Derivation and validation of a clinical index for prediction of rapid progression of kidney dysfunction

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Received 18 June 2006 and in revised form 6 November 2006

Summary

Background: Chronic kidney disease is common among the elderly, and these patients are at risk of progressive kidney dysfunction.

Aim: To develop an index to predict rapid progression of kidney dysfunction.

Design: Community-based cohort divided into derivation (n = 6789) and validation (n = 3395) subsets.

Methods: We identified 10 184 subjects aged ≥66 years from computerized laboratory data. Prescription drug data was used to define disease categories and medication exposure, and an index for predicting rapid progression of kidney dysfunction (≥25% decline in glomerular filtration rate over a 2-year period) was obtained from a logistic regression model in the derivation cohort. The risk score for each subject was calculated by summing the component variables together, which were subsequently categorized into five risk classes.

Results: Five predictors of rapid progression were identified: age >75 years, cardiac disease, diabetes mellitus, gout, and use of anti-emetic medications. Rates of rapid progression for risk classes I through V were 8.6%, 10.9%, 13.9%, 15.6%, and 24.1%, respectively, for the derivation cohort, and 8.4%, 11.6%, 15.5%, 17.3%, 21.9%, respectively, for the validation cohort. The risk index distinguished between low and high risk of rapid progression, with a 2.5-fold greater risk for the highest, compared to the lowest, risk decile.

Discussion: Readily available clinical data can be used to identify most elderly at risk of rapid progression of kidney dysfunction. This simple index could help clinicians to identify patients at risk, and implement strategies to slow the progression of kidney dysfunction.

Introduction

Chronic kidney disease (CKD) is common among the elderly, with an estimated prevalence of >20% in the US.¹ CKD is associated with poor outcomes, including increased rates of death from any cause²,³ and from cardiovascular causes,²,⁴ particularly among the elderly.⁵,⁶

Attention has recently been directed towards identifying factors associated with progression of kidney dysfunction, including age,⁷ diabetes mellitus,⁷,⁸ hypertension,⁷,⁹ and albuminuria.¹⁰ Although these individual risk factors may be associated with progression of kidney dysfunction, little is known...
regarding the combination of factors which increases an individual’s risk of progressive kidney dysfunction, and to the best of our knowledge, no tools are available to identify these high-risk individuals. The identification of subjects at highest risk of rapid progression of kidney dysfunction, with implementation of strategies to slow this decline, could benefit a large proportion of the population.

We sought to develop a clinical index to identify subjects at risk of rapid progression of kidney dysfunction, that was simple to use and based on readily available clinical data. We also validated the predictive accuracy of this index in a separate cohort of elderly subjects.

**Methods**

**Patient population, variable definition and classification of outcome**

We identified a community-based cohort from the Calgary Laboratory Services (CLS) computerized database, Alberta, Canada. CLS provides laboratory testing for the Calgary Health Region (catchment population 1.1 million) using a single regional laboratory. To be eligible subjects had to be ≥66 years of age and have had one or more out-patient serum creatinine measurements during each of two time periods: 1 July 2001 to 31 December 2001, and 1 July to 31 December 2003. Laboratory measurements associated with a hospital admission were excluded, to avoid episodes of acute renal failure. Subjects who were receiving dialysis at study entry were also excluded, as were subjects who had >12 out-patient measurements of serum creatinine in either of the 6-month observation periods, as they were likely to represent patients with transient unstable kidney function.

Medications dispensed in the 6 months prior to the 2001 index serum creatinine measurement were obtained from provincial administrative data, to determine disease categories and drug exposure based on classes of medications, as defined in the Chronic Disease Score. The disease categories and drug exposures considered included: cardiac disease, depression, diabetes mellitus, hypertension, dyslipidaemia, liver disease, Crohn’s disease, Parkinson’s disease, cystic fibrosis, peptic ulcer disease, peripheral vascular disease, respiratory disease, rheumatological disease, thyroid disease, anxiety disorder, bipolar disorder, epilepsy, glaucoma, gout, NSAIDs and COX-2 inhibitors, anti-emetics, narcotic analgesics, and anti-psychoctics.

