A Predictive Model of Progression of CKD to ESRD in a Predialysis Pediatric Interdisciplinary Program

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Abstract

Background and objectives The incidence of ESRD in children has increased over the last two decades. Nevertheless, there are still limited data on risk factors related to the emergence of ESRD among patients with CKD. The aim of this study was to develop a model of prediction of ESRD in children and adolescents with CKD (stages 2–4) enrolled in a predialysis interdisciplinary management program.

Design, setting, participants, & measurements In this retrospective cohort study, 147 patients with CKD admitted from 1990 to 2008 were systematically followed up at a tertiary pediatric nephrology unit for a median of about 4.5 years. The primary outcome was the progression to CKD stage 5. A predictive model was developed using Cox proportional hazards model and evaluated by c statistics.

Results The median renal survival was estimated at 98.7 months (95% confidence interval [95% CI], 68.7 to 129.6 months). The probability of reaching CKD stage 5 was estimated as 52% in 10 years. The most accurate model included eGFR, proteinuria at admission, and primary renal disease. Risk score ranged from 0 to 13 points (median, 4 points). The accuracy of the score applied to the sample was high, with c statistics of 0.865 (95% CI, 0.80 to 0.93) and 0.837 (95% CI, 0.76 to 0.91) at follow-up of 2 and 5 years, respectively. By survival analysis, it was estimated that at 10 years after admission, the probability of renal survival was about 63% for patients in the low-risk group and 43% for the medium-risk group; all patients assigned to the high-risk group had CKD stage 5 (P<0.001).

Conclusion The predictive model of progression of CKD might contribute to early identification of a subgroup of patients at high risk for accelerated renal failure.


Introduction

CKD leads to irreversible kidney damage that can further progress to ESRD (1). During the last 30 years, the incidence of pediatric patients with ESRD has increased almost two-fold, and the prevalence has increased 4-fold (2). The amount of available data on CKD and ESRD in children has recently increased (3). For instance, the Chronic Kidney Disease in Children Study, a large North American pediatric observational cohort multicenter study, has compiled noteworthy information regarding fundamental issues in this population, such as hypertension, anemia, dyslipidemia, neurocognitive development, and somatic growth (4–12).

Accurate prediction of risk could facilitate individualized decision-making, enabling early and appropriate patient care (13–16). Nevertheless, this issue is not clearly addressed in the current medical literature, with limited data regarding risk factors related to the progression of CKD. Therefore, there is a clear need to identify risk factors and to develop new methods to halt CKD progression in children (17).

We have previously described the clinical course of 107 children and adolescents admitted to our predialysis interdisciplinary management program (PDIMP) (18), and we identified variables that are possible predictors of progression to CKD stage 5 (19). In the present study, we extended our analysis with the goal of developing a clinical predictive model to stratify the risk for ESRD in pediatric patients with CKD with a longer follow-up time.

Materials and Methods

Patients

The records of 147 patients diagnosed with CKD were included in the analysis of this retrospective cohort study. Inclusion criteria were children and adolescents who were admitted to the PDIMP from 1990 to 2008 with CKD (stages 2–4) and had at least 6 months of follow-up.

Clinical Protocol

The PDIMP consisted of clinical management of children and adolescents with CKD and was conducted...
by an interdisciplinary team that included pediatric nephrologists, pediatricians, nurses, psychologists, nutritionists, and social workers. After the initial investigation, patients were followed according to a systematic protocol described in detail elsewhere (18–20).

Baseline Covariates
The variables included in the analysis were sex, ethnicity, primary renal disease, CKD stage, eGFR, proteinuria, hematuria, hypertension, age at admission, weight-for-age Z score, height-for-age Z score, body mass index (BMI), hemoglobin, serum levels of calcium, phosphorus, albumin, urea, and bicarbonate.

Definitions
Patients were classified into four groups according to primary renal disease: uropathies, GN, cystic/tubular disorders, and miscellaneous. For analysis purposes, primary renal disease was dichotomized into two groups: GN versus others. Ethnicity was established by clinical examination based on skin color and hair color and texture, according to the Brazilian Institute of Geography and Statistics (21). For analysis purposes, the black and intermediate color categories were merged here into a “non-white” group. BP was measured and evaluated according to the recommendations of the Fourth Task Force on Blood Pressure in Children, and the 95th percentile was used as the cutoff point (22). Proteinuria at baseline was classified into three categories: absent, mild (urinary protein excretion $2\,\text{g/d}$ or a urinary protein-to-creatinine [UpUc] ratio $<2$), and severe (urinary protein excretion $\geq2\,\text{g/d}$ or UpUc ratio $\geq2$). Weight-for-age and height-for-age Z scores were used to assess weight and stature. These measures were calculated using the public-domain software Epi Info (version 3.4.1) (23). We calculated eGFR using the formula of Schwartz (24).

Outcome
CKD stage 5 was assigned as a dependent variable. Renal survival was measured from the date of patient enrollment to the date of initiation of dialysis or to the date of first eGFR $<15\,\text{ml/min per 1.73 m}^2$.

