Novel Stratification of Mortality Risk by Kidney Disease Stage

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Key Words
Risk scores · Chronic kidney disease · Mortality · Intermountain risk score · Laboratory tests

Abstract
Background: Chronic kidney disease (CKD) is a common disorder with a variable clinical course and it is associated with increased mortality. The Intermountain Risk Score (IMRS) is an electronic risk calculator that utilizes complete blood count (CBC) and basic metabolic panel (BMP) values to predict mortality in various healthcare populations. We hypothesized that IMRS would predict mortality in patients with CKD even with adjustment for serum phosphate and urinary albumin. Methods: Three thousand eight hundred seventy-two patients with CKD classes IIIA–V had IMRS calculated retrospectively and survival analysis was performed investigating 1- and 5-year mortality. Kaplan–Meier survival curves were generated for predefined IMRS groups of low, medium and high risk for CKD patients overall and by sex and CKD stage. Serum phosphate and urinary albumin/creatinine ratios were modeled in multivariate Cox-proportional hazard models. Receiver operator characteristic curves were used to determine c-statistics for mortality. Results: For all patients with CKD, mortality was significantly greater for those with medium- or high-risk compared to low-risk IMRS categories, among each CKD stage. Overall, IMRS was predictive of mortality at both 1 and 5 years, even when adjusted for CKD stage and predicted mortality more accurately than CKD stage alone. Albuminuria was not independently associated with mortality and serum phosphate weakly predicted mortality.

Conclusion: IMRS is a strong predictor of mortality in patients with CKD and is robustly complementary to CKD stage in refining risk prediction. Given the universal availability and low cost of the CBC and BMP, IMRS may be of a substantial value in CKD risk assessment and management.

Introduction
Chronic kidney disease (CKD) is a common medical condition affecting up to 11% of the adult population in the United States [1], and the global prevalence of this disease is increasing [2]. While it is known that CKD is an independent risk factor for cardiovascular disease, heart failure, and mortality [3, 4] predicting these events in this population has been challenging because the clinical
course of CKD is highly variable. Improved prediction of the risk of mortality in this population could potentially aid in clinical decision making and help to better individualize treatment plans for patients with CKD.

The Intermountain Risk Score (IMRS) is an electronic risk calculator (www.intermountainhealthcare.org/IMRS) that utilizes a patient’s age and common laboratory values comprised of the complete blood count (CBC) and the basic metabolic panel (BMP) to predict clinical events, including mortality. It has been validated as a predictor of short- and long-term mortality in outpatient and inpatient populations including patients with cardiovascular disease [5, 6]. The IMRS has also been shown to be predictive of myocardial infarction, coronary disease, atrial fibrillation and incident heart failure [7]. Repeated measurement of IMRS at annual time intervals may enhance the prognostic information derived from a single IMRS [8]. A recent observational analysis of the JUPITER trial showed that elements of the CBC applied in a similar manner were associated with mortality [9]. Although the IMRS has been validated in multiple populations, it has never been studied in patients with established CKD.

Standard predictors of cardiovascular disease risk in patients with CKD include urinary albumin and serum phosphate levels. Urinary albumin has been established as a marker of advanced kidney disease and has been shown to be predictive of mortality in the general population [10] and of progression of kidney disease in the CKD population [11]. The relationship between elevated serum phosphate levels and vascular disease is well established in dialysis patients, and other studies suggest that higher serum phosphate levels correlate with mortality in patients with CKD [12] as well as those without CKD [13]. In an analysis of patients with established coronary artery disease (CAD), elevated serum phosphate was associated with greater risk of death, new heart failure, and myocardial infarction even after adjustment for age, race, sex, medication use and left ventricular ejection fraction [14].

Despite the use of glomerular filtration rate (GFR)-based CKD staging and other known risk factors for cardiovascular disease, the ability to predict mortality and other clinical endpoints in patients with CKD remains suboptimal. In this study, we hypothesized that the predictive ability for mortality of IMRS extends to patients with established CKD both overall and across the multiple stages of CKD. We further hypothesized that serum phosphate levels and levels of urinary albumin would also predict risk and would add to the predictive value of the IMRS.