The outcome of interest, rapid progression of kidney dysfunction, was defined as a ≥25% decline in mean estimated glomerular filtration rate (eGFR) between the two study periods. A progression of ≥25% was approximately the 88th percentile for progression within the entire cohort over this 2-year period. We estimated GFR using the four-variable MDRD GFR equation. Preliminary studies have validated this equation in the elderly population. Because of concerns about the validity of the MDRD GFR at higher levels of kidney function, we limited our study population to those with a mean eGFR <90 ml/min/1.73 m².

Serum creatinine measurements were performed in the same laboratory, eliminating potential for inter-laboratory variation in measurement. Intra-laboratory variation in measurement was assessed and corrected as previously reported.

**Development of risk index**

Of the 10,184 subjects, two thirds were randomly selected for the derivation cohort (n=6789) and the remaining 3395 were assigned to the validation cohort. To identify predictors of rapid progression, disease categories and drug exposures were considered in a stepwise logistic regression analysis, using a backward elimination process and maintaining variables with p≤0.05. We then derived the index based on two separate scoring systems: one in which a weight was assigned to each variable based on the β-coefficient from the logistic regression analysis (OR 1.0–1.4 = 1; 1.5–2.4 = 2; 2.5–3.4 = 3, etc.), and one in which all variables were assigned an equal value. The receiver operating characteristic curve (ROC) analyses showed a slight advantage using logistic regression weights, which were then used in developing the risk scores. The risk score for each subject was calculated by summing the component variables together. This score was subsequently categorized into risk classes for each subject, with scores of 0, 1, 2, 3 and 4+ corresponding to risk classes of I, II, III, IV and V, respectively. Rates of rapid progression and 95% CIs, by risk class, were calculated.

We validated the risk index by several methods, including comparison of the rates of rapid progression of kidney dysfunction for the risk classes, as well as evaluating model performance based on the c and Hosmer-Lemeshow statistics. We elected to include the c statistic, even though we anticipated that it would be low with the use of non-fatal endpoints. The c statistic is equivalent to the area under the ROC curve, and measures model discrimination, while the Hosmer-Lemeshow statistic measures calibration and goodness-of-fit across categories defined by deciles of model-predicted risk.
The institutional review board, University of Calgary, approved the study.

Results

The formation of the study cohort and reasons for exclusion are outlined in Figure 1. A total of 10,184 subjects were included in the study cohort, the majority (64.5%) of whom had a study mean eGFR (ml/min/1.73 m²) of 60–89, while 31.1 and 4.1% had study mean eGFRs of 30–59 and <30, respectively. Over the 2-year study period, 41% of subjects had an increase in their mean eGFR: median (IQR) increase of 7.0 (3.0–12.7) ml/min/1.73 m².

Derivation of the rapid progression risk index

The majority of study subjects in the derivation and validation cohorts were female, with a mean age of 76.1 (SD 6.7) in both cohorts, and a similar distribution of disease and drug exposure categories (Table 1).

Of the 25 variables initially entered into the multivariate logistic regression analysis, only one demographic, one medication and three disease variables remained significantly associated with rapid progression of kidney dysfunction. These five predictors of rapid progression included: age >75 years; cardiac disease; diabetes mellitus; gout; and use of anti-emetic medications; with adjusted ORs ranging from 1.0 to 2.9 (Table 1). The rate of rapid progression of kidney dysfunction showed a steady increase as the risk class increased (Table 2), with a rate of 8.6% (95% CI 7.5–9.8%) for Class I and 24.1% (95% CI 19.9–28.8%) for Class V.

Figure 2a demonstrates the ability of the model to predict increased probability of rapid progression of kidney dysfunction across deciles of risk grouping, with deciles of risk determined from the Hosmer-Lemeshow statistic. Observed and expected rates of rapid progression were similar within deciles, indicating the model’s ability to predict accurately across all levels of severity. The Hosmer-Lemeshow statistic shows goodness of fit ($\chi^2 = 0.77$). The model was able to distinguish between low and high risk of rapid progression, with a 2.5-fold greater risk for the highest, compared to the lowest, risk decile.

The c statistic for the derivation model was 0.59.

