

High Prevalence of Stage 3 Chronic Kidney Disease in Older Adults Despite Normal Serum Creatinine

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BACKGROUND: Serum creatinine is commonly used to diagnose chronic kidney disease (CKD), but may underestimate CKD in older adults when compared with using glomerular filtration rates (eGFR). The magnitude of this underestimation is not clearly defined.

OBJECTIVE: Using the Modification of Diet in Renal Disease (MDRD) equation, to describe both the prevalence and the magnitude of underestimation of stage 3 CKD (GFR 30–59 ml/min/1.73 m²), as well as ideal serum creatinine cutoff values to diagnose stage 3 CKD among Americans ≥65 years of age.

DESIGN: Cross-sectional.

PARTICIPANTS: A total of 3,406 participants ≥65 years of age from the 1999–2004 National Health and Nutrition Examination Surveys (NHANES).

MEASUREMENTS: Serum creatinine levels were used to determine eGFR from the MDRD equation. Information on clinical conditions was self-reported.

RESULTS: Overall, 36.1% of older adults in the US have stage 3 or greater CKD as defined by eGFR values. Among older adults with stage 3 CKD, 80.6% had creatinine values ≤1.5 mg/dl, and 38.6% had creatinine values ≤1.2 mg/dl. Optimal cutoff values for serum creatinine in the diagnosis of stage 3 CKD in older adults were ≥1.3 mg/dl for men and ≥1.0 mg/dl for women, regardless of the presence or absence of hypertension, diabetes, or congestive heart failure.

CONCLUSION: Use of serum creatinine underestimates the presence of advanced (stage 3 or greater) CKD among older adults in the US. Automated eGFR reporting may improve the accuracy of risk stratification for older adults with CKD.

KEY WORDS: chronic kidney disease; serum creatinine; older adults; glomerular filtration rate.

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The majority of Americans with chronic kidney disease (CKD) are 65 years or older. Although only a small number of these individuals will progress to end-stage renal disease (ESRD), many are at high risk of contrast-induced nephropathy after cardiac catheterizations or other procedures.^{1,2} In addition, moderate to severe CKD (stage 3 or greater) as defined by a glomerular filtration rate (GFR) <60 ml/minute/1.73 m² is strongly associated with new cardiovascular events, as well as increased mortality among patients who already have coronary heart disease, congestive heart failure, diabetes, and/or anemia.^{3–8} Therefore, early diagnosis and accurate staging of CKD in older populations are necessary to accurately assess the expected risk of acute renal failure with exposure to nephrotoxic agents, as well as to estimate the prognosis of patients with existing chronic conditions.

While the measurement of serum creatinine has been the traditional approach to assess CKD, many practicing physicians are unable to evaluate creatinine levels in the appropriate clinical context according to age, gender, and the presence of chronic conditions. A survey conducted by the National Kidney Disease Education Program found that 77% of primary care physicians incorrectly believed that a creatinine value of >1.5 mg/dl was necessary to diagnose CKD in a 65-year-old white woman with hypertension and diabetes.⁹ Suboptimal rates of CKD diagnoses by physicians likely contribute to limited awareness of CKD diagnoses among affected patients. Less than 20% of people with CKD are aware that they have the disease.^{9,10}

Estimated GFR (eGFR) derived from formulas such as the Modification of Diet in Renal Disease (MDRD) equation is superior to serum creatinine alone in the diagnosis of CKD.^{11–14} The National Kidney Foundation recommends strongly that all laboratories report eGFR automatically when serum creatinine is ordered.¹⁵ Health-care organizations such as the Veterans Administration system have adopted automated eGFR reporting in response to this recommendation.¹⁶ However, only 20% of laboratories in a 2005 survey reported eGFR automatically.¹⁷ Automated eGFR reporting may be particularly important for older persons, who are more likely to have false-negative creatinine values than younger persons due to lower muscle

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mass. Although recent work has identified under-ascertainment of CKD among older Europeans with normal serum creatinine,¹⁸ the extent of CKD among the US population ≥ 65 years with normal creatinine values and chronic conditions has not been reported. This information will be useful in establishing the clinical relevance and need of providing automated eGFR reporting for older patients in the US.