Methods

Study Population

The study population consisted of male (n = 1,865) and female (n = 2,007) adult patients (ages ≥18) with CKD stages IIIA, IIIB, IV, and V from any cause seen within the Intermountain Health Care system between September 2005 and January 2014 who also had both CBC and BMP values measured. This was a pre-specified analysis of retrospectively collected data from the Intermountain electronic medical records database. This study was approved by the Intermountain Healthcare Institutional Review Board and was determined to be a minimal risk, general data-only study that posed minimal risk to subjects. CKD was defined as an estimated GFR (eGFR) of <60 ml/min/1.73 m² at 2 time points at least 90 days apart. For patients included after April 2008, the eGFR measurements were calculated entering age, sex and serum creatinine values into the CKD-EPI formula, since this was when the intermountain laboratories began using isotope dilution mass spectrometry to measure serum creatinine [15]. For patients entering the study prior to April 2008, the Modification of Diet in Renal Disease study equation was used to calculate eGFR. Appropriate adjustments to eGFR were made for patients’ race. At the time of entry into the study, patients were stratified into 4 groups based on renal function: CKD stage IIIA (eGFR 45–60 ml/min/1.73 m²), CKD stage IIIB (eGFR 30–44 ml/min/1.73 m²), CKD stage IV (eGFR 15–29 ml/min/1.73 m²) and CKD stage V (eGFR <15 ml/min/1.73 m², including on, off, or unknown dialysis status). Serum phosphorous levels and quantified urinary albumin levels were included when available. Patients with electronic records indicating receipt of dialysis within 3 months prior to measurement of CBC and BMP laboratory panels were also noted.

Laboratory Analysis and Risk Calculation

Patients’ IMRS values were generated with patient age, sex and CBC and BMP laboratory measurements at the time of inclusion into the study [5]. Mathematically, IMRS is a sex-specific linear combination of weighted regression coefficients for hematocrit, RDW, mean corpuscular volume, platelet count, mean platelet volume, mean corpuscular hemoglobin concentration, white blood cell count, sodium, potassium, bicarbonate, creatinine, glucose, calcium, and age. CBC testing was performed using the COULTER Gen-S Hematology Analyzer (Beckman Coulter Corp., Hialeah, FL, USA). The BMP panel was tested on the VITROS 950 clinical laboratory system (Ortho Clinical Diagnostics, Raritan, N.J., USA). Levels of urinary albumin were measured by turbidimetric immunoassay, and patients were stratified as normal or abnormal by urinary albumin to creatinine ratio of <30 or ≥30 mg/g, respectively.

IMRS scores were calculated for all patients and divided into groups of low, medium and high risk based on prior work [5, 6, 14]. These were the respective scores of <11, 11–16, ≥17 for males at 1 year, <9, 9–14, and ≥15 for males at 5 years. For women, the scores were <9, 9–14, and ≥15 at 1 year and <11, 11–15, and ≥16 at 5 years.

Study Endpoints

The primary outcome in this study was all-cause mortality within pre-specified groups of IMRS and CKD stage. Death outcomes were determined from a combination of Intermountain Healthcare electronic records, Social Security Administration
death master file, and State of Utah death certificates. The study cohort was evaluated for mortality at 1 and 5 years after index laboratory testing.

**Statistical Considerations**

Survival curves were generated using the Kaplan–Meier method. Cox proportional hazards models were constructed separately for men and women at both 1 and 5 years within strata defined by stage of CKD (stages IIIA–V), using the independent explanatory variable as IMRS, categorized by previously derived thresholds of low, medium, or high risk for mortality [5, 6, 16]. Phosphorous and urinary albumin were modeled as continuous variables in multivariable Cox proportional hazards modeling. Receiver operator characteristic curves were used to determine the area under the curve (c-statistic) for CKD stage, IMRS alone, phosphate alone, and the IMRS combined with phosphate or CKD stage.

**Results**

**Demographics and Patient Distribution**

A total of 3,872 patients were included in the study. Baseline characteristics are shown in table 1. Patients were stratified into pre-specified low-, medium-, or high-risk IMRS groups. Patients with more advanced CKD had higher IMRS scores. Online supplemental figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000443776) shows the distributions of these groups based on stage of CKD at 1 and 5 years. IMRS scores increased with increasingly advanced CKD stages (p < 0.001).

