patients decreased and the prevalence of comorbid conditions other than diabetes increased (Table 1). The prevalence of diabetes was highest among those aged 55 to 64 yr and decreased thereafter. Median Charlson score also increased across age groups. The majority of cohort patients had moderate (estimated glomerular filtration rate [eGFR] 30 to 59 ml/min per 1.73 m^2) rather than severe CKD (eGFR 15 to 29 ml/min per 1.73 m^2) or renal failure (eGFR <15 ml/min per 1.73 m^2; Figure 1).

A total of 668,820 person-years were available for analysis of time to death and time to treated ESRD. From the time of cohort entry through September 30, 2004, 9227 (4.4%) patients were treated for ESRD. Dialysis was the initial modality in all but 47 patients, who received a transplant before starting long-term dialysis. Overall, 5774 (63%) cases of ESRD occurred among cohort patients who were ≥65 yr and 2601 (28%) occurred among patients who were ≥75 yr. During the same period, 45,772 (21.8%) patients died without ever being treated for ESRD. An additional 2925 (1.4%) patients died after starting treatment for ESRD.

As expected, patients with the lowest levels of eGFR at baseline experienced both the highest rates of death (Table 2) and the highest rates of treated ESRD (Table 3) during follow-up. However, among patients with comparable levels of eGFR at baseline, trends across age groups in rates of death (Table 2) and treated ESRD (Table 3) were in opposite directions: Among patients with comparable levels of baseline eGFR, rates of death were higher and rates of treated ESRD were lower for older than for younger patients. Among patients who were younger than 45 yr, the incidence of treated ESRD was greater than that of death at all eGFR levels <45 ml/min per 1.73 m^2 (Figure 2). Conversely, among those aged 65 to 84, only at eGFR levels <15 ml/min per 1.73 m^2 did risk for ESRD exceed risk for death. Among those aged 85 to 100, risk for death exceeded risk for ESRD even at eGFR levels <15 ml/min per 1.73 m^2. Adjustment for gender, race, comorbid conditions, and Charlson score in Cox proportional hazard analysis did not alter the direction of the association of age with either death or ESRD. Within each age group, the adjusted hazards for ESRD and for death increased with falling eGFR (data not shown).

Among patients whose initial eGFR was <45 ml/min per 1.73 m^2, the percentage of patients experiencing an annual decrement in eGFR of >3 ml/min per 1.73 m^2 decreased with advancing age (Table 4). Among those with an eGFR of 45 to 59 ml/min per 1.73 m^2 at baseline, the percentage of patients experiencing a decrement in eGFR of >3 ml/min per 1.73 m^2 was actually greater among older than among younger patients. The direction of these associations did not alter with adjustment for race, gender, comorbid conditions, and Charlson score and was similar among black patients, women, and patients with diabetes.

DISCUSSION

Among a large national cohort of US veterans who met criteria for stage 3 or higher CKD, the incidence of both death

Table 1. Patient characteristics by age group[a]

Characteristic	18 to 44 ($n = 1700$)	45 to 54 ($n = 10,255$)	55 to 64 ($n = 23,559$)	65 to 74 ($n = 75,048$)	75 to 84 ($n = 88,849$)	85 to 100 ($n = 10,211$)
Race (%)						
white	51.82	62.61	78.07	88.12	90.06	86.14
black	25.76	22.65	12.53	10.43	8.50	11.66
other	1.29	1.86	1.38	0.81	0.80	1.35
unknown	21.12	12.87	8.02	0.63	0.64	0.84
Female (%)	17.65	7.38	5.08	1.63	3.40	3.36
Diabetes (%)	25.53	41.61	47.65	47.06	40.97	31.59
Coronary artery disease (%)	18.12	35.33	49.85	60.84	65.51	63.66
Congestive heart failure (%)	11.00	19.78	27.04	33.09	38.36	43.37
Peripheral vascular disease (%)	6.24	13.18	21.37	29.84	33.68	34.28
Cerebrovascular disease (%)	6.06	12.88	19.73	26.91	32.02	32.83
Any of the listed comorbid conditions (%)	43.00	64.35	75.47	82.99	85.44	85.12
Median Charlson score (25th to 75th percentile range)	2 (0 to 4)	3 (1 to 5)	3 (1 to 5)	3 (2 to 6)	4 (2 to 6)	4 (2 to 6)

