Renal Impairment Predicts Long-Term Mortality Risk after Acute Myocardial Infarction

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ABSTRACT

Renal function predicts mortality after acute myocardial infarction (AMI), but it is unknown whether the prognostic importance of renal function persists over time. This study examined how the association between renal function and mortality changed in the 10 yr after AMI in a cohort of patients. In 118,753 patients (age ≥65 yr) from the Cooperative Cardiovascular Project, mean Cockcroft-Gault creatinine clearance was 55 ± 24 ml/min and estimated GFR was 57 ± 21 ml/min per 1.73 m^2 at baseline. By 10 yr, 68% of patients had died. Compared with normal renal function, even mild renal impairment increased the 10-yr risk for mortality risk by 10%. Severe renal impairment more than doubled the risk for mortality at 1 yr, and this increased risk persisted at both 5 and 10 yr. At 1 yr, the contribution of creatinine clearance to mortality risk rivaled traditional factors such as BP and systolic function; by 10 yr, creatinine clearance surpassed these other risk factors, rivaled only by patient age. Associations with estimated GFR demonstrated similar trends. In conclusion, renal function in hospitalized patients with AMI is an important and consistent predictor of mortality for up to 10 yr.

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Chronic kidney disease (CKD) is a risk factor for mortality in cardiovascular patients.[1–16] Despite growing appreciation for the importance of CKD in patients with acute myocardial infarction (AMI), no previous study has investigated long-term mortality risks associated with the entire spectrum of renal function. Furthermore, it is unclear whether the magnitude of mortality risks in patients with impaired function changes over time. In addition, no previous study has examined whether the relative importance of renal function, compared with other risk factors in AMI, also changes over time. Because a large proportion of deaths occur within the first 30 d after AMI,[1,16] it is possible that markers of severity of the acute event would dominate the explanation of short-term mortality risks, whereas comorbid conditions would dominate long-term mortality risks. Detection of renal impairment at the time

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of AMI may reflect a combination of acute global hemodynamic instability as well as chronic renal injury and therefore affect short- and long-term mortality risks.

Clarifying long-term risk associated with factors such as CKD in patients with AMI is increasingly important as survival after AMI improves.[17,18] Long-term prognostic information helps to stratify patients accurately, guiding management in both outpatient and acute inpatient settings and helping to quantify long-term benefits of potentially invasive interventions, yet, surprising, no long-term risk-stratification score in AMI incorporates the whole range of renal function, reflecting the paucity of data on the effect and importance of renal function on long-term outcomes.

Accordingly, in a nationally representative cohort of elderly Medicare patients who were hospitalized with AMI, we assessed the prognostic value of renal function on admission in patients with stable renal function during hospitalization. Specifically, we sought to identify whether (*1*) the magnitude of mortality risk associated with the entire spectrum of baseline renal function changed over time, (*2*) risks associated with mild impairment in renal function persisted over time, and (*3*) the relative importance of renal function in contributing to mortality risk surpassed nonrenal risk factors over time.

RESULTS

Patient Characteristics

In 118,753 patients, 51% were men, 91% were white, and mean age was 76 ± 7 yr. Twenty-eight percent had a history of MI, 19% of congestive heart failure, 60% of hypertension, and 29% of diabetes. Mean creatinine was 1.3 ± 0.7 mg/dl, creatinine clearance was 55 ± 24 m/min, and Modification of Diet in Renal Disease (MDRD) estimated GFR (eGFR) was 57 ± 21 ml/min per 1.73 m^2, with approximately normal distributions (Figures 1 and 2). Weighted κ for agreement in classification for deciles of creatinine clearance and MDRD eGFR was 0.58.

Unadjusted Mortality Risks

A total of 86,578 patients (27% of all patients) died by 1 yr, 60,907 (51%) by 5 yr, and 80,707 (68%) by 10 yr of follow-up. The majority of deaths occurred earlier, with 21% of deaths occurring within the first 30 d after AMI and 40% of all deaths occurring within 1 yr. Mortality rates were highest during the first year of follow-up and subsequently plateaued (Figure 3).

Mortality risk increased with worse levels (higher deciles) of renal impairment. For every higher decile, even in mild impairment, absolute risk for death was elevated compared with no impairment (lowest decile) for 1, 5, and 10 yr of follow-up.