Using nationally representative data, we describe the prevalence of stage 3 CKD (GFR 30–59 ml/min/1.73 m²) using the MDRD equation among participants ≥ 65 years with normal and with elevated serum creatinine and by specific chronic condition. We also present likelihood ratios for serum creatinine as a diagnostic test for eGFR, stratified by gender and chronic condition.

METHODS

The National Health and Nutrition Examination Survey (NHANES) is conducted by the National Center for Health Statistics, using a stratified multistage probability design to obtain a representative sample of the total civilian, non-institutionalized US population.¹⁹ Since 1999, the NHANES has released data at 2-year intervals. The 1999–2000, 2001–2002, and 2003–2004 NHANES collected questionnaire data during a face-to-face home interview and included a physical examination, as well as the collection of laboratory data. Details on the sampling strategy and weighting methods used in the NHANES are available in electronic form.¹⁹

Sample

For this analysis, we only included persons 65 years of age and older within the 1999–2000, 2001–2002, and 2003–2004 NHANES surveys (n=4,265). Respondents who did not participate in the examination component (n=57) or had missing serum creatinine measurements (n=802) were excluded from the analysis. The final sample therefore included 3,406 individuals who represent the 27 million adults ≥ 65 years of age in the US population.

Measures

Serum creatinine was measured with a standardized assay. We used serum creatinine data to estimate GFR using the four-variable MDRD study equation as follows: Estimated GFR (eGFR) = $186.3 \times (\text{serum creatinine mg/dl})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})$.²⁰ In addition, we added 0.13 mg/dl to the NHANES IV serum creatinine levels to adjust for calibration differences between NHANES IV and the MDRD study.²¹ The four-variable MDRD equation is a simplified version of the original six-variable equation, and has been validated against the original equation, using a standardized serum creatinine assay such as that measured in the NHANES.²⁰ Using the CKD staging system from the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, eGFR values were then categorized based on the following cutpoints: ≥ 90 ml/min/1.73 m² without microalbuminuria (no CKD); ≥ 90 ml/min/1.73 m² in the presence of microalbuminuria (stage 1 CKD); 60–89 in the presence of microalbuminuria (stage 2 CKD); 30–59 ml/min/1.73 m² (stage 3 CKD); 15–

29 ml/min/1.73 m² (stage 4 CKD); and < 15 ml/min/1.73 m² (stage 5 CKD).²²

The standardized medical examinations, including blood pressure checks, were conducted in a mobile examination center. Three or four blood pressure measurements were obtained for each participant, and the average systolic and diastolic blood pressure readings were calculated from all available measurements. Quality control was safeguarded by procedural checklists, quarterly recertification, and review of the data to exclude systematic errors.¹⁹ Body weight and height were measured according to a standard protocol, and body mass index ≥ 30 (calculated as weight in kilograms divided by the square of height in meters) was used to define obesity. We constructed a hybrid variable to measure hypertension, classifying participants as hypertensive if their measured blood pressure was $\geq 140/90$ mmHg or they reported taking anti-hypertensive medications. Similarly, we classified participants as anemic if their measured hemoglobin was < 13 mg/dl if male, < 12 mg/dl if female, or if they had used medications to treat anemia within the prior 3 months.

Participants provided socio-demographic information such as race/ethnicity (non-Hispanic white, African American, Hispanic, other race) and age, along with self-reported clinical information on multiple chronic conditions including hypertension, diabetes, congestive heart failure (CHF), prior myocardial infarctions (MIs), and prior cerebrovascular accidents (CVAs). Participants indicated whether they used any non-steroidal anti-inflammatory medications (NSAIDs) and whether they had recently taken any medications for anemia.