[a]Coronary artery disease was defined on the basis of the presence of either diagnostic codes for coronary artery disease, angina, or myocardial infarction or procedure codes for coronary artery bypass graft or angioplasty. Peripheral arterial disease was based on the presence of either diagnostic codes for peripheral arterial disease or procedure codes for lower extremity amputation or revascularization procedures. Cerebrovascular disease was defined on the basis of the presence of diagnostic codes for stroke or transient ischemic attack.

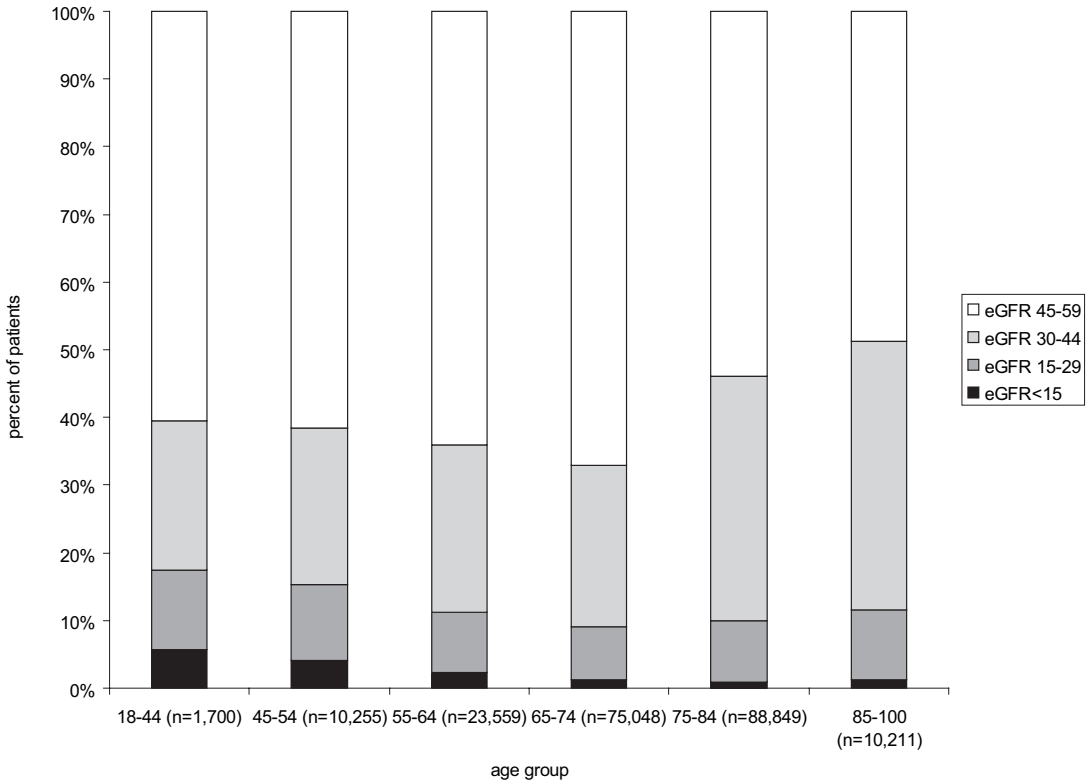

Figure 1. Distribution of eGFR among cohort patients in each age group.

and ESRD was inversely related to eGFR among patients of all ages; however, the relative frequency of these outcomes among patients with a comparable level of eGFR varied considerably by age. Most older members of this cohort, especially those ≥75 yr, were far more likely to die than to develop ESRD, even when their eGFR was severely reduced (15 to 29 ml/min per 1.73 m^2). Conversely, younger patients with severe or even moderate reductions in eGFR (30 to 44 ml/min per 1.73 m^2) were far more likely to develop ESRD than to die. Collectively, our findings indicate that age is an important effect modifier in CKD. Similar to conditions such as hypertension and subclinical hypothyroidism,[18,19] an equivalent level of eGFR can have very different prognostic implications in patients of different ages.