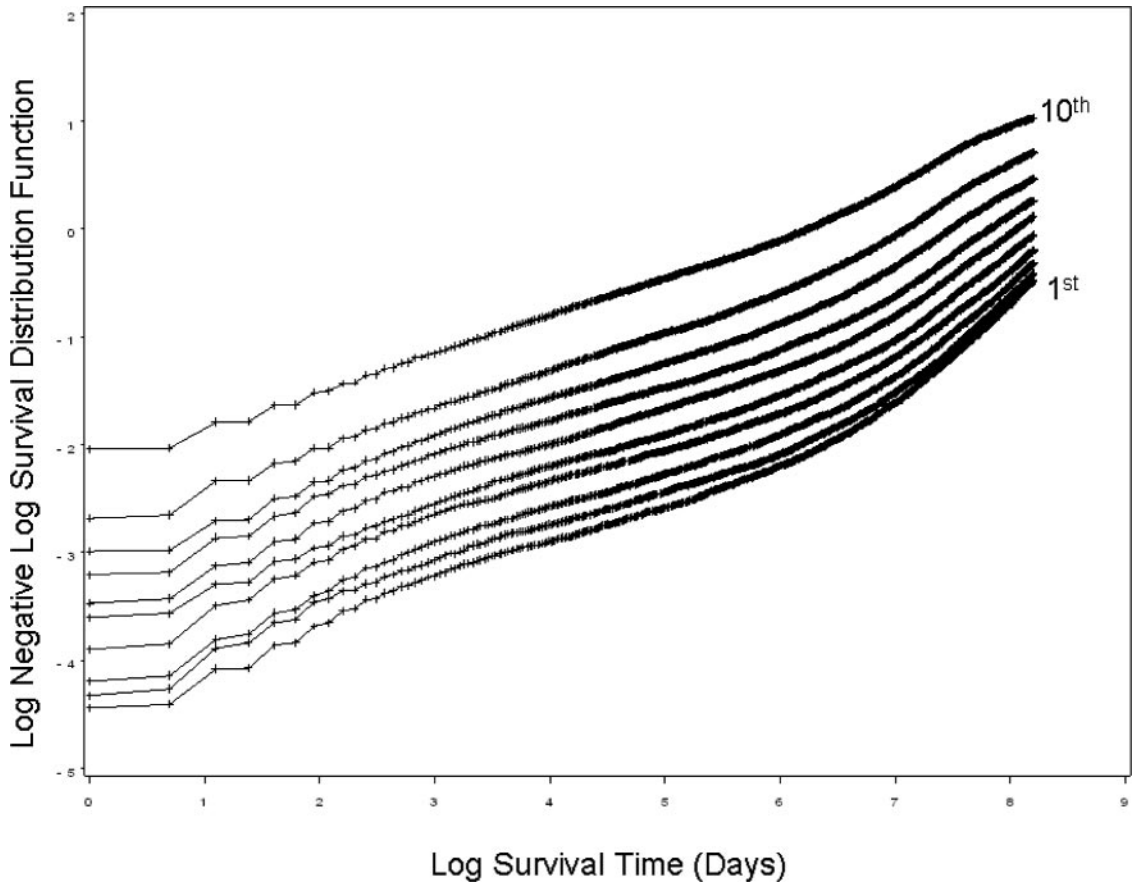

Figure 1. Distribution of admission C-G CrCl.

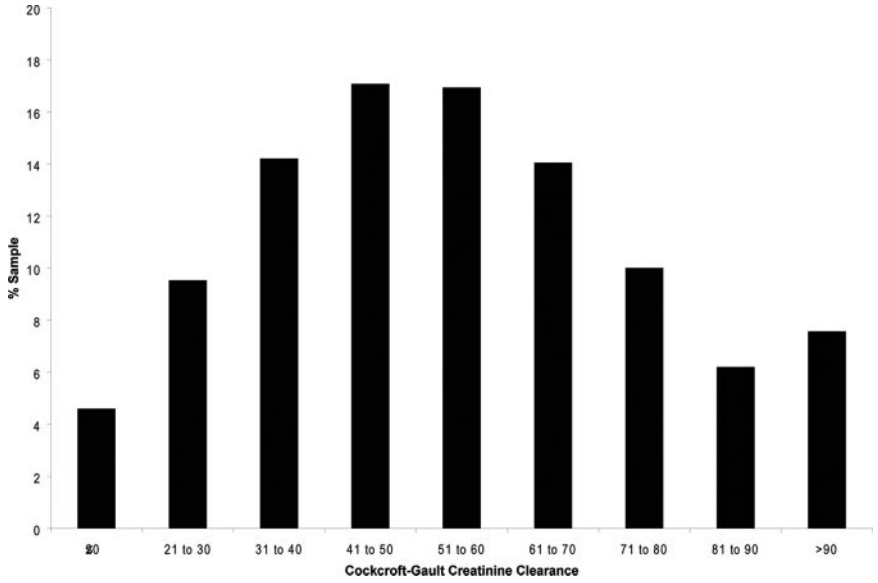

Figure 2. Distribution of admission MDRD eGFR.

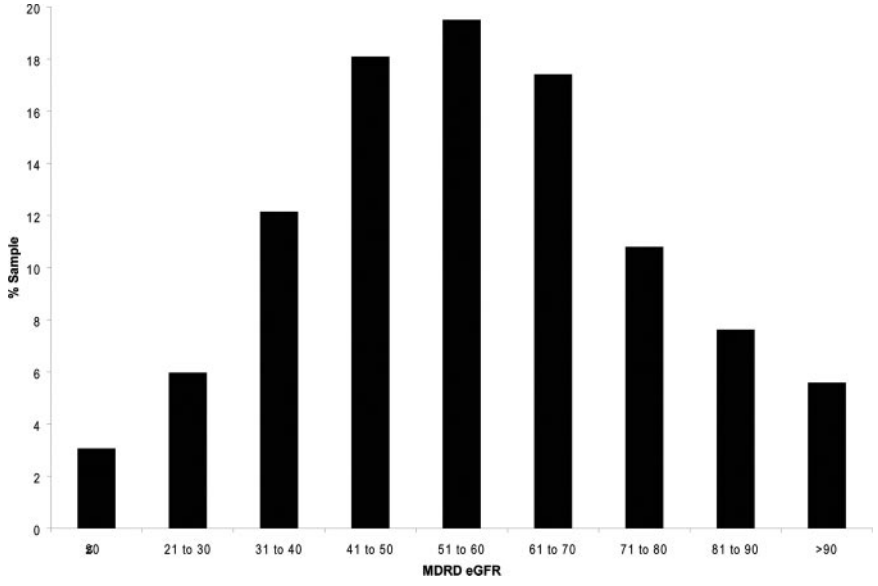

Figure 3. Mortality rates during each year of follow-up.