**Patient Outcomes by CKD Class and IMRS**

For all patients, mortality was significantly higher with greater IMRS category at 1 and 5 years (fig. 1). Males and females have separate risk stratification variables in the IMRS, but outcomes were very similar (fig. 1a), and therefore, the 3 risk categories were combined for other overall analyses. The ability of IMRS to stratify risk was also observed within each CKD stage (fig. 1b; stages IV and V were combined due to small sample size of stage V).

In comparison to low-risk IMRS categories, mortality was significantly greater in the medium- and high-risk IMRS categories (hazard ratio (HR) 4.60, 95% CI 2.97–7.12 for medium-risk, HR 17.6, 95% CI 11.46–27.14 for high-risk at 1 year, and HR 2.5, 95% CI 1.9–3.2 for medium-risk, HR 6.87, 95% CI 5.44–8.68 at 5 years, p < 0.001 for all comparisons). When adjusted for CKD stage, medium and high IMRS remained highly predictive at 1 and 5 years (HR 3.85, 95% CI 2.47–5.99 for medium-risk, HR 12.66, 95% CI 8.11–19.76 for high-risk at 1 year, and HR 2.30, 95% CI 1.80–2.95 for medium-risk, HR 5.55, 95% CI 4.36–7.06 for high-risk at 5 years, p < 0.001 for all comparisons; fig. 2). As expected, patients with CKD stage IIIA had the lowest mortality, followed by those with CKD stages IIIB, IV, and V (online suppl. fig. S2).

**Comparative and Combined Mortality Prediction**

Overall, the IMRS alone outperformed the CKD stage as a predictor of mortality. Modeling the risk of mortality at 1 year based on IMRS alone produced a c-statistic

**Table 1. Baseline characteristics of patients at the time of entry into the study by CKD stage**

<table>
<thead>
<tr>
<th></th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
<th>Stage IV</th>
<th>Stage V</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>2,396 (61.9)</td>
<td>759 (19.6)</td>
<td>425 (11.0)</td>
<td>292 (7.5)</td>
<td>3,872</td>
</tr>
<tr>
<td>Age, years</td>
<td>67.3±14.1</td>
<td>71.3±13.9</td>
<td>68.8±15.8</td>
<td>61.7±16.3*</td>
<td>67.3±15.2</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>1,169 (48.8)</td>
<td>358 (47.2)</td>
<td>197 (46.4)</td>
<td>141 (48.3)*</td>
<td>1,865 (48.1)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>1,568 (65.4)</td>
<td>480 (63.2)</td>
<td>257 (60.5)</td>
<td>195 (66.8)*</td>
<td>2,500 (64.5)</td>
</tr>
<tr>
<td>Tobacco use, %</td>
<td>609 (25.4)</td>
<td>189 (24.9)</td>
<td>115 (27.1)</td>
<td>102 (34.9)*</td>
<td>1,015 (26.2)</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>1,798 (75.0)</td>
<td>560 (73.8)</td>
<td>267 (62.8)</td>
<td>192 (65.8)*</td>
<td>2,817 (72.7)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>2,062 (86.1)</td>
<td>702 (92.5)</td>
<td>396 (93.2)</td>
<td>273 (93.5)*</td>
<td>3,433 (88.6)</td>
</tr>
<tr>
<td>CAD, %</td>
<td>986 (41.2)</td>
<td>373 (49.1)</td>
<td>192 (45.2)</td>
<td>137 (46.9)*</td>
<td>1,688 (43.5)</td>
</tr>
<tr>
<td>CVA, %</td>
<td>113 (4.7)</td>
<td>41 (5.4)</td>
<td>27 (6.4)</td>
<td>17 (5.8)*</td>
<td>198 (5.1)</td>
</tr>
<tr>
<td>PVD, %</td>
<td>166 (6.9)</td>
<td>79 (10.4)</td>
<td>52 (12.2)</td>
<td>56 (19.2)*</td>
<td>353 (9.1)</td>
</tr>
<tr>
<td>Dialysis Hx, %</td>
<td>4 (0.1)</td>
<td>1 (0.1)</td>
<td>11 (2.5)</td>
<td>36 (12.3)*</td>
<td>52 (1.3)</td>
</tr>
<tr>
<td>Albumin (n = 1,865), mean ± SD</td>
<td>11.6±47.1</td>
<td>22.6±67.9</td>
<td>48.7±137.2</td>
<td>217.9±196.7*</td>
<td>16.1±61.22</td>
</tr>
<tr>
<td>Serum phosphate (n = 2,091), mean ± SD</td>
<td>3.2±0.9</td>
<td>3.4±1.0</td>
<td>3.9±1.2</td>
<td>5.4±1.8*</td>
<td>3.7±1.3</td>
</tr>
</tbody>
</table>

