Refined characterization of the association between kidney function and mortality in patients undergoing cardiac catheterization

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Aims Chronic kidney disease is associated with an increased risk of cardiovascular morbidity and mortality. The level of kidney function at which this risk increases remains to be determined. We sought to characterize the relationship between kidney function and survival among patients with cardiovascular disease (CVD) undergoing cardiac catheterization using estimated glomerular filtration rate (eGFR) and graded refinements in the classification of kidney function.

Methods and results We included 8521 of 11 778 (72.3%) consecutive patients undergoing cardiac catheterization between 1 January 1999 and 31 December 2001 from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease database. eGFR as a categorical and continuous variable was used to define kidney function. The outcome was all-cause mortality. During a median (interquartile range) follow-up of 2.2 (1.5–3.1) years, and after adjustment for clinical risk factors and severity of coronary disease, there was a steady incremental decrease in survival post-catheterization corresponding to a decline in eGFR categories of 10 mL/min/1.73 m². When eGFR was modelled as a continuous variable, there was an increased risk of death noted at an eGFR below 79 mL/min/1.73 m². Below an eGFR of 70 mL/min/1.73 m², there was an approximate 17.2% relative increase in risk for every 10 unit decrease in eGFR (95% CI 8.4–26.6%).

Conclusion The risk of death post-cardiac catheterization is elevated when eGFR is ≤79 mL/min/1.73 m². These findings provide considerable refinement in our understanding of eGFR as a powerful prognostic marker in patients with CVD undergoing cardiac catheterization.

KEYWORDS
Kidney; Coronary disease; Mortality; Epidemiology

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with end-stage renal disease, but cardiovascular risk is not limited to end-stage renal disease, and in fact begins well before its onset. Research has recently focused on determining the level of kidney function at which the risk of adverse CVD outcomes increases.

Community-based studies, with subjects at lower risk for CVD, produced conflicting results regarding the association between kidney function and CVD outcomes. Earlier studies reported no association, whereas recent studies support an association. In contrast, patients at higher risk for CVD consistently demonstrate an association between kidney function and adverse CVD outcomes.

The majority of these studies, however, have been limited by their assessment of kidney function based on serum creatinine measurement alone without an estimate of glomerular filtration rate (eGFR) or a broad categorization of kidney function based on eGFR and mortality outcomes. In addition, none of these studies have been able to determine the threshold of kidney function at which the risk of adverse CVD outcomes increases. To the best of our knowledge, only three previous studies have attempted to determine such a threshold, none of which were able to adjust for severity of coronary artery disease (CAD) to determine the independent effect of kidney function on adverse CVD outcomes.

The purpose of this study was to characterize the association between kidney function and survival among patients undergoing cardiac catheterization using graded refinements in the classification of kidney function. We also...
sought to determine the level of kidney function associated with an increased mortality risk among these subjects with documented CAD.

Methods

Study population

Data were derived from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH), a prospective data collection initiative that captures detailed clinical information on all patients undergoing cardiac catheterization in Alberta, Canada. Cardiac catheterization is performed using a femoral approach when possible and non-ionic contrast. At the time of catheterization, data are collected on clinical risk factors including age, sex, diabetes, peripheral vascular disease, chronic lung disease, cerebrovascular disease, congestive heart failure, hyper-tension, hyperlipidaemia, liver or gastrointestinal disease, and neoplastic disease. The results of the cardiac catheterization, specifically left ventricular ejection fraction (LVEF) and coronary anatomy are also recorded as are events after catheterization (death and cardiac procedures). Patients with normal (absence of any coronary lesions) or missing coronary anatomy were excluded as we wanted to confine this prognostic study to patients with documented CAD. The cohort consisted of all Alberta resident patients undergoing cardiac catheterization from 1 January 1999 to 31 December 2001 in Calgary, Alberta. The cohort entry data were the date of their cardiac catheterization, irrespective of treatment commenced CAD. The cohort consisted of all Alberta resident patients undergoing cardiac catheterization from 1 January 1999 to 31 December 2001 in Calgary, Alberta. The cohort entry data were the date of their cardiac catheterization, irrespective of treatment received.