In addition, the association between renal function and mortality remained approximately linear (Figures 4 and 5).

Adjusted Mortality Risks

In adjusted models, renal function (including mild impairment) remained an independent predictor of mortality (Tables 1 through 3). Adjusted survival curves for 1, 5, and 10 yr underscored the stable independent effect and dose-response of this association (Figures 6 and 7).

A comparison of hazard ratios (HR) for 1-, 5-, and 10-yr mortality showed that effect sizes were fairly stable over time, with slightly lower risks for later follow-up time periods (Tables 1 through 3). For example, patients with the 50th percentile creatinine clearance (CrCl) of 53 to <59 (compared with a baseline 10th percentile CrCl of ≥86) was associated with an HR of 1.43 for 1-yr mortality (95% confidence interval [CI] 1.33 to 1.55), compared with HR of 1.32 for 5-yr mortality (95% CI 1.26 to 1.39) and HR of 1.24 for 10-yr mortality (95% CI 1.19 to 1.29); however, absolute effect sizes of mortality risks associated with worse levels of renal impairment remained high after 10 yr of follow-up, with the worst decile of CrCl (<27) doubling the mortality risk at 10 yr of follow-up (HR 1.99; 95% CI 1.91 to 2.08). This result was comparable to 5 yr (HR 2.21; 95% CI 2.12 to 2.33) and 1 yr (HR 2.52; 95% CI 2.33 to 2.71). In the subset of 102,174 patients who survived beyond 30 d, the dose-response and magnitude of the association between worse levels of renal function and 10-yr mortality remained consistent (Tables 1 through 3). Results were similar

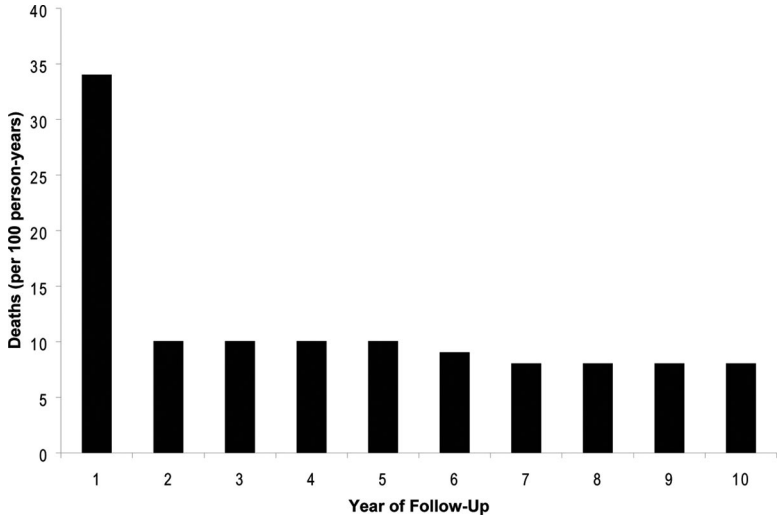

Figure 4. Mortality risks by renal function: C-G CrCl and the MDRD equation.