Age differences in the prognostic significance of eGFR observed here probably reflect a variety of different phenomena. The lower incidence of ESRD among older compared with younger patients with similar levels of eGFR is likely due, at least in part, to their greater competing risk for death. Other considerations include the greater likelihood that older patients in this prevalent cohort (and in the clinical setting) are long-term CKD survivors and thus by definition have nonprogressive or slowly progressive disease. Differences in outcomes may also reflect age differences in the underlying cause of low eGFR. Perhaps in older patients, low eGFR functions more commonly as a "marker" for a variety of other age-related coexisting comorbid conditions and thus tends to be a better predictor of "global" health outcomes (*e.g.*, mortality) than of more "specific" renal outcomes. In contrast, in younger patients, perhaps low eGFR results more frequently from a single disease affecting the kidney and thus may better predict renal outcomes. An additional consideration is that some loss of GFR is believed to occur as part of "normal" aging.[20] Although the distinction may be somewhat semantic, it is possible that in some patients, moderate reductions in eGFR (*e.g.*, 45 to 59 ml/min per 1.73 m^2) occur as part of "normal aging" rather than as a "disease process" *per se*. An additional consideration is that the Modification of Diet in Renal Disease (MDRD) equation used here to estimate GFR has not been validated across the range of age and eGFR levels examined here; therefore, age differences in the accuracy of the equation for estimating true GFR may introduce age differences in its prognostic significance. Finally, although the lower incidence of treated ESRD in the elderly is broadly consistent with slower rates of eGFR decline among those with eGFR levels <45 ml/min per 1.73 m^2, it is also possible (particularly in the oldest patients with the lowest levels of eGFR) that the lower incidence of treated ESRD may reflect a greater reluctance on the part of patients and/or physicians to initiate dialysis when indications arise.

It is broadly accepted that rates of death exceed those of ESRD, even among patients with severe reductions in eGFR. This phenomenon was first described by Keith *et al.*[12] among 27,998 members of a large health maintenance organization with a sustained eGFR of <90 ml/min per 1.73 m^2. The mean age of this cohort was >60 yr. Foley *et al.*[5] reported a similar

Table 2. Incidence and risk for death by age and eGFR at baseline[a]