Assessment of kidney function

The cohort entry date chosen was 1 January 1999, as that represents the date following which serum creatinine measurements were recorded in APPROACH. We limited our study to Calgary, one of three cardiac catheterization centres in Alberta, where serum creatinine measurements (using the modified Jaffe method) were available on 83.6% of patients. The most recent creatinine measurement prior to catheterization was used. Creatinine measurements were analysed by a single regional laboratory, Calgary Laboratory Services (CLS), using standardized methods, with a reported coefficient of variation of <2%. We estimated eGFR, in mL/min/1.73 m², using the Modification of Diet in Renal Disease (MDRD) equation. The equation was simplified to exclude the variable “race”, as we were unable to identify African Americans from the data source. Given that only 1% of the Alberta population is reported to be ‘African American’, this missing variable is unlikely to bias the results.

A need for international standardization of serum creatinine measurements has been recognized. Because serum creatinine measurements may vary across different laboratories, we used a two-step process to indirectly calibrate serum creatinine to the Cleveland Clinic Laboratory, where the MDRD equation was derived. The creatinine calibration correction factor was obtained using data from NHANES III and outpatient laboratory data from CLS, both representing community-based populations. First, serum creatinine values from NHANES III were calibrated to the Cleveland Clinic using the established correction factor of 20.3 μmol/L (0.23 mg/dL). Then, the median serum creatinine measurements for the CLS outpatient population for April 2003 by sex-specific age groups (20–39, 40–59, 60–69, >70) were calculated and aligned to the NHANES III sex-specific age group values. Serum creatinine values between the two community-based populations were very similar, and as a result of this assessment, we added an average 0.70 μmol/L (0.0079 mg/dL) to the male and 0.67 μmol/L (0.0076 mg/dL) to the female age-specific strata serum creatinine values within the APPROACH cohort before application of the MDRD formula.

Outcome

Patients were followed from the time of cardiac catheterization through 31 December 2002 (i.e. a follow-up period from 1 January 1999 to 31 December 2002) for the ascertainment of the primary outcome of all-cause mortality, determined through semi-annual linkage to the Alberta Bureau of Vital Statistics.

Classification of kidney function

We used three separate and complimentary graded refinements in classification of kidney function. For the initial assessment, we categorized eGFR into five broad categories (in mL/min/1.73 m²): >90 (reference group), 60–89, 30–59, <30, and dialysis-dependent. These cut-points were chosen because they correspond to the stages defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative and are commonly used in research. We then used finer gradations of eGFR, based on categories of 10 mL/min/1.73 m² (e.g. ≤20, 21–30, 31–40, and so on, up to >90 mL/min/1.73 m²), the smallest groups practical to assess this risk. Given the concern of possible misclassification of renal function at higher levels of eGFR, we combined patients with eGFR >90 mL/min/1.73 m² together. Patients with an eGFR <20 were also combined given the small number of subjects. Dialysis patients were treated as a separate category.

Finally, the eGFR-mortality association was also explored using eGFR as a continuous variable in a spline analysis. This more sophisticated statistical approach was undertaken to empirically determine the level of kidney function associated with an increased mortality risk. Dialysis patients were excluded from this analysis.

Statistical analysis

Clinical characteristics of study subjects, stratified by estimated eGFR, were compared using χ² tests for categorical variables and ANOVA for continuous variables. Cox proportional hazard models were used to determine the association between eGFR categories and survival at up to 4 years post-cardiac catheterization, adjusting for all clinical risk factors and severity of CAD. Survival time was calculated from the date of cardiac catheterization to the date on which the data were censored or an endpoint (all-cause mortality) occurred. Data were censored if follow-up ended or the patient was still alive at the end of the study. Risk-adjusted survival curves were plotted from the proportional hazards model using the corrected group prognosis method. The proportional hazards assumption was evaluated and satisfied for these multivariable survival analyses.