Statistical Analyses

For the main analyses, we first defined normal serum creatinine as values ≤ 1.5 mg/dl, since many practicing physicians consider this to be the upper limit of normal and are therefore unlikely to initiate clinical action in response to lower values.⁹ We then estimated the overall prevalence of CKD using eGFR and calculated the distribution of CKD stages among participants. In additional analyses, we estimated the prevalence of stage 3 CKD using a threshold of ≤ 1.2 mg/dl for normal creatinine. We examined the prevalence of demographic variables and comorbid conditions among participants with both normal (≤ 1.5 mg/dl or ≤ 1.2 mg/dl) and elevated serum creatinine values. Finally, we calculated positive and negative likelihood ratios to assess the performance of serum creatinine as a diagnostic test for stage 3 CKD. Positive likelihood ratios of > 10 are highly indicative of the presence of the “disease” in question, while negative likelihood ratios of < 0.1 indicate that the “disease” is almost certainly absent.²³

The 1999–2000, 2001–2002, and 2003–2004 NHANES files include sample weights based on counts from the year 2000 Census.¹⁹ We used these sample weights, as well as non-response weights, in order to represent the entire civilian, non-institutionalized US population. Estimates with a sample size smaller than the recommended size for each calculated design effect were considered unreliable, although we report all results in keeping with the NHANES analytic guidelines.¹⁹

All analyses were performed with the use of SUDAAN software (RTI, Research Triangle Park, NC), a statistical package that adjusts all estimates for the complex NHANES survey design. Since the observations contributed by each participant in the sample are weighted for the differential

probabilities of selection and nonresponse, actual sample sizes are not reported along with percentages.

RESULTS

The final analytic sample included 3,406 NHANES participants ≥65 years of age. Compared to participants who were included in the analytic sample, those who were excluded due to missing physical examination or serum creatinine data were more likely to be African American (10.4% vs. 7.6%, p=0.02), more likely to be female (62.8% vs. 56.1%, p=0.003), more likely to have congestive heart failure (12.0% vs. 7.8%, p=0.003), more likely to have had a prior CVA (13.0% vs. 7.8%, p<0.001), but less likely to be using NSAIDs (38.2% vs. 45.9%, p=0.002). No differences in body mass index, prevalence of diabetes, or history of a prior MI were observed between included and excluded participants.

Among included participants, 34.1% had stage 3 CKD as defined by eGFR, and 2.0% had either stage 4 or stage 5 CKD (Table 1). Among the included study sample, stage 3 CKD was common in the setting of chronic conditions and was identified in 40.1% of patients with diabetes, 41.8% of patients with anemia, 52.9% of patients with congestive heart failure, 49.6% of patients with a prior CVA, and 40.9% of patients with a prior MI. Stage 3 CKD was also common among non-Hispanic whites (35.7%) and females (39.0%).

As shown in Table 2, among the study sample with stage 3 CKD by eGFR, 80.6% had normal serum creatinine values as defined by ≤1.5 mg/dl. Non-Hispanic whites and females with stage 3 CKD were more likely than African Americans and males, respectively, to have creatinine values ≤1.5 mg/dl (p<0.001 for both race and gender comparisons). No differences in the likelihood of creatinine ≤1.5 mg/dl were seen in regard to

age. Among patients with stage 3 CKD and chronic conditions, the prevalence of hypertension, NSAID use, and obesity were similar regardless of serum creatinine level. Compared to patients with creatinine ≤1.5 mg/dl, the prevalence of diabetes mellitus (27.4% vs. 16.2%, p=0.002) and anemia (23.8% vs. 11.0%, p=0.001), as well as history of a CVA (17.6% vs. 9.8%, p=0.01) or an MI (20.5% vs. 12.6%) were significantly greater among patients with creatinine >1.5 mg/dl.

Using 1.2 mg/dl as a cutoff threshold for elevated creatinine results in a lower prevalence of older adults with stage 3 CKD despite normal creatinine (38.6%, Table 2). Unlike the findings seen using a threshold of ≤1.5 mg/dl, patients between 65 and 74 years of age were more likely than similar patients 75 years and older to have normal creatinine as defined by <1.2 mg/dl (p=0.01). Other findings were similar to those seen with the 1.5 mg/dl threshold, including a greater prevalence of normal creatinine among non-Hispanic whites and females as compared to African Americans and males (p<0.001 for both race and gender comparisons). Differences in the prevalence of normal or elevated creatinine among patients with anemia, congestive heart failure, and history of an MI or CVA were also similar to those observed using the ≤1.5 mg/dl threshold (Table 2).