Baseline eGFR (ml/min per 1.73 m^2)	Age Group	No. of Patients	Time at Risk (yr)	Deaths	Incidence of Death, per 100 Person-Years (95% CI)[b]	Adjusted Hazard Ratio (95% CI)[c]
≥60	18 to 44	239,265	844,574	4087	0.6 (0.59 to 0.65)	1.00 (referent)
	45 to 54	462,109	1,621,215	21,852	1.41 (1.37 to 1.44)	2.15 (2.08 to 2.22)
	55 to 64	390,676	1,363,669	23,681	1.74 (1.70 to 1.77)	2.39 (2.31 to 2.47)
	65 to 74	476,643	1,636,256	46,596	2.98 (2.89 to 3.07)	2.93 (2.84 to 3.03)
	75 to 84	307,137	1,010,044	53,023	5.43 (5.29 to 5.58)	4.55 (4.40 to 4.70)
	85 to100	21,928	64,655	21,928	11.58 (10.80 to 12.35)	8.57 (8.23 to 8.91)
45 to 59	18 to 44	1029	3659	52	1.79 (1.02 to 2.55)	1.00 (referent)
	45 to 54	6308	22,101	583	2.83 (2.49 to 3.17)	1.48 (1.12 to 1.97)
	55 to 64	15,075	52,885	1490	2.93 (2.70 to 3.16)	1.46 (1.11 to 1.93)
	65 to 74	50,368	172,317	7396	4.31 (4.13 to 4.50)	1.93 (1.46 to 2.54)
	75 to 84	47,860	156,334	10,743	6.94 (6.70 to 7.17)	2.90 (2.21 to 3.82)
	85 to100	4979	14,526	1928	13.43 (12.38 to 14.49)	5.29 4.01 to 6.98)
30 to 44	18 to 44	374	1208	32	2.85 (1.38 to 4.32)	1.00 referent)
	45 to 54	2379	7699	337	4.43 (3.71 to 5.15)	1.42 (0.99 to 2.04)
	55 to 64	5854	19,125	1020	5.55 (5.05 to 6.04)	1.57 (1.10 to 2.24)
	65 to 74	17,893	57,288	4097	7.12 (6.74 to 7.51)	1.90 (1.34 to 2.69)
	75 to 84	32,164	99,030	9656	9.85 (9.49 to 10.21)	2.61 (1.84 to 3.70)
	85 to100	4059	11,219	1824	16.46 (15.11 to 17.81)	4.42 (3.11 to 6.27)
15 to 29	18 to 44	200	478	16	2.92 (0.02 to 5.82)	1.00 (referent)
	45 to 54	1147	2778	159	6.09 (4.72 to 7.47)	1.48 (0.89 to 2.48)
	55 to 64	2106	5247	393	7.58 (6.45 to 8.71)	1.68 (1.02 to 2.77)
	65 to 74	5828	14,939	1727	11.68 (10.64 to 12.71)	2.36 (1.44 to 3.87)
	75 to 84	7968	20,193	3099	15.39 (14.43 to 16.36)	3.11 (1.90 to 5.09)
	85 to100	1040	2358	584	25.35 (22.17 to 34.05)	4.96 (3.01 to 8.17)
<15	18 to 44	97	92	4	2.86 (−2.04 to 7.75)	1.00 (referent)
	45 to 54	421	410	30	5.97 (2.36 to 9.59)	1.49 (0.52 to 4.23)
	55 to 64	524	540	45	9.24 (5.80 to 12.67)	1.51 (0.54 to 4.22)
	65 to 74	959	1182	193	16.60 (12.86 to 20.34)	2.72 (1.00 to 7.39)
	75 to 84	857	1045	280	27.03 (21.24 to 32.81)	4.44 (1.64 to 22.67)
	85 to100	133	169	84	49.36 (35.20 to 63.52)	8.24 (2.99 to 22.67)

[a]CI, confidence interval.
[b]Rates standardized to the gender-race mix of the entire study population.
[c]Adjusted for race, gender, diabetes, coronary artery disease, peripheral arterial disease, congestive heart failure, cerebrovascular disease, and Charlson score.

phenomenon among a 5% sample of Medicare beneficiaries who were aged ≥67 yr and had diagnosed CKD. Similar to these studies, rates of death among older members of our cohort far exceeded rates of ESRD across a wide eGFR spectrum; however, after stratifying by age, we identified a very different pattern in younger patients. In younger cohort members, rates of ESRD exceeded those of death among patients with severe reductions in eGFR and in some with moderate reductions. This observation is broadly consistent with other studies showing that the rate of progression of CKD may decrease with advancing age[11,21–23] and is often slow in older patients.[24,25]

With the future prospect of more widespread eGFR-based screening for CKD in the primary care setting,[3,26] it is critical that providers understand how the clinical implications of eGFR vary by age and that practice guidelines address this variation. At the same time, any effective management strategy must embrace the reality that, although less likely to develop ESRD than their younger counterparts with similar levels of eGFR, older patients comprise a large and growing percentage (and number) of all new cases of ESRD in the United States.

The considerable heterogeneity in outcomes among patients of different ages with similar levels of eGFR observed here suggests that the uniform stage-based approach advocated in most practice guidelines is probably not adequate (http://www.renal.org/CKDguide/ckd.html, http://www.cari.org.au/guidelines.php).[15] Because such a small percentage of elderly patients with severe reductions in eGFR go on to be treated for ESRD, there is a clear need for prognostic tools that will enable clinicians to target CKD-related interventions to the subgroup of older patients who are most likely to benefit. In contrast, interventions that address the exceedingly high mortality rates among elderly patients with severe reductions in eGFRare likely to be of greater benefit to a greater number of patients in this group. At the opposite end of the spectrum, high rates of progression to ESRD in younger patients with

