Serum Urea Nitrogen, Creatinine, and Estimators of Renal Function

Mortality in Older Patients With Cardiovascular Disease

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Background: Renal dysfunction predicts increased mortality in cardiovascular patients, but the best renal estimator for quantifying risks is uncertain. We compared admission serum urea nitrogen (SUN) level, creatinine level, Modification of Diet in Renal Disease (MDRD) rate, and Mayo estimated glomerular filtration rate (eGFR) for predicting mortality.

Methods: In a retrospective cohort of Medicare patients (aged ≥65 years) hospitalized for myocardial infarction (n=44,437) and heart failure (n=56,652), renal estimators were compared for linearity with 1-year mortality risk, magnitude of risk, and relative importance for predicting risk (percentage variance explained) in proportional hazards models.

Results: The SUN level, creatinine level, and Mayo eGFR had linear associations with mortality. These measures predicted steadily increased risk in patients who experienced a myocardial infarction with a SUN level greater than 17 mg/dL (>6.1 mmol/L), a creatinine level greater than 1.0 mg/dL (>88.4 µmol/L), and a Mayo eGFR of less than 100 mL/min per 1.73 m²; and in patients who experienced heart failure with a SUN level greater than 16 mg/dL (>5.7 mmol/L), a creatinine level greater than 1.1 mg/dL (>97.2 µmol/L), and a Mayo eGFR of 90 mL/min per 1.73 m² or less. In contrast, the MDRD eGFR had a J-shaped association and failed to identify increased risks in 50.0% of patients who experienced a myocardial infarction (with an MDRD eGFR >55 mL/min per 1.73 m²) and 60.0% of patients who experienced heart failure (with an MDRD eGFR >44 mL/min per 1.73 m²). The SUN level and Mayo eGFR had the greatest magnitude of risks. In myocardial infarction and heart failure patients, adjusted mortality increased by 3% and 7%, respectively, per 5-U increase in SUN, and by 3% and 9%, respectively, per 10-U decrease in Mayo eGFR (P<.001), based on models including both renal measures. Of all the measures, SUN had the greatest magnitude of relative importance for predicting mortality.

Conclusions: In older cardiovascular patients, SUN- and creatinine-based measures were powerful predictors of postdischarge mortality. Only MDRD eGFR was less adequate in quantifying risks for patients with mild impairment. Novel estimators, such as the Mayo eGFR, may play an important role in outcomes’ prognostication for these patients.

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PATIENT COHORTS

Excluded from the initial sample of 71,120 MI patients were those younger than 65 years (n=6042), transfers from other hospitals because of a missing baseline renal function measure (n=11,878), those with no clinical confirmation of MI (based on creatine kinase–MB or troponin level, symptom, and electrocardiographic criteria) (n=7902), or those with a terminal illness (n=133).

Excluded from the initial sample of 78,882 HF patients were second visits of patients in the sample appearing more than once (n=3732); those younger than 65 years (n=6598); transfers from other hospitals (n=2419); those with no evidence of HF on admission by clinical symptoms or chest x-ray film (n=3003); patients with aortic stenosis (n=3493) and mitral stenosis (n=243), to exclude valvular HF; and patients undergoing long-term renal dialysis (n=3493). Patients may have had 1 or more reasons for exclusion.

Patients with a missing admission creatinine level (MI group, n=1089; and HF group, n=1746); a missing SUN level (MI group, n=1244; and HF group, n=3362); missing, nonblack, or nonwhite race (effectively missing MDRD estimate) (MI group, n=5401; and HF group, n=3216); and unknown date of death (MI group, n=303; and HF group, n=969) were excluded from analysis, for a total sample of 44,437 in the MI cohort and 56,652 in the HF cohort.

RENAL FUNCTION

Measured renal function estimators included first-admission SUN and creatinine levels (measured in milligrams per deciliter) (based on tests within the first 6 hours of admission). Calculated GFR estimates included the simplified MDRD prediction equation:

\[
\text{GFR} = \frac{186 \times \text{CREAT}}{(\text{AGE}^{0.203}) \times (\text{SUN}^{0.742})} \times (\text{IF FEMALE})
\]

where CREAT is the serum creatinine level, SUN is the serum urea nitrogen level, AGE is the age, and IF FEMALE is a binary variable indicating sex (1 for female). The MDRD equation was also used:

\[
\text{MDRD eGFR} = \frac{186 \times \text{CREAT}}{(\text{AGE}^{0.203}) \times \text{SUN}^{0.742}} \times (\text{IF FEMALE})
\]

OUTCOMES AND COVARIATES

All-cause mortality was assessed using the Medicare enrollment database and the Medicare part A database. Up to 1-year follow-up was calculated from admission date.