The ideal cutoff values for serum creatinine as a diagnostic test for stage 3 CKD varied by gender (Table 3). Among men ≥65 years, a serum creatinine value of ≥1.3 mg/dl indicated stage 3 CKD. Among women ≥65 years, a serum creatinine of ≥1.0 mg/dl indicated stage 3 CKD.

DISCUSSION

We provide nationally representative estimates on CKD prevalence in the older US population with chronic conditions, using eGFR as compared to serum creatinine alone. We show

Table 1. Sample Characteristics Stratified by eGFR-based Stage of Chronic Kidney Disease

N=3,406	No chronic kidney disease (n=1,569, 47.5%)	Chronic kidney disease by stage		
		Stages 1 and 2 (n=623, 16.4%)	Stage 3 (n=1,125, 34.1%)	Stages 4 and 5 (n=89, 2.0%)
Demographics				
Age				
65–74 years (%)	56.5	16.2	25.7	1.6
75–84 years (%)	39.3	16.7	42.1	1.8
≥85 years (%)	18.1*	16.8	59.2	6.0
Race/ethnicity				
Non-Hispanic White (%)	46.5	15.9	35.7	1.9
African American (%)	51.3	18.3*	27.4	3.0
Hispanic (%)	55.5*	21.1	21.4*	2.0*
Female gender (%)	45.9	13.0	39.0*	2.1*
Clinical characteristics				
Hypertension (%)	43.1	17.6	36.7	2.5
Diabetes (%)	32.1	23.2	40.1	4.6
History of a cerebrovascular accident (%)	27.6*	19.0*	49.6	3.7*
History of a myocardial infarction (%)	36.0	17.2	40.9	5.8*
Congestive heart failure (%)	23.3*	15.7*	52.9	8.0*
Anemia (%)	31.0	16.3	41.8	10.9
Non-steroidal anti-inflammatory (NSAID) use (%)	45.0	17.6	35.2	2.2
Body mass index				
<25 (%)	46.7	18.1	33.1	2.0
25–29 (%)	50.2	14.8	33.6	1.3
>30 (%)	47.7	16.3	33.9	2.1

*Estimate is unreliable, as the sample size was smaller than that recommended in the NHANES analytic guidelines for the design effect and estimated proportion¹⁹

Table 2. Normal and Elevated Creatinine Among NHANES Participants ≥65 Years with Stage 3 Chronic Kidney Disease

N=1,125	Threshold of ≤1.5 mg/dl as “normal” serum creatinine			Threshold of ≤1.2 mg/dl as “normal” serum creatinine		
	Normal creatinine (n=855, 80.6%)	Elevated creatinine (n=270, 19.4%)	p value for difference using chi-square test	Normal creatinine (n=362, 38.6%)	Elevated creatinine (n=763, 61.4%)	p value for difference using chi-square test
Demographics						
Age						
65–74 years (%)	43.9	41.6	0.82	50.5	39.1	0.01
75–84 years (%)	41.9	42.8		38.3	44.5	
>85 years (%)	14.1	15.6		11.1*	16.4	
Race/ethnicity						
Non-Hispanic White (%)	91.1	82.5	<0.001	92.4	87.5	<0.001
African American (%)	4.0*	14.9		2.0*	8.7*	
Hispanic (%)	4.9*	2.6*		5.6*	3.7*	
Gender						
Female (%)	73.4	25.7	<0.001	100	41.6	<0.001
Clinical characteristics						
Hypertension (%)	76.7	80.6	0.2	76.5	78.1	0.57
Diabetes mellitus (%)	16.2	27.4	0.002	16.7*	19.4	0.63
History of cerebrovascular accident (%)	9.8	17.6	0.01	7.7*	13.7	0.01
History of myocardial infarction (%)	12.6	20.5	0.01	10.6*	16.4	0.03
Congestive heart failure (%)	9.3*	24.4	<0.001	8.4*	14.6	0.01
Anemia (%)	11.0	23.8	0.001	9.9*	15.7	0.003
Non-steroidal anti-inflammatory (NSAID) use (%)	48.3	44.2	0.33	44.1	49.6	0.2
Body mass index ≥30 kg/m ² (%)	35.9	41.5	0.325	38.9	35.8	0.33