Table 3. Incidence and risk for ESRD by age and eGFR at baseline

Baseline eGFR (ml/min per 1.73 m^2)	Age Group	No. of Patients	Time at Risk (yr)	Treated ESRD	Incidence of Treated ESRD, per 100 Person-Years (95% CI) [a]	Adjusted Hazard Ratio (95% CI)[b]
≥60	18 to 44	239,265	844,574	105	0.02 (0.01 to 0.02)	1.00 (referent)
	45 to 54	462,109	1,621,215	476	0.03 (0.02 to 0.03)	1.58 (1.27 to 1.95)
	55 to 64	390,676	1,363,669	377	0.03(0.02 to 0.03)	1.25 (1.00 to 1.56)
	65 to 74	476,643	1,636,256	480	0.03(0.02 to 0.04)	0.95 (0.76 to 1.19)
	75 to 84	307,137	1,010,044	306	0.03 (0.02 to 0.04)	0.90 (0.71 to 1.14)
	85 to 100	21,928	64,655	11	0.01 (0.00 to 0.01)	0.48 (0.26 to 0.90)
45 to 59	18 to 44	1029	3659	10	0.29 (−0.03 to 0.61)	1.00 (referent)
	45 to 54	6308	22,101	142	0.58 (0.42 to 0.73)	1.63 (0.86 to 3.11)
	55 to 64	15,075	52,885	160	0.32 (0.24 to 0.40)	0.77 (0.40 to 1.46)
	65 to 74	50,368	172,317	326	0.19 (0.15 to 0.23)	0.43 (0.23 to 0.81)
	75 to 84	47,860	156,334	172	0.11 (0.08 to 0.15)	0.26 (0.14 to 0.50)
	85 to 100	4979	14,526	13	0.09 (0.03 to 0.15)	0.22 (0.09 to 0.49)
30 to 44	18 to 44	374	1208	67	6.19 (3.98 to 8.39)	1.00 (referent)
	45 to 54	2379	7699	307	3.59 (2.94 to 4.23)	0.59 (0.45 to 0.77)
	55 to 64	5854	19,125	418	2.15 (1.82 to 2.47)	0.32 (0.25 to 0.42)
	65 to 74	17,893	57,288	750	1.27 (1.12 to 1.43)	0.19 (0.15 to 0.24)
	75 to 84	32,164	99,030	576	0.61 (0.52 to 0.71)	0.10 (0.08 to 0.13)
	85 to 100	4059	11,219	25	0.23 (0.10 to 0.35)	0.04 (0.03 to 0.07)
15 to 29	18 to 44	200	478	106	20.29 (13.35 to 27.22)	1.00 (referent)
	45 to 54	1147	2778	531	17.19 (14.82 to 19.56)	0.75 (0.61 to 0.93)
	55 to 64	2106	5247	843	15.01 (13.40 to 16.61)	0.60 (0.49 to 0.73)
	65 to 74	5828	14,939	1463	9.31 (8.41 to 10.21)	0.36 (0.30 to 0.45)
	75 to 84	7968	20,193	1251	6.31 (5.65 to 6.96)	0.26 (0.21 to 0.32)
	85 to 100	1040	2358	63	2.65 (1.64 to 3.67)	0.12 (0.09 to 0.17)
<15	18 to 44	97	92	83	67.49 (39.39 to 95.58)	1.00 (referent)
	45 to 54	421	410	355	80.83 (65.64 to 96.00)	0.93 (0.73 to 1.19)
	55 to 64	524	540	431	78.51 (66.93 to 90.09)	0.81 (0.63 to 1.03)
	65 to 74	959	1182	634	51.10 (44.20 to 58.00)	0.55 (0.43 to 0.70)
	75 to 84	857	1045	467	44.78 (38.26 to 51.30)	0.47 (0.37 to 0.60)
	85 to 100	133	169	34	29.23 (0.03 to 58.43)	0.22 (0.15 to 0.34)

[a]Rates standardized to the gender-race mix of the entire study population.
[b]Adjusted for race, gender, diabetes, coronary artery disease, peripheral arterial disease, congestive heart failure, cerebrovascular disease, and Charlson score.