Potential confounders, selected based on prior studies and clinical relevance, included age, race, and sex; history of HF, MI, hypertension, angina, coronary artery bypass graft, percutaneous coronary intervention, diabetes mellitus, stroke, smoking, chronic obstructive pulmonary disease, and dementia; mobility; presenting peripheral edema; heart rate, respiratory rate, and systolic blood pressure; left ventricular systolic function (normal, mild, moderate, severe, and not documented); admission serum sodium, potassium, glucose, hematocrit, and albumin levels; preadmission use of aspirin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, diuretics, digoxin, antiarrhythmics, and calcium channel blockers; prearrival setting; hospital setting (urban vs rural); and treating physician specialty. Covariates lacking linear relationships with outcomes were coded categorically as dummy variables in multivariable analyses, including a dummy variable for missing values. All variables had less than 3% missing values, except for “not documented” left ventricular systolic function.
MORTALITY RISKS

By 1 year after discharge, 33.8% of MI patients and 37.7% of HF patients died. Worse renal function was associated with progressively higher mortality risks. The SUN level, creatinine level, and Mayo eGFR had approximately linear associations with mortality risks (Figure 1). Furthermore, in multivariable models, SUN level, creatinine level, and Mayo eGFR were each significant (P<.001) independent predictors of mortality, even in normal to near-normal ranges. Progressively and significantly increased mortality risk was associated with a SUN level greater than 17 mg/dL (>6.1 mmol/L), a creatinine level greater than 1.0 mg/dL (>88.4 µmol/L), and a Mayo eGFR of less than 100 mL/min per 1.73 m² in MI patients; and with a SUN level greater than 16 mg/dL (>5.7 mmol/L), a creatinine level greater than 1.1 mg/dL (>97.2 µmol/L), and a Mayo eGFR of 90 mL/min per 1.73 m² or less in HF patients (Table 2 and Table 3, respectively).

In contrast, MDRD eGFR had a J-shaped association with mortality and failed to identify increased mortality risks in those patients with a normal to near-normal eGFR (>60 mL/min per 1.73 m²). Specifically in multivariable models, the MDRD eGFR provided no additional prognostic information for the 50.0% of MI patients with an MDRD eGFR greater than 55 mL/min per 1.73 m² or the 60.0% of HF patients with an MDRD eGFR greater than 44 mL/min per 1.73 m² (Figure 1 and Table 2 and Table 3, respectively).

Of all 4 measures, SUN level and Mayo eGFR had the greatest magnitude of adjusted mortality risks (Table 2 and Table 3). In multivariable models that included SUN level and Mayo eGFR as continuous variables, both remained independent significant (P<.001) predictors of mortality. For example, after adjusting for Mayo eGFR, the incremental 1-year mortality risk in MI patients increased by 3% per 5-U increase in SUN level (hazard ratio, 1.03; 95% confidence interval, 1.02-1.04; P<.001); and in HF patients, it increased by 7% per 5-U increase in SUN level (hazard ratio, 1.07; 95% confidence interval, 1.07-1.08; P<.001). This translates into a 12% relative increase in mortality risk for a 20-U increase in SUN level for MI patients and a 33% relative increase for HF patients (Table 4). Weighting and clustering by state and hospital did not alter estimates.
Figure 1. Mortality curves for 5th to 95th percentile values of serum urea nitrogen (SUN) level (A and B), creatinine level (C and D), Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) (E and F), and Mayo eGFR in patients who experienced a myocardial infarction (A, C, E, and G) and heart failure (B, D, F, and H). To convert SUN to millimoles per liter, multiply by 0.357; and to convert creatinine to micromoles per liter, multiply by 88.4.
### Table 2. Data for SUN, Creatinine, and eGFR: Associated Mortality Risks in Patients With MI*  

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Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; SUN, serum urea nitrogen.  
*SI conversion factors: See the second footnote to Table 1.  
†Adjusted models included age, sex, race, comorbidities, medications, and hospital and physician characteristics.

level rivaled the prognostic importance of traditional factors used to risk stratify cardiovascular patients, such as systolic blood pressure, ejection fraction, and age. Although SUN level and most creatinine-based estimators showed significant, incremental, predictive information across their entire ranges, surprisingly, the MDRD estimate performed poorly for identifying increased mortality risks, particularly among patients with an eGFR greater than 60 mL/min per 1.73 m².  