Finally, we performed an analysis to determine the functional form of the relationship between level of kidney function and mortality risk post-cardiac catheterization. For this analysis, we used a smoothing spline in a penalized Cox proportional hazards model. As smoothing a spline is a smooth function that is sensitive to changes in the relationship between a predictor variable and an outcome across the range of the predictor. This analysis included a test for non-linearity in the relationship, as well as a graphic examination of the mortality risk (with 95% confidence intervals) across the range of kidney function. Statistical analyses were performed using SAS, version 8.1 (SAS Institute, Cary, NC, USA) and S-Plus for the spline analysis (version 6.1 for Windows; Insightful Corp., Seattle, WA, USA). We did not account for multiple hypotheses testing in our analysis. A two-tailed P-value of <0.05 was defined as statistically significant. The APPROACH study protocol was approved by the ethics review boards of the Universities of Calgary and Alberta.

Results

A total of 11 778 patients underwent cardiac catheterization in Calgary Alberta between 1 January 1999 and 31 December 2001.
2001. We excluded 1935 (16.4%) patients with missing serum creatinine, 24 (0.2%) with implausible (serum creatinine < 30 μmol/L) measurements, 20 (0.2%) with missing coronary anatomy, and 1278 (10.8%) with normal coronary anatomy for a final study population of 8521. The median (interquartile range) follow-up for the cohort was 2.2 (1.5–3.1) years. Excluding dialysis patients, the mean (standard deviation) eGFR at the time of cardiac catheterization was 76.8 (23.6) mL/min/1.73 m².

Other than known hyperlipidaemia, the prevalence of clinical risk factors tended to increase as kidney function declined (Table 1). The most common indication for cardiac catheterization was myocardial infarction and unstable angina for all categories of kidney function, and ‘other’ indications in dialysis patients. Other indications most frequently cited were congestive heart failure, suspected silent ischaemia, and atypical symptoms.

The majority of patients on dialysis, and those with an eGFR < 30 mL/min/1.73 m², were treated with medical therapy alone rather than coronary revascularization, despite having a similar high-risk coronary anatomy profile as patients with an eGFR > 30 mL/min/1.73 m² (Table 2).

eGFR in five broad categories and mortality risk

Crude survival at 30 days post-cardiac catheterization was 99, 97, 92, and 92% for eGFR (mL/min/1.73 m²) of 90, 60–89, 30–59, <30, and dialysis, respectively. Adjusted survival at up to 4 years post-cardiac catheterization decreased as kidney function declined, with survival rates of 90, 86, 80, and 72% for eGFR (mL/min/1.73 m²) >90, 60–89, 30–59, <30, and dialysis, respectively (Table 2).