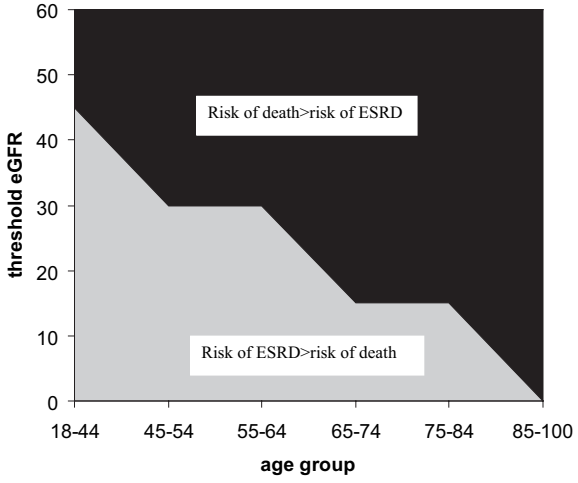

Figure 2. Baseline eGFR threshold below which risk for ESRD exceeded risk for death for each age group.

severe (and in some cases moderate) decrements in eGFR provide a more compelling case for an inclusive proactive approach toward slowing progression and preparing for dialysis in this group.

Although our study leverages the unique strengths of the VA system to examine clinical outcomes in CKD across a wide age spectrum, there are a number of limitations to consider in interpreting our results. First, specific point estimates for each outcome may not be generalizable to nonveteran groups, women, or VA patients who had a low eGFR and did not have the minimum number and spacing of creatinine measurements required to fulfill criteria for CKD. Because the frequency with which creatinine is measured in our system is probably affected by how sick patients are perceived to be, our results probably overestimate rates of both treated ESRD and death among the wider population of veterans with CKD. This may be of particular concern in younger patients, in whom serum creatinine may not be incorporated into routine care to the same extent as for older patients. A second concern

Table 4. Rate of change in eGFR by age and eGFR at baseline

Baseline eGFR (ml/min per 1.73 m^2)	Age Group	% with Annual eGFR Decrement >3 ml/min per 1.73 m^2	Adjusted Odds[a] of Annual Decrement in eGFR >3 ml/min per 1.73 m^2
45 to 59 (n = 117,922)	18 to 44	16.62	1.00 (referent)
	45 to 54	21.93	1.23 (1.02 to 1.47)
	55 to 64	22.95	1.23 (1.30 to 1.47)
	65 to 74	25.07	1.28 (1.08 to 1.53)
	75 to 84	28.00	1.48 (1.24 to 1.76)
	85 to 100	34.10	2.00 (1.67 to 2.41)
30 to 44 (n = 57,339)	18 to 44	45.87	1.00 (referent)
	45 to 54	35.30	0.57 (0.45 to 0.72)
	55 to 64	29.90	0.43 (0.34 to 0.54)
	65 to 74	25.41	0.33 (0.27 to 0.41)
	75 to 84	24.30	0.33 (0.27 to 0.42)
	85 to 100	26.03	0.39 (0.31 to 0.49)
15 to 29 (n = 15,694)	18 to 44	52.51	1.00 (referent)
	45 to 54	48.90	0.81 (0.58 to 1.12)
	55 to 64	44.33	0.67 (0.49 to 0.93)
	65 to 74	34.12	0.46 (0.34 to 0.63)
	75 to 84	26.70	0.36 (0.26 to 0.49)
	85 to 100	24.91	0.35 (0.25 to 0.49)
<15 (n = 1768)	18 to 44	46.94	1.00 (referent)
	45 to 54	49.80	1.19 (0.64 to 2.23)
	55 to 64	43.03	0.92 (0.49 to 1.71)
	65 to 74	36.85	0.74 (0.40 to 1.36)
	75 to 84	36.47	0.76 (0.41 to 1.41)
	85 to 100	26.39	0.50 (0.23 to 1.10)

[a]Adjusted for race, gender, diabetes, coronary artery disease, peripheral arterial disease, congestive heart failure, cerebrovascular disease, and Charlson score.

related to cohort selection is that limiting the cohort to patients with an eGFR <60 ml/min per 1.73 m^2 and stratification of results by initial eGFR may have introduced some bias as a result of regression to the mean. This bias could have occurred differentially by age group if the accuracy of eGFR varies by age; however, it is unlikely that either of these biases would have had a substantial impact on the ratio of death to ESRD in this cohort.