**ROLE OF eGFR IN CARDIOVASCULAR PATIENTS**  

With increasing recognition of renal dysfunction as a potential cardiovascular disease equivalent, guidelines from the American Heart Association, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the National Kidney Foundation, and the National Kidney Disease Education Program have recommended routine assessment of renal function in patients with cardiovascular risk factors or recognized cardiovascular disease using creatinine-based prediction equations, particularly the MDRD calculation. Given these recommendations, some laboratories have begun routine reporting of MDRD eGFR and numerous studies of HF and MI patients have attempted to risk stratify patients using the MDRD eGFR. Recently, Anavekar et al² reported a 10% increase in risk of mortality and nonfatal cardiovascular events for every 10-U decrease of MDRD eGFR below 81 mL/min per 1.73 m² in patients with MI and HF or left ventricular systolic dysfunction, prompting assertions that the MDRD equation is the best of commonly available estimates of renal function in cardiovascular patients, and a valid and powerful predictor of outcomes in this group. The MDRD calculation provides a more valid estimate of true GFR than direct serum creatinine measurement and the traditional Cockcroft-Gault creatinine clearance estimate, and furthermore avoids the difficult to
obtain ideal body weight\textsuperscript{12} required for Cockcroft-Gault creatinine clearance\textsuperscript{23} (excluded from our analysis also because of lack of weight data). However, the validity and generalizability of this equation has also been questioned,\textsuperscript{17} particularly because the MDRD equation does not effectively discriminate among persons with an eGFR of greater than 60 mL/min per 1.73 m\textsuperscript{2}.\textsuperscript{24}

The role of the MDRD equation in mortality risk prediction has particularly been debated,\textsuperscript{17,21,25-29} especially for patients with mild renal dysfunction,\textsuperscript{28,30,31} because this equation was derived in a clinical trial population that was relatively young and also had relatively severe renal impairment. Limitations of the MDRD eGFR are especially concerning when applying the equation to risk stratification of cardiovascular patients, given that many of these patients have only mild renal impairment yet still have appreciable increased mortality risk. The J-shaped association with mortality found in our study may be cause of overestimation or misclassification of true GFR in this range, particularly for elderly patients, in whom lower creatinine values could indicate unmeasured frailty or comorbidity, reflected by lower muscle mass.

Interestingly, although originally derived from a relatively limited patient population, in our study cohort, the Mayo eGFR equation performed quite well in identifying an excess mortality risk for patients with an eGFR of greater than 60 mL/min per 1.73 m\textsuperscript{2}, suggesting that the Mayo eGFR estimate warrants further consideration as a clinical tool.\textsuperscript{32-34}

However, further validation of this equation is also necessary because this formula was based on a relatively young and racially homogeneous population.

### ROLE OF SUN LEVEL

Despite the difficulties inherent in characterizing GFR in cardiovascular patients, studies have focused on creatinine. For patients with mild renal dysfunction, \textsuperscript{28,30,31} because the generalizability of this equation has also been questioned,\textsuperscript{17,21,25-29} especially concerning when applying the equation to risk stratification of cardiovascular patients, given that many of these patients have only mild renal impairment yet still have appreciable increased mortality risk. The J-shaped association with mortality found in our study may be cause of overestimation or misclassification of true GFR in this range, particularly for elderly patients, in whom lower creatinine values could indicate unmeasured frailty or comorbidity, reflected by lower muscle mass.

### Table 3. Data for SUN, Creatinine, and eGFR: Associated Mortality Risks in Patients With HF*

<table>
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Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; SUN, serum urea nitrogen.

*SI conversion factors: See the second footnote to Table 1.

*Each renal function estimator was modeled separately.

†Adjusted models included age, sex, race, comorbidities, medications, and hospital and physician characteristics.
amine-based measures for risk stratification, while SUN level has been generally underappreciated as an important prognostic renal function measure. In fact, most clinical trials of cardiovascular patients rely on creatinine level alone for inclusion, exclusion, and stratification criteria. Because SUN level can simultaneously reflect alterations in GFR and global volume, it is the least precise estimator of GFR. Nevertheless, in our study, it was at least as important a prognostic indicator for mortality as eGFR, especially in HF patients, likely because it is an independent marker of HF severity. Moreover, SUN level is particularly important in this elderly population because creatinine may weaken its ability to reflect changes in GFR as muscle mass decreases.

Prior studies of smaller cohorts of HF patients have provided conflicting results regarding the significance of SUN level for predicting long-term mortality. Fonarow et al recently showed that an extreme elevation in SUN

Table 4. Incremental Adjusted Mortality Risks Associated With Elevated SUN and Decreased Mayo eGFR

<table>
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<tr>
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<th>% Increased 1-y Mortality Risk by Unit*</th>
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<tr>
<td>Patients With MI</td>
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<td>SUN (95% CI)</td>
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<td>Mayo eGFR (95% CI)</td>
<td>0.3 (0.2-0.3)</td>
</tr>
<tr>
<td>Patients With HF</td>
<td></td>
</tr>
<tr>
<td>SUN (95% CI)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Mayo eGFR (95% CI)</td>
<td>1 (1-1)</td>
</tr>
</tbody>
</table>

Abbreviations: SUN, serum urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; MI myocardial infarction.