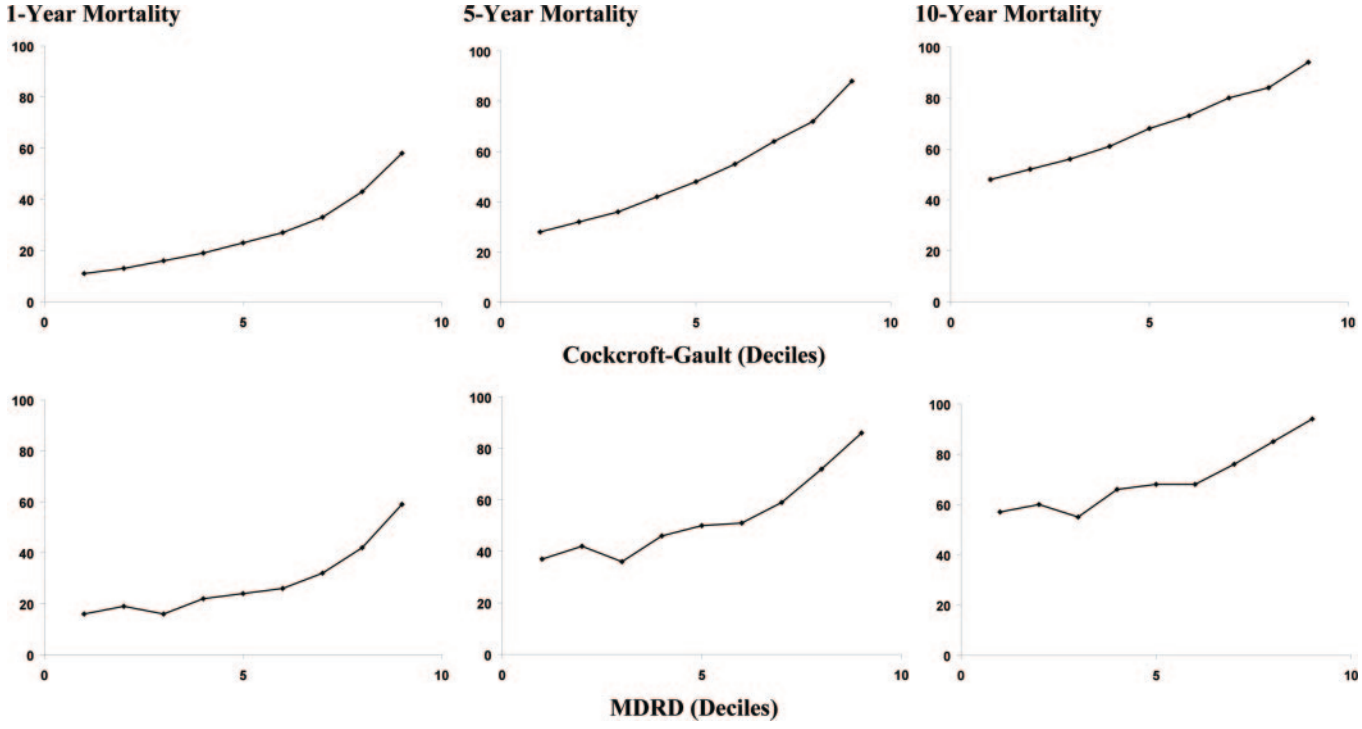

Figure 5. Mortality risk by renal function: Creatinine and BUN.

when renal function was classified using National Kidney Foundation categories, with the highest risk associated with MDRD eGFR <30 (HR 1.77; 95% CI 1.73 to 1.82) and eGFR 30 to 60 (HR 1.21; 95% CI 1.19 to 1.23) compared with eGFR >60. Sensitivity analyses censoring deaths up to 1 yr and up to 5 yr found similar results, with a small decrement in effect size for 1- *versus* 5- *versus* 10-yr mortality over time but persistent dose-response effect, with the highest relative mortality risk in patients with the worst renal function (data not shown).

Relative Importance of Renal versus Nonrenal Factors

Compared with nonrenal risk factors, the relative importance of renal function for contributing to the variance in mortality risk persisted and increased over time. Renal function dominated as a more important predictor explaining mortality risk at 5 and 10 yr than traditional prognostic risk factors measured in the acute setting, such as left ventricular systolic function, and systolic BP. At 10 yr, only age rivaled the importance of renal function in contributing to mortality risk (Table 4). Renal function and age remained the most important contributors to 10-yr mortality after stratification by gender and age.

Secondary Analyses

In 92,903 patients with complete discharge medication data,

Table 1. Adjusted risks of 1-, 5-, and 10-yr mortality by decile of CrCl[a]

Parameter	Decile									
	1	2	3	4	5	6	7	8	9	10
C-G	≥86	74 to <86	66 to <74	59 to <66	53 to <59	47 to <53	41 to <47	35 to <41	27 to <35	<27
1-yr										
HR	1.00	1.04	1.18	1.36	1.43	1.66	1.77	1.88	2.10	2.52
95% CI	–	0.96 to 1.14	1.08 to 1.28	1.26 to 1.48	1.33 to 1.55	1.53 to 1.79	1.64 to 1.91	1.75 to 2.03	1.95 to 2.26	2.33 to 2.71
5-yr										
HR	1.00	1.02	1.13	1.24	1.32	1.47	1.60	1.72	1.90	2.21
95% CI	–	0.97 to 1.08	1.07 to 1.19	1.18 to 1.30	1.26 to 1.39	1.40 to 1.55	1.52 to 1.68	1.64 to 1.80	1.81 to 1.99	2.12 to 2.33
10-yr										
HR	1.00	1.02	1.09	1.16	1.24	1.36	1.46	1.55	1.70	1.99
95% CI	–	0.98 to 1.07	1.05 to 1.14	1.12 to 1.21	1.19 to 1.29	1.31 to 1.42	1.40 to 1.51	1.49 to 1.61	1.63 to 1.77	1.91 to 2.08
Subset HR	1.00	1.02	1.08	1.14	1.22	1.33	1.42	1.52	1.69	2.00
MDRD	≥83	72 to <83	67 to <72	61 to <67	55 to ≤60	51 to <55	46 to <51	40 to <46	31 to <40	<31
1-yr										
HR	1.00	1.03	1.12	1.09	1.18	1.24	1.33	1.43	1.63	2.01
95% CI	–	0.96 to 1.10	1.04 to 1.20	1.02 to 1.17	1.10 to 1.26	1.16 to 1.32	1.24 to 1.42	1.34 to 1.52	1.53 to 1.73	1.89 to 2.13
5-yr										
HR	1.00	1.01	1.07	1.02	1.09	1.19	1.23	1.32	1.50	1.87
95% CI	–	0.96 to 1.05	1.02 to 1.12	0.98 to 1.07	1.04 to 1.14	1.14 to 1.24	1.18 to 1.29	1.26 to 1.38	1.44 to 1.56	1.79 to 1.95
10-yr										
HR	1.00	0.99	1.05	1.00	1.07	1.14	1.18	1.26	1.43	1.81
95% CI	–	0.96 to 1.03	1.01 to 1.10	0.97 to 1.04	1.04 to 1.11	1.10 to 1.18	1.14 to 1.22	1.22 to 1.31	1.38 to 1.48	1.75 to 1.88
Subset HR	1.00	0.97	1.02	0.97	1.04	1.09	1.11	1.20	1.35	1.70

[a]Adjusted models include age, gender, race, comorbidities, laboratory values, hospital events, and hospital/physician characteristics. Subset refers to the adjusted 10-yr HR after exclusion of patients who died within 30 d of hospitalization (n = 102,174 patients included).

patients with worse renal function were less likely to receive discharge β blockers and aspirin but more likely to receive discharge angiotensin-converting enzyme inhibitors ($P < 0.001$). After adjustment for discharge medications, the magnitudes and relative importance of the associations between renal function levels and mortality were not substantially changed.