*Estimate is unreliable, as the sample size was smaller than that recommended in the NHANES analytic guidelines for the design effect and estimated proportion¹⁹

that only 19.4% of older persons with stage 3 CKD as calculated by eGFR had creatinine values >1.5 mg/dl, the threshold that many practicing physicians use to diagnose CKD. Women and non-Hispanic whites were particularly likely to have stage 3 CKD despite normal creatinine values, defined as either ≤1.5 mg/dl or ≤1.2 mg/dl. Older adults with stage 3 CKD and significant chronic conditions such as diabetes mellitus or congestive heart failure can also have normal creatinine values. The ideal creatinine cutpoints for diagnosing

stage 3 CKD in older patients are markedly lower than 1.5 mg/dl, and differ for men and women.

These findings are important for community-based primary care physicians who provide care for the majority of older patients. Primary care physicians need to accurately diagnose stage 3 or greater CKD in these patients to both minimize the ordering of studies that involve the use of contrast dye and also consider intensifying medical therapy for blood pressure and cholesterol control to prevent cardiovascular and renal com-

Table 3. Likelihood Ratios for Creatinine as a Predictor of Stage 3 or Greater Chronic Kidney Disease (eGFR <60 ml/min/1.73 m²) Among NHANES Participants ≥65 Years

	Serum creatinine (mg/dl)											
	Likelihood ratio (+)						Likelihood ratio (-)					
	≥1.0	≥1.1	≥1.2	≥1.3	≥1.4	≥1.5	<1.0	<1.1	<1.2	<1.3	<1.4	<1.5
Men												
Overall	1.4	2.2	5.5	>10	>10	>10	<0.1	<0.1	<0.1	<0.1	0.36	0.56
Diabetes	1.5	2.4	7.3	>10	>10	>10	<0.1	<0.1	<0.1	<0.1	0.25	0.40
Hypertension	1.4	2.2	5.5	>10	>10	>10	<0.1	<0.1	<0.1	<0.1	0.32	0.52
Congestive heart failure	1.4	2.1	4.3	>10	>10	>10	<0.1	<0.1	<0.1	<0.1	0.15	0.31
Women ≥65												
Overall	>10	>10	>10	>10	>10	>10	<0.1	0.36	0.57	0.72	0.81	0.87
Diabetes	>10	>10	>10	>10	>10	>10	<0.1	0.29	0.52	0.68	0.74	0.80
Hypertension	>10	>10	>10	>10	>10	>10	<0.1	0.33	0.54	0.72	0.80	0.86
Congestive heart failure	>10	>10	>10	>10	>10	>10	<0.1	0.22	0.41	0.53	0.65	0.71

Likelihood ratios of >10 and <0.1 are strongly predictive of positive and negative tests and are shown in bold

plications. However, busy clinicians are unlikely to act on values not marked as abnormal or routinely calculate eGFR from serum creatinine for all of their older patients and may not remember to interpret creatinine values in the context of patient age and gender. While at least 15 states have proposed legislation in recent years to mandate automated eGFR reporting for all patients, these bills have failed to pass in most cases because of concerns about the resulting burden on clinical laboratories.²⁴ Our data support the importance of providing automated eGFR reporting, especially for persons 65 years and older. Until this becomes standard procedure, primary care physicians who do not receive automatic eGFR reports should request eGFR when ordering laboratory workup for older patients under their care, including those for whom creatinine values appear “normal.”

A recent study describing the development of a risk score for contrast-induced nephropathy after cardiac catheterization illustrates the potential benefits of automated GFR reporting as compared with ordering serum creatinine alone.²⁵ The authors created an eight-variable model to predict nephropathy risk, including age >75 years, congestive heart failure, anemia, diabetes, and eGFR (categorized as 40–60, 20–40, and <20 ml/min/1.73 m²) as independent risk factors. Estimated GFR between 40–60 ml/min/1.73 m² was a risk factor for contrast-induced nephropathy, and when present together with age >75 or congestive heart failure, the combination predicted a doubling in the risk of nephropathy from 7% to 14%. In a parallel model, the authors substituted serum creatinine >1.5 as a measure of CKD, which was a stronger predictor of nephropathy than eGFR-estimated stage 3 CKD. However, about 15% of the sample had eGFR<60 ml/min/1.73 m², but serum creatinine ≤1.5 mg/dl, and consequently did not receive “risk points” in the creatinine-based model. The post-contrast nephropathy risk for older, sicker patients would be underestimated using this model.