*Data are given per unit increase in SUN and unit decrease in eGFR. The 1 SD is 17 for SUN and 28 for Mayo eGFR in MI patients and 20 for SUN and 28 for Mayo eGFR in HF patients. Risks derived from an adjusted model including SUN, Mayo eGFR, age, sex, race, comorbidities, medications, and hospital characteristics.

†The value was 6% before adjusting for Mayo eGFR.
‡The value was 6% before adjusting for SUN.
§The value was 8% before adjusting for Mayo eGFR.
¶The value was 5% before adjusting for SUN.

Figure 2. Relative prognostic importance of serum urea nitrogen (SUN) level, creatinine level, Modification of Diet in Renal Disease estimated glomerular filtration rate (MDRD eGFR), Mayo eGFR and other risk factors as indicated by percentage of explained variance of mortality risks in patients who experienced a myocardial infarction (MI) (A) and heart failure (HF) (B). The asterisk indicates that there was an improvement in explained variance ($R^2$) compared with a model without the predictor of interest, relative to the explained variance for the full model with all the covariates (actual value for the MI group, $R^2=0.25$; and for the HF group, $R^2=0.20$). These models were adjusted for age, sex, race, comorbidities, medications, and hospital characteristics. All variables were significant predictors of mortality at $P<.001$, except for prior MI ($P<.05$). The dagger indicates this was an alternative model using Mayo eGFR instead of MDRD eGFR. ACEI indicates angiotensin-converting enzyme inhibitor; and LVSF, left ventricular systolic function.
level (≥43 mg/dL [≥15.4 mmol/L]) was the most important predictor of in-hospital mortality in HF patients with acute decompensation. This study, however, did not address whether less severe elevations in SUN level could also be meaningful, especially after considering the effect of eGFR, and did not explore whether SUN level was useful for risk stratification in long-term follow-up. In our study, no single cut point for SUN level to predict mortality risk existed, because the incremental risks across the whole spectrum were informative, alongside the incremental risks across the whole spectrum of eGFR.

In MI patients, many risk scores have not included renal function.8-41 The PREDICT82 (Predicting Risk of Death in Cardiac Disease Tool) and Cooperative Cardiovascular Project43 risk scores for long-term outcomes consider severe elevations in SUN or creatinine level. Yet, similar to most studies of HF patients, they fail to take advantage of the rich prognostic information provided by a continuous spectrum of renal function, particularly in the presumed "normal" range.44 Therefore, our novel comparison of renal function measures may help to prompt reappraisal of current risk scores in MI and HF patients, first to account for the full range of renal impairment, second to consider the use of novel estimators of GFR in patients with only mild dysfunction, and third to include elevations in SUN level as a unique predictor distinct from GFR. Because SUN level may reflect multiple facets of cardiorenal pathophysiological features, particularly in the short-term setting of hospitalization, it may maintain a significant role in risk stratifying cardiovascular patients even as promising assays for estimating GFR, such as cystatin C, potentially supersede existing creatinine-based measures in outpatients.45

LIMITATIONS

Our cohorts included only older Medicare beneficiaries with baseline renal estimators measured in the hospital and, thus, may not be generalizable to younger MI and HF patients with renal function assessed in a stable outpatient context. The contribution of acute vs chronic and intrinsic vs prerenal dysfunction could not be distinguished in our study; however, even simple single measures of renal function remained surprisingly linear and robust in predicting outcomes. Our study did not have a gold standard measurement of GFR and was based on creatinine measurements from numerous hospitals (thus, nonstandardized). However, our study demonstrates the predictive ability that can be expected of these renal function estimates in hospitals across the country based on available methods of measurement. Therefore, it is not intended to identify the most precise estimator of GFR, only to evaluate renal function measures as predictors of mortality risks. However, the role of empirical validation of renal function measures used in clinical stratification for predicting outcomes can serve as an important complement to physiologically validating estimates with actual gold standards.

In conclusion, the empirical comparison of renal function measures is important for informing current practice for risk stratifying cardiovascular patients, because up to half of older MI and HF patients have some degree of renal dysfunction. The entire ranges of SUN level and GFR are powerful predictors of 1-year mortality following hospitalization for MI or HF. Optimal cardiovascular disease risk prediction should consider including SUN level and eGFR, with novel estimators of GFR, such as the Mayo eGFR equation, playing a new and important role.

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