Finally, in 118,753 patients with blood urea nitrogen (BUN) and creatinine values, weighted κ for agreement in classification with CrCl were 0.35 and 0.42, respectively. Dose-response trends of the association between worse levels of these renal function measures and mortality remained consistent; however, effect sizes for BUN at 10 yr were lower than associations with other measures (Tables 1 through 3).

DISCUSSION

Renal function on hospitalization for AMI was a consistent, important predictor of mortality up to 10 yr in patients with stable renal function over admission. The association between renal function and mortality remained persistently linear, with a strong dose-response and consistent effect size over time. In addition, the prognostic value of the whole spectrum of renal function, including mild impairment, remained statistically significant on long-term follow-up. Furthermore, the magnitude of risk remained consistent, with only a small decrement at 10 yr compared with 1 yr. At 10 yr, there still was up to 10% increased risk for death associated with mild levels of renal impairment (CrCl <74 ml/min) and a doubling of the risk for

Table 2. Adjusted risks of 1-, 5-, and 10-yr mortality by BUN level[a]

Parameter	BUN									
	<12	12 to <14	14 to <16	16 to 17	>17 to <19	19 to <21	21 to <24	24 to <28	28 to <36	≥36
1-yr										
HR	1.00	1.00	1.07	1.11	1.11	1.18	1.25	1.31	1.52	1.84
95% CI	–	0.93 to 1.08	1.00 to 1.14	1.03 to 1.20	1.04 to 1.18	1.11 to 1.26	1.18 to 1.33	1.23 to 1.39	1.42 to 1.61	1.73 to 1.96
5-yr										
HR	1.00	0.94	0.99	1.03	1.03	1.08	1.14	1.22	1.40	1.72
95% CI	–	0.89 to 0.98	0.95 to 1.04	0.97 to 1.07	0.98 to 1.07	1.04 to 1.13	1.09 to 1.18	1.17 to 1.27	1.34 to 1.46	1.65 to 1.80
10-yr										
HR	1.00	0.94	0.96	0.99	1.00	1.03	1.09	1.16	1.33	1.64
95% CI	–	0.90 to 0.98	0.92 to 0.99	0.95 to 1.03	0.96 to 1.03	0.99 to 1.06	1.05 to 1.13	1.12 to 1.20	1.29 to 1.38	1.59 to 1.70
Subset HR	1.00	0.94	0.94	0.97	0.99	1.01	1.08	1.14	1.31	1.67

[a]Adjusted models include age, gender, race, comorbidities, laboratory values, hospital events, and hospital/physician characteristics. Subset refers to the adjusted 10-yr HR after exclusion of patients who died within 30 d of hospitalization (n = 102,174 patients included).

Table 3. Adjusted risks of 1-, 5-, and 10-yr mortality by creatinine level[a]

Parameter	Creatinine									
	≤0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4 to 1.5	1.6 to 1.8	≥1.9
1-yr										
HR	1.00	0.98	1.03	1.06	1.14	1.17	1.26	1.37	1.57	1.95
95% CI	–	0.91 to 1.06	0.96 to 1.10	0.99 to 1.13	1.06 to 1.22	1.09 to 1.26	1.17 to 1.35	1.28 to 1.46	1.46 to 1.67	1.82 to 2.08
5-yr										
HR	1.00	0.98	1.03	1.04	1.08	1.12	1.22	1.31	1.50	1.86
95% CI	–	0.93 to 1.03	0.98 to 1.08	0.99 to 1.08	1.03 to 1.13	1.07 to 1.17	1.16 to 1.28	1.26 to 1.37	1.44 to 1.57	1.78 to 1.94
10-yr										
HR	1.00	0.98	1.00	1.01	1.06	1.10	1.17	1.26	1.44	1.80
95% CI	–	0.94 to 1.02	0.97 to 1.04	0.98 to 1.05	1.02 to 1.10	1.06 to 1.14	1.13 to 1.22	1.21 to 1.31	1.38 to 1.50	1.73 to 1.87
Subset HR	1.00	0.97	0.99	0.98	1.01	1.05	1.13	1.21	1.37	1.68

[a]Adjusted models include age, gender, race, comorbidities, laboratory values, hospital events, and hospital/physician characteristics. Subset refers to the adjusted 10-yr HR after exclusion of patients who died within 30 d of hospitalization (n = 102,174 patients included).