Third, the MDRD equation has not been validated in the elderly, and given the dependence of serum creatinine on muscle mass, there is particular concern that eGFR slope in the elderly may be affected by changes in muscle mass over time. In addition, there are more general concerns about the accuracy of this equation at eGFR levels close to and above 60 ml/min per 1.73 m^2, particularly when creatinine assays are not calibrated to the MDRD laboratory, as is the case in the VA. Thus, eGFR slope for patients with an eGFR 45 to 59 ml/min per 1.73 m^2 should be interpreted with caution; however, we argue that the accuracy of MDRD estimates for true GFR does not detract from the clinical significance of our findings. Although potentially inaccurate as in indicator of true GFR, eGFR is widely used in the clinical setting and does seem to have prognostic value for both death and ESRD. It is therefore important that clinicians using these estimates understand that outcomes for patients with a given level of eGFR vary by age. Fourth, in interpreting the incidence of ESRD, it is important to keep in mind that onset of ESRD is essentially a treatment decision; unfortunately, our data sources did not allow us to identify patients who had indications for dialysis but were not started on dialysis. Finally, because we followed patients only for a mean of 3.2 yr, our study does not provide information on long-term outcomes associated with low eGFR.

In a large national cohort of veterans who fulfilled criteria for stage 3 or higher CKD, the prognostic implications of eGFR for death and ESRD varied greatly depending on the age of the patient. These findings question the wisdom of a uniform "age neutral" approach to the management of CKD and underline the critical need for better prognostic tools with which to identify the small percentage but large and growing number of older individuals who will progress to ESRD.

CONCISE METHODS

Data Sources

The data sources and methods used to assemble the analytic data set for the analyses described here have been described in detail else-

where.[2] In brief, we used laboratory data from the VA Decision Support System Laboratory Results file to ascertain outpatient serum creatinine test results that were obtained as part of routine clinical care. We used inpatient and outpatient VA and Medicare administrative data to ascertain demographic and comorbidity information for cohort patients at the time of cohort entry on the basis of diagnostic and procedure codes entered between January 1, 1999, and the date of cohort entry. We used death data from the VA Beneficiary Identification and Records Locator Subsystem. These data were then linked to the US Renal Data System, a national ESRD registry, to exclude patients who were already on dialysis or had already received a transplant, and to identify new cases of treated ESRD that occurred during follow-up.

Patients

Our goal was to identify a cohort of patients who met the current National Kidney Foundation definition of stage 3 or higher CKD and thus had an eGFR <60 ml/min per 1.73 m^2 that had been present for at least 3 mo.[15] The study cohort was selected from the larger population of all patients who had at least one outpatient serum creatinine measurement within the VA between October 1, 2000, and September 30, 2001 ($n = 2{,}352{,}584$). We excluded patients who were already on dialysis or had received a kidney transplant ($n = 11{,}125$) at the time of their initial creatinine measurement during this time frame. Among the remaining patients, we estimated GFR at the time of the first creatinine measurement using the abbreviated form of the MDRD equation that is based on serum creatinine, age, race, and gender.[27] We excluded from the cohort patients who had an eGFR ≥ 60 ml/min per 1.73 m^2 ($n = 1{,}897{,}758$); however, these patients were retained to calculate referent rates and adjusted risk for death and ESRD for each age group. Among the remaining 443,701 patients whose eGFR was <60 ml/min per 1.73 m^2, we identified a subset of 209,622 patients who had a previous eGFR that was also <60 ml/min per 1.73 m^2 recorded at least 3 mo before cohort entry and after October 1, 1999 (the first date for which creatinine measurements are available in the national data sources available to us). Each patient's date of first creatinine measurement between October 1, 2000, and September 30, 2001, was taken as the point of cohort entry.

Outcomes

By age and eGFR group at cohort entry, we calculated the incidence of treated ESRD, incidence of death without treatment for ESRD, and annual rate of change in eGFR. Follow-up for all outcomes was available through September 30, 2004. To avoid analyzing creatinine measurements occurring near the time of death or onset of ESRD (which may not reflect chronic rates of progression), we limited the analysis of change in eGFR to the period between cohort entry and 90 d before onset of the first occurrence of ESRD or death or September 30, 2004.