Validation of the risk index

To validate this index we applied the prediction model and simple scoring rule to the validation cohort. This validation cohort also revealed the same stepwise increased risk of rapid progression with increasing risk class (Table 2), with a model c statistic of 0.59. Figure 2b demonstrates the model’s predictive ability, and shows the same graded increase in outcome with increasing severity, with a 2.2-fold greater risk for the highest, compared to the lowest, Hosmer-Lemeshow risk decile.

Discussion

Our findings suggest that a simple model based on readily available clinical data can be used to predict rapid progression of kidney dysfunction in most elderly subjects. Age >75 years, cardiac disease, diabetes mellitus, gout, and use of anti-emetics were the strongest predictor variables. Using a simple scoring system, a score of $\geq 4$ (Class V) almost tripled the risk of rapid progression. This index has clinical utility, and can be used to identify individuals at risk of progression who require more intensive monitoring and management to prevent ongoing loss of kidney function.

Our model predicting rapid progression has face validity, with the variables plausibly associated with rapid progression of kidney dysfunction. Older age,7 cardiac disease17 and diabetes mellitus7,8 have all been associated with progression of kidney dysfunction. Gout, as defined by the use of uricosuric medications, allopurinol, and/or colchicine, may
be a marker for hyperuricaemia, which has been identified as a risk factor for progressive kidney disease. Whether treatment of hyperuricemia slows progression of kidney dysfunction remains to be determined. Alternatively the presence of gout may lead to the use of anti-inflammatory medications (both prescribed and over-the-counter), which are also associated with a reduction in kidney function.

Use of anti-emetics was the strongest predictor of rapid progression, and, in the setting of nausea and vomiting, may reflect a pre-renal (volume depletion) component resulting in deterioration of kidney function. This may be exacerbated by a number of mechanisms particularly relevant in the elderly, including more pronounced effects of water loss due to decreased total-body-water, impaired renal sodium handling, blunted renin release, and a decreased thirst mechanism.

Although hypertension appeared to be a risk factor for development of CKD in previous observational studies, use of antihypertensive...
medications was not a significant predictor in this study. This may be due to misclassification of the diagnosis of hypertension based on medications dispensed; alternatively, use of antihypertensives, including ACE-inhibitors and angiotensin receptor blockers, may reduce the risk of rapid progression.

The validated c statistic for our model was only 0.59, suggesting a modest ability to discriminate between patients with and without risk of rapid progression. Non-fatal endpoints in other settings have also been shown to have a lower c statistic than do fatal endpoints.25,26 However, both Table 2 and Figure 1 speak to the predictive ability of the model and overall model performance. It is possible that factors beyond the clinical variables included in our model may enhance our ability to predict progression of kidney dysfunction.

The prediction model developed does not include albuminuria, a variable associated with a decline in kidney function,10 but instead was based on readily available clinical data. The decile of risk figure, however, clearly indicates that our model was able to distinguish higher risk cases of rapid progression from lower risk cases, even without the presence of albuminuria. The addition of albuminuria, obtained at a later stage of clinical evaluation, may further enhance the clinicians’ ability to predict risk of rapid progression in this population.

The study findings should be interpreted in the context of their limitations. First, the possibility of reverse causality can not be excluded, although the assessment of risk factors prior to the determination of rapid progression should reduce this possibility. Second, our study only included subjects who had a serum creatinine measurement. Subjects with kidney dysfunction who may be at risk of progression yet did not have a serum creatinine measurement would not be included. Given that our study was based on the elderly, who are more likely to access the health care system and have laboratory testing completed, this is unlikely to bias our study results substantially. In addition, results from a cohort identified by laboratory-based case finding are easily generalized to primary care practice. Third, disease categories were based on medication use, which may result in misclassification and underestimate the true prevalence of these conditions. Finally, the risk index was validated in
a single cohort; further validation in other settings is required.

In conclusion, significant predictors of rapid progression of kidney dysfunction in the elderly population included the presence of cardiac disease, diabetes mellitus, gout, use of anti-emetic medications and age greater than 75 years, with a score ≥ 4 (Class V) almost tripling the likelihood of rapid progression of kidney dysfunction. This simple index could help clinicians to identify subjects at risk of rapid progression, and guide clinical management and decision making. Future studies are needed to determine whether variables such as albuminuria can add to the predictive ability of the model, and to validate its use in other settings.

References