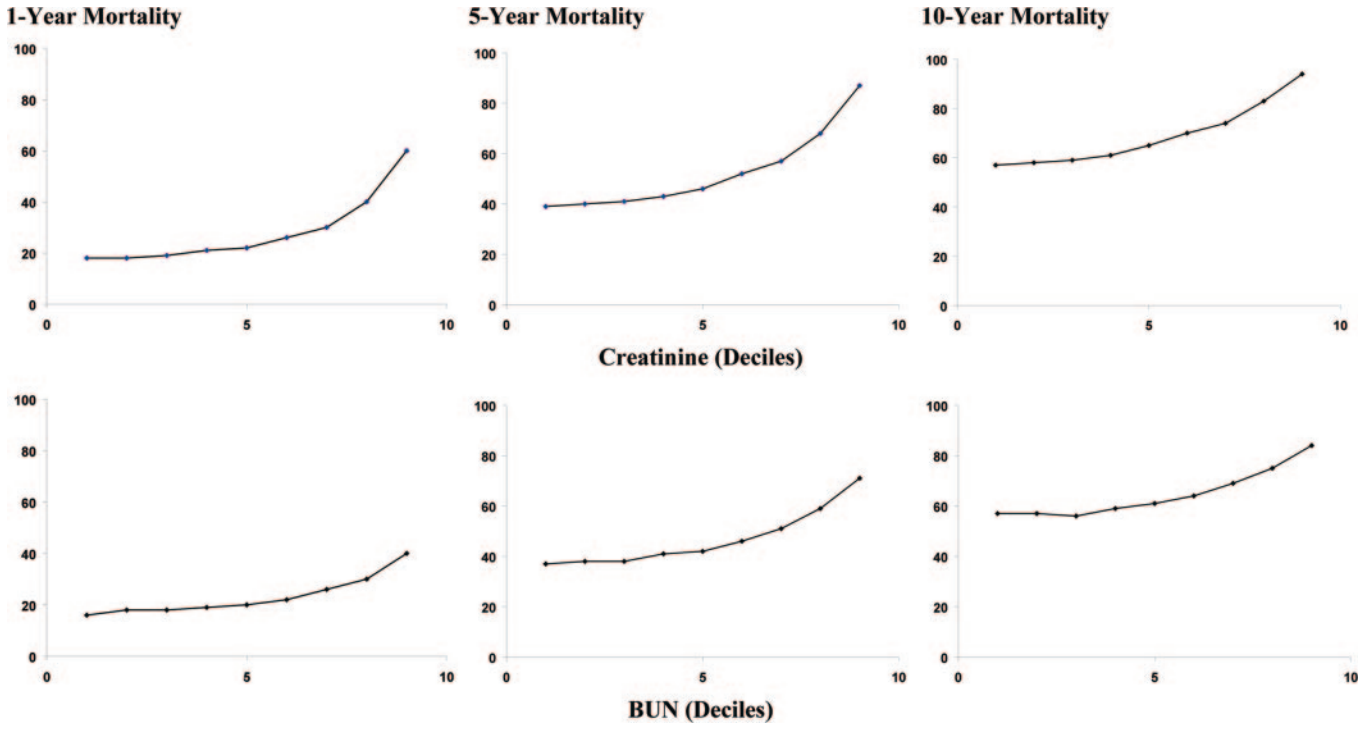

Figure 6. Adjusted survival curves for C-G CrCl, with follow-up to 10 yr. Deciles refer to level of renal function, with decile 1 as the best level of renal function (CrCl ≥86) and decile 10 as the worst level of renal function (CrCl <27). Covariates used in the final model were identical to multivariable models shown in Tables 1 and 2.

death associated with severe impairment (CrCl <27 ml/min). Finally, at 10 yr, the importance of baseline renal function as a contributor to mortality risk compared with nonrenal risk factors was rivaled only by age. This finding suggested that contribution of nonrenal factors reflecting severity of the acute event (BP and systolic function) to long-term mortality were eventually eclipsed in importance by competing risks and chronic comorbidities, including CKD. Renal function was the only risk factor to persist as a dominant explanatory factor in mortality risk over time.

Previous Studies

Previous studies demonstrated significant associations between renal function and short-term mortality in a variety of cardiovascular populations. We previously reported an approximately linear association between renal impairment and mortality risk when patients were followed up to 1 yr. Patients demonstrated more than double the risk for death associated with the worst level of renal impairment.[16] Similar results were found for in-hospital mortality risk.[6] In a secondary analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), Anavekar *et al.*[1] found increased risk for cardiovascular events and death in patients with AMI and heart failure or left ventricular dysfunction also across a range of renal impairment, especially patients with eGFR <81 ml. Analysis of the Survival and Ventricular Enlargement (SAVE) sample also showed worsening renal function after AMI was as-

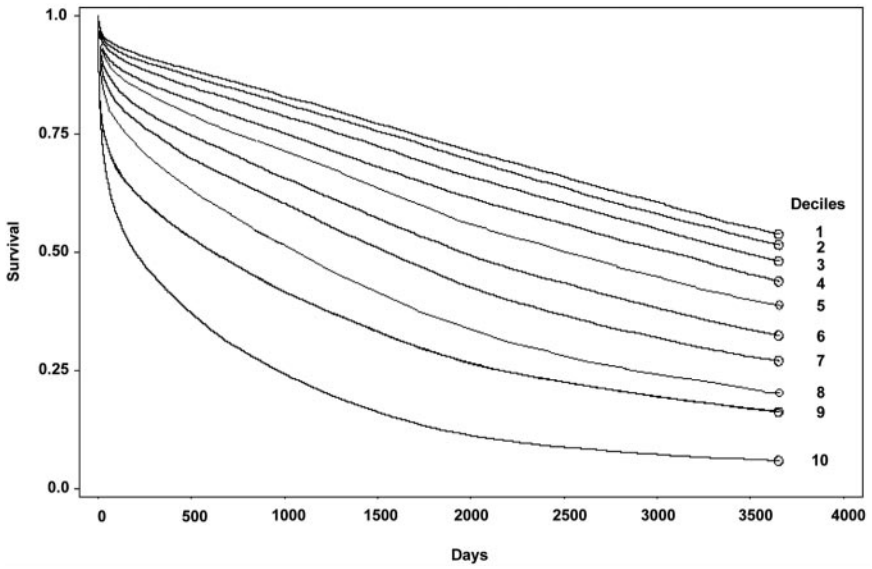

Figure 7. Adjusted survival curves for MDRD GFR, with follow-up to 10 yr. Deciles refer to level of renal function, with decile 1 as the best level of renal function (eGFR ≥83) and decile 10 as the worst level of renal function (eGFR <31). Covariates used in the final model were identical to multivariable models shown in Tables 1 and 2.