* All characteristics differed significantly across CKD stages with p < 0.05. PVD = Peripheral vascular disease; CVA = cerebral vascular accident. Note that albumin and serum phosphate were available only in a subset of patients.
of 0.735 (SE 0.013). CKD staging predicted mortality less efficiently with a c-statistic of 0.660 (SE 0.013). Together, 1-year IMRS and CKD staging substantially improved mortality prediction: c-statistic for 1-year mortality 0.759 (SE 0.014). In contrast, albuminuria was not independently associated with mortality (HR 1.01, 95% CI 0.99–1.01, p = 0.16). Serum phosphate weakly predicted mortality (HR 1.23, 95% CI 1.15–1.31, p < 0.001; c-statistic 0.572, SE 0.016), and the addition of serum phosphate weakened the predictive value of 1-year IMRS (c-statistic 0.716, SE 0.016 for the combined analysis, vs. c-statistic 0.735, SE 0.013). At 5 years, the IMRS in combination with CKD stage remained the strongest predictor of mortality (c-statistic 0.709, SE 0.008). This was followed by the IMRS alone (c-statistic 0.686, SE 0.008), then IMRS in combination with serum phosphate (c-statistic 0.695, SE 0.01). CKD stage alone and serum phosphate alone were weaker predictors of mortality at 5 years (c-statistic 0.618, SE 0.007 and c-statistic 0.578, SE 0.01, respectively). Thus, the strongest predictor of mortality in this study was the 1-year IMRS score in combination with CKD at both 1 and 5 years (table 2). Importantly, when patients who had undergone dialysis within 3 months prior to CBC and BMP testing were excluded, results for IMRS were essentially the same (final column; table 2).

**Discussion**

In this study, IMRS was a robust and complementary predictor of mortality in both men and women across the spectrum of CKD. IMRS outperformed CKD stage alone as a predictor of mortality and, in combination with CKD stage, provided substantial improvement in prediction of risk. The presence of elevated serum phosphate levels added minimally to the predictive ability of IMRS, whereas albuminuria was not predictive of mortality.

Patients in this study with more advanced renal failure had higher IMRS scores. This is not surprising since sev-
eral laboratory derangements are common in advanced renal failure including anemia, metabolic acidosis, and electrolyte disturbances, which all contribute to a higher IMRS. Also not surprisingly, patients with more advanced CKD stage had higher mortality. Survival at each CKD stage is a variable, and our study indicates that applying IMRS overall and to each category of CKD further improves mortality risk prediction. One of the laboratory values incorporated into IMRS is serum creatinine, which is the principle measurement that is used to define and classify CKD in clinical practice and in this study. For this reason, patients with more advanced CKD had higher serum creatinine values. Original data tables developed for generating an IMRS included creatinine values in increments of 0.1 mg/dl ranging between 0.8 and 1.2 mg/dl with the highest category being ≥ 1.3 mg/dl [5]. Because most if not all patients included in this study had serum creatinine values > 1.3 mg/dl the patients studied here had reached the maximum number of IMRS points within the category of creatinine, and creatinine did not contribute

**Fig. 1.** Kaplan–Meier survival curves for all patients for 1- and 5-year mortality by IMRS categories (low-, moderate-, and high-risk) stratified by sex (b, comparisons of high- vs. low-risk were all significant at p < 0.001 for all CKD stages for 1- and 5-year endpoints, while moderate vs. low had the following for 1 and 5 years, respectively: stage IIIA: p < 0.001 and p < 0.001, stage IIIB: p = 0.031 and p = 0.045, and stage IV/V: p = 0.38 and p = 0.55).
importantly to the differentiation of IMRS scores among these CKD patients. This illustrates that the IMRS generated for patients in this study was essentially independent of the creatinine value or GFR.