Table 1 Baseline characteristics by category of kidney function

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Dialysis (n = 162) (%)</th>
<th>eGFR &lt; 30 (n = 130) (%)</th>
<th>eGFR 30–59 (n = 1734) (%)</th>
<th>eGFR 60–89 (n = 4381) (%)</th>
<th>eGFR &gt; 90 (n = 2114) (%)</th>
<th>P-valuea</th>
<th>P-value for trendb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>67.3</td>
<td>52.3</td>
<td>59.7</td>
<td>71.8</td>
<td>76.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>63.5 (12.4)</td>
<td>68.6 (11.2)</td>
<td>71.1 (9.2)</td>
<td>64.7 (10.6)</td>
<td>57.9 (11.3)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50.0</td>
<td>41.5</td>
<td>22.6</td>
<td>18.0</td>
<td>20.9</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>25.9</td>
<td>23.9</td>
<td>15.1</td>
<td>9.2</td>
<td>7.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>17.9</td>
<td>21.5</td>
<td>11.6</td>
<td>7.0</td>
<td>5.9</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>35.2</td>
<td>37.7</td>
<td>26.1</td>
<td>11.8</td>
<td>10.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84.0</td>
<td>75.4</td>
<td>65.4</td>
<td>55.3</td>
<td>51.4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Known hyperlipidaemia</td>
<td>47.5</td>
<td>54.6</td>
<td>56.0</td>
<td>61.4</td>
<td>62.6</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>27.8</td>
<td>23.9</td>
<td>20.6</td>
<td>13.8</td>
<td>12.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gl or liver disease</td>
<td>11.1</td>
<td>9.2</td>
<td>8.7</td>
<td>4.9</td>
<td>5.0</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>9.3</td>
<td>10.8</td>
<td>7.6</td>
<td>5.5</td>
<td>5.4</td>
<td>0.0007</td>
<td>0.0001</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>44.4</td>
<td>54.6</td>
<td>54.3</td>
<td>50.4</td>
<td>48.4</td>
<td>0.002</td>
<td>0.019</td>
</tr>
<tr>
<td>Prior thrombolytic therapy</td>
<td>1.9</td>
<td>1.5</td>
<td>3.3</td>
<td>3.7</td>
<td>3.5</td>
<td>0.489</td>
<td>0.291</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>9.3</td>
<td>6.9</td>
<td>8.0</td>
<td>7.1</td>
<td>5.0</td>
<td>0.0016</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>8.0</td>
<td>7.7</td>
<td>10.0</td>
<td>9.0</td>
<td>8.0</td>
<td>0.262</td>
<td>0.149</td>
</tr>
<tr>
<td>Indication for cardiac catheterization</td>
<td>Stable angina</td>
<td>19.2</td>
<td>15.4</td>
<td>20.9</td>
<td>28.3</td>
<td>27.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>26.1</td>
<td>36.2</td>
<td>32.4</td>
<td>32.2</td>
<td>36.4</td>
<td>0.489</td>
<td>0.291</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>26.1</td>
<td>28.5</td>
<td>33.0</td>
<td>30.5</td>
<td>27.2</td>
<td>0.489</td>
<td>0.291</td>
</tr>
<tr>
<td>Other</td>
<td>28.6</td>
<td>20.0</td>
<td>13.8</td>
<td>9.1</td>
<td>9.2</td>
<td>0.262</td>
<td>0.149</td>
</tr>
<tr>
<td>Treatment post-cardiac catheterization</td>
<td>CABG</td>
<td>19.1</td>
<td>25.4</td>
<td>25.4</td>
<td>23.5</td>
<td>19.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI</td>
<td>17.9</td>
<td>25.4</td>
<td>28.9</td>
<td>35.1</td>
<td>38.0</td>
<td>0.0016</td>
<td>0.002</td>
</tr>
<tr>
<td>Medical</td>
<td>63.0</td>
<td>49.2</td>
<td>45.7</td>
<td>41.4</td>
<td>42.4</td>
<td>0.149</td>
<td>0.149</td>
</tr>
</tbody>
</table>

Gl, gastrointestinal.

aP-value calculated by χ² tests for categorical variables and ANOVA for continuous and represents differences across categories of kidney function.
bP-value test for linear trend.
post-cardiac catheterization increased exponentially (i.e., with an upward curvature indicating acceleration of risk) between an eGFR cut-point of ~80 mL/min/1.73 m² and an eGFR of 70 mL/min/1.73 m², and then increased in an approximately linear fashion below an eGFR of 70. The point estimate for the adjusted hazard ratio crossed one at an eGFR of 79 mL/min/1.73 m², suggesting an increased risk of death associated with an eGFR < 79 mL/min/1.73 m². The slope for the linear portion (between an eGFR of 0 and 70 mL/min/1.73 m²) indicated that there was an ~17.2% relative increase in the risk of death for every 10 unit decrease in eGFR (95% confidence interval 8.4–26.6%).

**Discussion**

In this study, using graded refinements in the characterization of kidney function, we report a dose–response relationship between declining kidney function and increased risk of death post-cardiac catheterization. These findings demonstrate that level of kidney function can be used as a powerful independent predictor of mortality among patients with CVD. For every 10 unit decrease in eGFR (between an eGFR of 0 and 70 mL/min/1.73 m²), there was a ~17.2% relative increase in the risk of death.

These results are consistent with the only other study able to adjust for severity of CAD, where a two-fold increase in the risk of death was reported for patients with an eGFR < 41 mL/min, compared with those with an eGFR > 86 mL/min. Although categorization of eGFR into quartiles precluded Beddu et al. from determining the threshold of eGFR at which the risk of death increased, the conclusion obtained was similar to ours and supports the notion that the association between kidney function and increased CVD events is not fully explained by severity of underlying CAD.