Table 4. Relative importance of renal function for predicting mortality compared with other risk factors[a]

Parameter	χ^2 for Each Variable[b]		
	1-Yr	5-Yr	10-Yr
Renal function			
CrCl	1606	2325	2296
MDRD eGFR[c]	1261	2031	2310
Other predictors			
LVSF	1687	1498	1350
Age	121	1090	2232
Systolic BP	1440	923	660
Hematocrit	63	242	283
Previous HF	18	304	407
Previous MI	9	63	150

[a]A higher χ^2 value indicates higher relative importance. χ^2 values for other predictors derived from model using CrCl for renal function. Adjusted models include age, gender, race, comorbidities, laboratory values, hospital events, and hospital/physician characteristics. All variables were significant predictors of mortality at $P < 0.001$ except for previous MI ($P < 0.002$). HF, heart failure; LVSF, left ventricular systolic function.
[b]Full model with all covariates likelihood ratio χ^2 = 36,184; 52,814; and 56,558 for 1-, 5-, and 10-yr models, respectively, using CrCl; and likelihood ratio χ^2 = 35,810; 52,463; and 56,508 using MDRD eGFR.
[c]Alternative model using MDRD eGFR instead of CrCl.

sociated with 62% excess cardiovascular mortality risk[2]; however, follow-up in these studies was 36 and 42 mo, respectively. Other studies, although limited in follow-up, reported consistent findings in patients with non-ST elevation MI and stable angina.[5,19] Whereas CKD has been found to be a risk factor for increased all-cause mortality up to 10 yr in the general population,[20–24] to our knowledge, no previous study addressed long-term mortality specifically in patients who were hospitalized with AMI.

We further add to the literature an analysis of the relative importance of renal function compared with traditional risk factors. Notably, in our study, renal function was the only risk factor measured at baseline that remained one of the most important predictors during short- and long-term follow-up. We previously reported comparable or greater importance of nonrenal predictors including systolic BP, ejection fraction, and age during short-term follow-up, but, to our knowledge, no previous study directly compared the relative importance of these predictors during long-term follow-up.[16]

Long-Term Mortality

Survival after AMI continues to improve[17,18]; therefore, clarifying long-term impact of prognostic factors is increasingly important. Our findings highlight the significance of identifying for patients with AMI and CKD specific management strategies that truly have an impact on long-term survival. Notably, patients with relatively mild CKD also have the potential to benefit from mortality risk reduction: Our study found that even patients with Cockcroft-Gault (C-G) CrCl of approximately 50 to 60 still had a 17 to 25% increased risk for mortality at 10 yr, yet previous investigators commented on the difficulty of establishing the best management strategy for patients with CKD, given potential renal toxicity of therapeutic agents.[25,26] The impressive effect size of the association between CKD and mortality in our study highlights the important potential impact of further studies to quantify risks and benefits of pharmacotherapeutic strategies in this high-risk group.

To risk-stratify appropriately patients with AMI in the postdischarge setting, it will also be crucial to derive validated long-term mortality risk prediction scores that incorporate renal function with other known risk factors. Currently used scores predict up to 6-yr mortality.[27,28] Furthermore, available risk scores dichotomize only renal function and focus only on effects of severe renal impairment. Future studies deriving risk scores for long-term

mortality will benefit from incorporating this range of renal function.

Our finding of the dominant and persistent predictive value of renal function in long-term follow-up for patients with AMI highlights novel strengths of baseline renal function as a unique factor in risk-stratifying cardiovascular patients. Our finding of the persistent effect of renal function even excluding patients with acute kidney injury help to affirm the role of CKD as an independent risk factor, not simply a marker of acute severity of cardiovascular disease. Second, our finding of the stable effect of renal function measures contrasts with studies of new biomarkers such as brain natriuretic peptide and C-reactive protein, which tend to reflect acute illness. Because creatinine and, thus, calculated estimation of renal function are ubiquitously available, this highlights the importance of calculated renal function in patients with AMI for long-term outcomes prognostication.

Limitations

Our cohort was limited to older patients, and only a single measure of renal function at admission was used, with no proteinuria or albuminuria data available; therefore, risk estimates require validation in other populations. Future studies may also seek to validate results using stable outpatient renal function measured within the first several weeks after AMI. Creatinine measurements used for eGFR were not obtained with a standardized calibration; therefore, potential misclassification of measurements may have occurred, although this limitation would have likely biased results toward the null. In addition, C-G creatinine clearance was calculated only in the subset of patients with weight data, although risk estimates in the subset of patients with C-G CrCl were consistent with other renal function measures.

Baseline renal function is a powerful predictor of outcomes after AMI in older patients for up to 10 yr, with the spectrum of renal function demonstrating a graded relationship with mortality. In addition, renal function persistently dominates as one of the most important prognostic factors over time, underscoring the need to identify management strategies that truly have an impact on long-term mortality in patients with renal impairment.