The addition of serum phosphate levels was also independently associated with greater mortality risk, although it only weakly improved the predictive power of IMRS (at 1-year but not 5-year). The albumin/creatinine ratio was not predictive of mortality in our study, for unclear reasons. We chose to test these 2 variables separately and in combination with the IMRS because they are commonly measured in patients with CKD and historically associated with mortality in this population [10, 11].

The IMRS is a useful clinical tool that uses common, inexpensive and easily available elements of the BMP and CBC to predict the risk of all-cause mortality. In many instances, these laboratory tests are already collected as part of routine clinical care, making the calculation of the IMRS available at no additional cost. It is also now freely available to the public at www.intermountainhealthcare.org/IMRS. Previous studies have shown that the IMRS has a predictive value in the general medical population, including in patients with and without known cardiac disease [5]. The IMRS is also predictive of other morbidity endpoints including heart failure, CAD, and atrial fibrillation [7], but its value in CKD prognostication had not previously been studied.

Greater cardiovascular morbidity and mortality in patients with CKD is well established, and the presence of CKD can be considered a coronary risk equivalent in many instances [3, 17]. In spite of significant progress made in the diagnosis and management of CKD, predicting clinical outcomes in this group of patients has been poor. Predicting mortality risk in patients with CKD can help guide decision-making for clinicians. Age and other

![Figure 2: HRs for mortality prediction of the IMRS group, adjusted for CKD stage (p < 0.001 for all comparisons). * Dotted line represents a HR of 1. All HRs use low IMRS (1-year or 5-year) as their reference category.](image)

**Table 2.** Receiver operator characteristic curve results: c-statistics for mortality prediction

<table>
<thead>
<tr>
<th>Prediction of mortality at 1 year</th>
<th>c-statistic (SE)</th>
<th>c-statistic (SE), with dialysis patients excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphate alone</td>
<td>0.572 (0.016)</td>
<td>0.573 (0.016)</td>
</tr>
<tr>
<td>CKD stage alone</td>
<td>0.660 (0.013)</td>
<td>0.650 (0.013)</td>
</tr>
<tr>
<td>IMRS alone</td>
<td>0.735 (0.013)</td>
<td>0.739 (0.014)</td>
</tr>
<tr>
<td>IMRS and serum phosphate</td>
<td>0.716 (0.016)</td>
<td>0.723 (0.016)</td>
</tr>
<tr>
<td>IMRS and CKD stage</td>
<td>0.759 (0.014)</td>
<td>0.762 (0.014)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prediction of mortality at 5 years</th>
<th>c-statistic (SE)</th>
<th>c-statistic (SE), with dialysis patients excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphate alone</td>
<td>0.578 (0.010)</td>
<td>0.576 (0.011)</td>
</tr>
<tr>
<td>CKD stage alone</td>
<td>0.618 (0.007)</td>
<td>0.612 (0.007)</td>
</tr>
<tr>
<td>IMRS alone</td>
<td>0.686 (0.008)</td>
<td>0.687 (0.008)</td>
</tr>
<tr>
<td>IMRS and serum phosphate</td>
<td>0.695 (0.010)</td>
<td>0.698 (0.011)</td>
</tr>
<tr>
<td>IMRS and CKD stage</td>
<td>0.709 (0.008)</td>
<td>0.707 (0.008)</td>
</tr>
</tbody>
</table>

The left column indicates which variables were included in each of the models evaluated for 1- or 5-year mortality.
comorbidities are critical components that have been traditionally used to guide long-term management of patients with CKD. For instance, an older patient with multiple comorbidities and stable CKD may be more likely to die than progress to end-stage renal disease (ESRD), while the opposite may be true for a younger patient with CKD and fewer comorbidities. This evaluation of mortality risk based on age and CKD stage is an important point to consider fully in this population, given the finding that younger individuals and those in stages IV and V are at higher risk of developing ESRD prior to death than either older individuals or those in stage III who tend to pass away without developing ESRD [18]. Thus, while IMRS aids in the identification of risks associated with standard age-related risks of poor outcomes, consideration of CKD stage and the associated age-based risk considerations such as for development of ESRD should be performed jointly using both risk measures to fully assess and balance a patient’s care plan.