A small number of studies have explored the relation between kidney function and cardiovascular outcomes by estimating kidney function as a continuous variable. Anavekar et al. reported that each 10 unit reduction in eGFR < 81 mL/min/1.73 m² was associated with a 10%
increase in the relative risk of death or non-fatal CVD complications. Dries et al. also reported a 24% increased risk of mortality for every 30 mL/min decrease in creatinine clearance among patients with LV systolic dysfunction, although a cut-point associated with increased risk not determined. Finally, Manjunath et al. was unable to establish a clear threshold level of eGFR associated with increased CVD risk, although each 10 mL/min/1.73 m² decrease in eGFR was associated with a 5% increase in the risk of developing CVD.

When eGFR was treated as a continuous variable, we found an increased risk of death at an eGFR of ≈79 mL/min/1.73 m². The metabolic complications of chronic kidney disease, including elevated serum calcium-phosphate product and anaemia, are reported to develop at an eGFR of ≈60 mL/min/1.73 m². Therefore, our empirical findings are consistent with the literature and suggest that these phenomena, which may increase the risk of CVD, may even be at play at a slightly higher eGFR of ≈79 mL/min/1.73 m².

Our findings and those of others consistently reveal an association between kidney disease and survival in patients with CAD. Whether this association is causal or not is less clear and is not possible to determine based solely on observational data. There are, however, a number of factors drawing on Hill’s criteria that suggest a possible causal association. First, the temporal sequence of the observed association is obviously correct. Secondly, the association is strong, with hazard ratios greater than 3. Thirdly, the association has consistently been demonstrated from a variety of research groups studying varied patient populations. Fourthly, and perhaps most notably, our study and others have demonstrated a clear ‘dose–response’ relationship with a greater degree of kidney dysfunction predicting poorer prognosis.

Biological plausibility is also an important criterion to assess, and again, the criterion appears to be met in this instance. It has been proposed that anaemia creates an atherogenic milieu, resulting in the introduction of non-traditional risk factors. A decline in kidney function is associated with a number of changes in vascular pathobiology, all of which may increase the risk of CVD, including abnormal vascular calcification, chronic inflammation, and oxidant stress. The observational nature of our data prevents us from determining which of these possibilities may account for the association between the decline in kidney function and increased mortality in patients with CVD.

Our study has limitations. First, the inception point for the cohort was cardiac catheterization. These patients are a subset of all patients with CVD and may not reflect the outcomes of all patients with CVD. Certain factors may have influenced patient referral for cardiac catheterization, including a lower likelihood in patients with severe kidney dysfunction due to concern of deterioration in kidney function with administration of dye. This selection bias, however, would potentially decrease the association between kidney function and survival, as patients with more severe kidney dysfunction would be excluded.
Secondly, although the study population may not necessarily represent a large ethnic mix given the small number of blacks, it otherwise is reflective of the demographic mix of large urban American centres. Furthermore, these demographic limitations aside, there are many reasons to believe that the relationship described would hold true for other ethnic groups as well. Thirdly, follow-up of kidney function, and specifically the progression of kidney function post-cardiac catheterization, was not available from the APPROACH database. Fourthly, available data limited our study endpoint to all-cause mortality. Fifthly, given its observational nature, it is not possible to determine a causal relationship between kidney function and mortality risk among patients undergoing cardiac catheterization. A final caveat relates to potential interlaboratory variability in creatinine measurements, which may impact the accuracy of the eGFR using the MDRD equation. We attempted to increase the accuracy of the MDRD eGFR through an indirect calibration to the laboratory where the equation was derived. Although there is still a potential for measurement error, until an agreed upon approach to standardize serum creatinine measurements is available, dialogue around eGFR thresholds of risk will always have this as a background concern.

In conclusion, we found that among patients with CVD undergoing cardiac catheterization, there is a graded inverse relationship between kidney function and risk of death, a risk that was independent of underlying severity of coronary disease and clinical risk factors. The mechanism behind this association is unclear, though many features hint at the association being causal, mediated through an interplay of traditional and non-traditional risk factors. These results should encourage the systematic ascertainment of kidney function in all patients with CVD to facilitate refined prognostication in this high-risk population.

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Conflict of interest: none to disclose.

Appendix


References