CONCISE METHODS

Study Sample

The study population included 234,771 patients from the Cooperative Cardiovascular Project, a Centers for Medicare and Medicaid Services quality improvement initiative. Patients who were hospitalized for AMI between January 1994 and February 1996, with principal discharge diagnosis of AMI (*International classification of Diseases, Ninth Revision, Clinical Modification* codes 410.xx), were randomly sampled by state. Hospital and physician data were derived from the American Hospital Association survey and American Medical Association Physician Masterfile. Details have been published previously.[29]

Exclusions

We excluded patients who were younger than 65 ($n = 17,593$), had no clinical diagnosis of AMI confirmed during hospitalization ($n = 31,188$), were readmissions for AMI ($n = 23,773$), were hospital transfers ($n = 42,279$; baseline characteristics unavailable), had terminal illness (documented life expectancy <6 mo) or metastatic cancer ($n = 3931$), had missing/invalid baseline creatinine ($n = 11,058$), experienced acute kidney injury during admission ($n = 45,343$; peak creatinine ≥0.3 mg/dl from admission,[30] reflecting patients with unstable renal function during hospitalization), were on chronic peritoneal dialysis or hemodialysis ($n = 3058$; to reduce misclassification of any of these patients with BUN and creatinine in the near-normal range), or had invalid follow-up time ($n = 17$), leaving 118,753 patients in the study sample.

Renal Function

Primary measures of renal function included the C-G equation for CrCl[31]: $\{[(140 - \text{age}) \times \text{weight (kg)}]/(72 \times \text{serum admission creatinine})\} \times 0.85$ (if female; ml/min); and the simplified MDRD equation for eGFR[32,33]: $186 \times (\text{serum admission creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$ (if black) $\times$ 0.742 (if female) (ml/min per 1.73 m^2). A total of 108,592 patients had complete data for weight (kg), and this subset was used for all analyses involving the C-G creatinine clearance. Secondarily, we tested admission creatinine and BUN (mg/dl). Results for renal function are presented using deciles to delineate detailed effects of renal function from mild to severe impairment. Higher deciles represent worse renal impairment. Results are also presented using categories based on National Kidney Foundation guidelines for MDRD eGFR—>60, 60 to 30, and ≤30—to allow comparison with previous studies using these categories.

Outcomes and Covariates

All-cause mortality was assessed using the Medicare enrollment database and Part A database. Follow-up was calculated from discharge. Covariates included in models were clinically significant (based on clinical judgment) or statistically significant in bivariate tests and previous studies.[16] Models were adjusted for age; gender; race; admission Killip class, left ventricular systolic function, systolic BP, heart rate, white blood cell count, albumin, and hematocrit; anatomic site of infarction; use of fibrinolytic therapy; percutaneous coronary intervention and coronary artery bypass graft during admission; comorbid illness including history of AMI, heart failure, hypertension, diabetes, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, dementia and smoking, impaired mobility, urinary incontinence, trauma during the previous month, and admission from nursing home; in-hospital events including shock, admission with stroke, and "do not resuscitate" status; and physician (specialty, number of patients enrolled in the Cooperative Cardiovascular Project) and hospital (teaching status and availability of on-site cardiac procedures) characteristics. In secondary analyses, discharge medications (angiotensin-converting enzyme inhibitors, β blockers, and aspirin) were also included.

Statistical Analyses

We compared characteristics of the association between each renal function measure and mortality risk at 1, 5, and 10 yr to assess changes in the association during each follow-up period. To assess linearity and slope of the association, we graphically compared unadjusted mortality risks for each renal function decile (calculated as number of deaths during the period divided by total study sample). Unadjusted mortality rates for each year of follow-up, taking into consideration deaths and losses to follow-up, were also calculated. Second, we compared strength and magnitude of adjusted associations for each follow-up period, in proportional hazards models truncated at 1, 5, and 10 yr. Complementary log-log plots confirmed proportionality assumptions (Supplementary Figure 1). Continuous covariates were included on the basis of linearity in bivariate analyses. Thus, this component of the analysis compared the relative mortality risk of patients with higher deciles of renal impairment against patients with the lowest decile of renal impairment. Third, we used the models to compare the relative importance of renal function at 1, 5, and 10 yr with other nonrenal risk factors for mortality, on the basis of a comparison of type 3 Wald χ^2 values (an indicator of the contribution of covariates to total explained variance). C-G CrCl and MDRD eGFR were separately used to characterize renal function in these models, on the basis of the strength and magnitude of this renal function measure in multivariable models compared with the other measures. Thus, this component of the analysis compared relative importance of renal *versus* nonrenal risk factors over time.

We conducted subset analyses by race and by gender to evaluate importance of renal function in patient subgroups. In sensitivity analyses for models, we also censored all deaths up to 1 yr and in a separate model censored all deaths up to 5 yr to validate results in subsets of patient who would have met the assumption of surviving at least 1 yr and at least 5 yr, respectively.

We also conducted an additional analysis excluding the 16,596 patients who died within 30 d after admission, to clarify whether effect sizes for late mortality risks were driven by early mortality. In this analysis, 102,174 patients were included in proportional hazards models truncated at 10 yr of follow-up. Finally, we conducted a secondary analysis excluding the 25,867 patients without complete discharge medication data. In this analysis, 92,903 patients were included.

Analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC), and tests assumed two-tailed $\alpha = 0.05$. Use of these data was approved by the Yale University School of Medicine Human Investigation Committee.

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DISCLOSURES

F.A.M. is on advisory boards for Amgen, Takeda, and UnitedHealth.

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