Covariates

Patient age was categorized as 18 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and 85 to 100 yr. Patients were classified as having an eGFR 45 to 59 or 30 to 44 (moderate CKD), 15 to 29 (severe CKD), or <15 ml/min per 1.73 m^2 (renal failure) at cohort entry. For some analyses, we also present results among the referent group of patients who were not included in the cohort and had an eGFR ≥ 60 ml/min per 1.73 m^2. Among cohort patients, we examined the distribution of race (black *versus* nonblack), gender, and the following comorbid conditions across age groups at the time of cohort entry: Diabetes, coronary artery disease, congestive heart failure, peripheral arterial disease, and cerebrovascular disease (see footnote to Table 1 for operational definitions of these conditions). We also used the Deyo adaptation of the Charlson comorbidity index for administrative data to measure comorbidity burden.[28] We calculated each patient's Charlson score using VA and Medicare inpatient and outpatient diagnoses during the year before cohort entry.

Statistical Analyses

After stratification by age and eGFR, we obtained maximum likelihood estimates of the annual incidence of treated ESRD and of death using a parametric survival-time model fitted to an exponential distribution. To account for differences in the race and gender distribution across age groups, we standardized these estimates to the race and gender composition of the overall study population. To measure risk for treated ESRD among patients who were still alive, we censored for death in the analysis of time to treated ESRD. Similarly, because we were interested in risk for death among patients who had not reached ESRD, we censored at the time of onset of ESRD in the analysis of time to death. To account for potential confounding by comorbidity, we also present adjusted hazard ratios for death and for ESRD by age group after stratification by baseline eGFR.

We estimated the rate of change in eGFR (ml/min per 1.73 m^2/yr) for each individual with at least one follow-up creatinine measurement ($n = 192{,}723$), using within-person linear regression on all of his or her outpatient GFR estimates that were spaced at least 1 d apart from the time of cohort entry to 90 d before treatment for ESRD, death, or the end of follow-up. For each age and eGFR group, we present the percentage of patients who experienced an estimated annual decrement in eGFR of >3 ml/min per 1.73 m^2. To confirm that age differences in the rate of change in eGFR did not reflect confounding by differences in race, gender, and comorbidity, we conducted logistic regression analysis stratified by baseline eGFR to calculate for each age group the adjusted odds for experiencing a decrement of >3 ml/min per 1.73 m^2/yr. We also conducted subgroup analyses among women, black patients, and patients with diabetes. All analyses were conducted using either Stata Version 9 (Stata Corp., College Station, TX) or SAS version 9.2 (SAS Institute, Cary, NC). The study was approved by the institutional review board at the University of California and the Research and Development Committee at the VA San Francisco.

ACKNOWLEDGMENTS

A.M.O. is supported by a Paul B. Beeson Career Development Award in Aging (K23 AG28980-01). Part of this work was completed with support from a Research Career Development Award from the Department of Veterans Affairs Health Services Research and Develop-

ment Service to A.M.O. A.X.G. was supported by a Clinician Scientist Award from the Canadian Institutes of Health Research. M.A.S. and L.C.W. are supported by Research Career Development Awards from the Department of Veterans Affairs Health Services Research and Development Service. M.A. is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (K24-DK59818-01). D.B. is supported by the VA San Francisco Health Services Research and Development Program Research Enhancement Award Program. A.I.C. is supported by a fellowship grant from the National Kidney Foundation. C.S.L. is supported by the VA National Quality Scholars Program, an NIA Academic Leadership Award (AG000912), and a grant from the John A. Hartford Foundation (2003-0244).

We acknowledge the insightful comments of Dr. Kenneth Covinsky on several drafts of this manuscript.

DISCLOSURES

M.A. serves as a consultant for Arrow International. J.S.K. receives grant support from Hoffmann-La Roche and Keryx Pharmaceuticals and serves as a consultant for Hoffmann-La Roche, Amgen, Genzyme, and Advanced Magnetics. These funding sources had no involvement in the design or execution of this study.

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