The potential utility of the IMRS in this population extends to patients being considered for renal transplant. A shortened life expectancy is an accepted contraindication to renal transplant, which can be very difficult for physicians to estimate or objectively quantify. When considering the substantial costs of kidney transplantation, a predictive model of mortality that can identify who would benefit the most from advanced therapy could lead to more effective utilization of healthcare resources. An electronic risk calculator tool was recently developed for patients with CKD that utilizes clinical factors and lab values including phosphate and urinary albumin to predict progression to ESRD and need for renal-replacement therapy [19]. The IMRS adds to the armamentarium of decision-support tools that can aid the clinician caring for this unique population of patients.

**Study Limitations**

Our study has several limitations. First, our study is a pre-specified analysis of a retrospective observational database, which may be limited by uncontrolled confounding factors and selection bias. The potential population selection issues include that a comparator group with high cardiovascular risk and early-stage CKD was not included, as well that the study population was hospital-based patients who are not representative of a cross-section of the CKD population and, thus, it is difficult to extrapolate these results to other cohorts. Additional investigation of IMRS in a more broadly representative outpatient CKD population is required. Second, a relatively few patients in the study had CKD stage V and this was addressed by combining stages IV and V for statistical analysis. Although dialysis may cause fluctuations in electrolytes and other lab values, which could artificially ‘normalize’ some values, our analysis did show a consistent trend of increasing mortality across all stages of CKD, with the worst prognosis in stage V patients, as expected, and exclusion of dialysis patients exhibited little effect overall. Including patients on dialysis increases the generalizability of our study findings and illustrates that mortality prediction is maintained even in ESRD.

Further, IMRS does not account for a patient’s medical therapies that are very important for patients with CKD. Although the laboratory parameters that IMRS utilizes may become worse with the progression of renal disease and consequently with the CKD stage, therapy may be a confounding factor between the stages because higher CKD stage subjects may receive therapy that corrects the laboratory parameters, but IMRS does not account for such therapy. Despite this limitation, it may be that the use of IMRS can help identify lower-stage CKD patients who would benefit from earlier correction through such therapies. Finally, we had expected albuminuria to be an independent predictor of mortality in our population but did not find it to be. This may be explained in part only by about half of patients having available albuminuria data.

**Future Directions**

Future directions for CKD risk stratification may include utilizing repeated measurements of the IMRS to provide dynamic prediction of mortality in patients with CKD over time [8]. An emerging body of evidence suggests that cystatin-C may be a more accurate way of evaluating renal function than traditional serum creatinine levels and may be more predictive of mortality [20, 21]. Incorporating cystatin-C along with the IMRS and other markers of renal function could further refine the predictive value of our model. We intend to re-derive the IMRS equation specifically for patients with known CKD, which would involve altering the weighting coefficients of current lab values, increasing the range of serum creatinine utilized in the calculation, and incorporating serum phosphorous. Furthermore, we hope to retrospectively apply the IMRS to living and deceased renal transplant recipients to further expand the applicability of the IMRS in this population. Finally, randomized trials testing whether and how to use IMRS in therapeutic decision-making to improve outcomes should eventually be performed.
Conclusions

IMRS is a strong predictor of mortality in patients with CKD and is robustly complementary to CKD stage in refining risk prediction. Given the universal availability and low cost of CBC and BMP, IMRS may be of substantial value in CKD risk assessment and management.

Acknowledgments

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Disclosure Statement

B.D.H. and J.L.A. are named inventors of IMRS, which has been licensed to Scriplogix, Inc., for commercial development. The authors have no other conflicts of interest to report.

References