Concerns about the validity of the MDRD equation in patients ≥65 years may limit interest in automated eGFR reporting. Some investigators have found that this equation significantly underestimates measured GFR by 18 ml/min/1.73 m² or more,^{26,27} while others have shown that the MDRD equation underestimates measured GFR by only 0.5 to 3.7 ml/min/1.73 m² among patients ≥65 years, albeit with only moderate precision.^{28,29} Much of this bias is attributable to the younger age of the MDRD cohort upon which the formula is based.³⁰ Thus, while the MDRD equation has not been validated in older adults and has significant limitations, particularly for the oldest old, it provides the best estimate of eGFR currently available to practicing clinicians caring for older persons.³¹

Concerns have also been raised about the use of the MDRD equation for persons with chronic conditions.^{32–34} While the MDRD equation has not been systematically evaluated in this population, recent analyses confirmed that the MDRD equation is relatively accurate in patients with congestive heart failure or advanced liver disease and measured GFR <60 ml/min/1.73 m².^{35,36} The MDRD equation may in fact overestimate GFR among individuals with chronic medical conditions, since the original equation was derived from CKD patients without overt comorbidities. Individuals with severe chronic illness often lose muscle mass because of malnutrition, inflammation, and deconditioning, and thus are likely to have lower serum creatinine values than healthier, but otherwise

demographically similar adults.³¹ The true prevalence of stage 3 CKD among older Americans with chronic conditions therefore likely exceeds our conservative estimates.

While the MDRD equation is not perfect, it can easily be used to calculate eGFR, and its widespread use might increase provider awareness of CKD in the older population. Currently, awareness of existing CKD is troublingly low for both patients and primary care providers, impeding needed care.⁹ Although coding practices may underestimate provider awareness and practice patterns, a study of a major Midwestern laboratory found that diagnostic coding for CKD was only 11% sensitive for patients with eGFR <60 ml/min/1.73 m² who were ≥60 years of age or had hypertension or diabetes.³⁷ This suggests that providers may not be appropriately recognizing CKD in high-risk patients. The institution of automatic eGFR reporting has been shown to increase recognition of stages 3–5 CKD from 22% to 85% of primary care physicians,³⁸ suggesting that widespread adoption of automated eGFR reporting may be important in expediting a culture shift in how primary care physicians discuss and evaluate CKD.

Our study has several limitations. First, the MDRD equation has not been validated among older adult populations. Second, we calculated eGFR using single random creatinine measurements and cannot confirm whether these values represented baseline values for the sampled individuals. However, the NHANES dataset is the source for national CKD estimates since it is a sampling of a clinically stable population.³⁹ The likelihood of acute renal failure is remote, and therefore the NHANES estimates are considered valid despite not meeting the Kidney Disease Outcomes Quality Initiative definition of at least two eGFR measurements 3 months apart.²² Third, we used single measurements of albuminuria to classify patients as having stage 1 or stage 2 CKD, although the presence of urinary protein excretion can vary over relatively short periods of time.⁴⁰ However, any potential misclassification should not include directional bias and therefore should not dramatically alter our results, which focus on stage 3 CKD. Finally, NHANES did not include nursing home residents in the sampling frame, and our results cannot be generalized to this population, which presumably has high rates of CKD and other chronic medical conditions.

In summary, use of serum creatinine in comparison to the MDRD eGFR markedly underestimates the presence of advanced (stage 3 or greater) CKD among older persons in the US, including those with chronic conditions. The use of automated eGFR reporting for older persons may facilitate provider awareness of CKD, thereby improving the accuracy of risk stratification and effectiveness of disease management for these complicated patients in the primary care setting.

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