Statistical Analyses and Development of Risk Prediction Model
The values are expressed as medians and interquartile range (IQRs). Univariate analyses of continuous prognostic factors were performed using Cox regression, and categorical prognostic factors were analyzed using the Kaplan–Meier and the log-rank methods. Variables at admission examined in univariate analysis included age, sex, race, primary renal disease, PDIMP registry year (before 2000 and after), CKD stage, weight-for-age Z score, height-for-age Z score, BMI Z score, uncontrolled hypertension, proteinuria, and hematuria. Baseline laboratory tests were also evaluated: eGFR, hemoglobin, serum calcium, serum phosphorus, and serum albumin. The Cox proportional hazards model was applied to identify variables that were independently associated with progression to ESRD. Only variables that were associated with the event of interest by univariate analysis ($P<0.25$) were included in the initial Cox regression model. Then, using a backward elimination strategy, we included in the final model variables that retained a significant independent association. Possible interactions between variables that remained in the final model were evaluated, including interaction terms in the model. Proportional hazard assumption was checked graphically by log–log versus time plots for each variable (25,26).

A predictive model was then constructed from these data by dividing each $\beta$ coefficient in the final multivariable model with significant predictors by the lowest $\beta$ coefficient. The $\beta$ coefficients were used for factor weighting; points were assigned to each independent prognostic factor, their coefficients being rounded to the nearest integer (27,28). Finally, a prediction score was calculated for each patient by summing up the points. The prognostic score derived was then grouped into three categories: low-risk, medium-risk, and high-risk groups. We assessed the predictive accuracy of the derived model by looking at the components of accuracy (i.e., discrimination and calibration) (27–30). Discrimination was evaluated using the c statistic, which represents the area under the receiver-operating characteristic curve (for which larger values indicate better discrimination) (31). To assess model calibration, or how closely the predicted probabilities reflect actual risk, observed risk was calculated on the basis of 2, 5, and 10 years of follow-up. We used Kaplan–Meier univariate survival analysis by comparing observed and predicted risk in each of the three categories of risk for the outcome (low risk, medium risk, and high risk) (32–34). Calibration was also assessed graphically by a Kaplan–Meier plot of renal survival for patients in different risk groups (35). To adjust for overfitting and overoptimistic performance of the model, we performed an internal validation of our model with a bootstrapping technique (36). In each bootstrap sample, the entire modeling process was repeated, resulting in shrinkage of the regression coefficients when applicable (27,29,37).

All reported $P$ values are two sided, and a $P$ value $<0.05$ was considered to represent a statistically significant difference.

Ethical Aspects
The Ethics Committee of the Federal University of Minas Gerais approved the study and the parents or persons responsible for the children gave written informed consent to participate.

Results
Baseline Findings
A total of 147 patients (82 boys) with predialysis CKD were included in the analysis. The median eGFR at admission was $37\,\text{ml/min per 1.73 m}^2$ (IQR, 23.8–47.2 ml/min per 1.73 m$^2$). The most prevalent disorders were congenital anomalies of the kidney and urinary tract (CAKUT) (59.9%). Posterior urethra valves were the predominant pathology, with 24 (16.3%) cases, followed by vesicoureteral reflux, neurogenic bladder, and FSGS, with 20 (13.6%), 18 (12%), and 15 (10%) patients, respectively. The median age at admission was 9 years (IQR, 2–13 years). A majority of patients ($n=79\,[33.7\%]$) were in
Table 1. Baseline clinical characteristics of 147 children and adolescents admitted to a predialysis interdisciplinary program

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>82 (55.8)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (44.2)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80 (50.4)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>67 (45.6)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>0−2 yr</td>
<td>33 (22.4)</td>
</tr>
<tr>
<td>2−5 yr</td>
<td>19 (12.9)</td>
</tr>
<tr>
<td>5−10 yr</td>
<td>27 (18.4)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>68 (46.3)</td>
</tr>
<tr>
<td><strong>Primary renal disease</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital nephrouropathies</td>
<td>88 (59.9)</td>
</tr>
<tr>
<td>GN</td>
<td>30 (20.4)</td>
</tr>
<tr>
<td>Cystic diseases/tubular disorders</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>9 (6.1)</td>
</tr>
<tr>
<td><strong>CKD stage</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>13 (8.8)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>79 (53.7)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>55 (37.4)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>69 (46.9)</td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>53 (36.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>25 (17.0)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>58 (39.5)</td>
</tr>
<tr>
<td>Present: controlled hypertension</td>
<td>58 (39.5)</td>
</tr>
<tr>
<td>Present: uncontrolled hypertension</td>
<td>31 (21.0)</td>
</tr>
<tr>
<td><strong>Z score for height/age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;−3.0</td>
<td>41 (27.9)</td>
</tr>
<tr>
<td>−2.99 to −2.0</td>
<td>39 (26.5)</td>
</tr>
<tr>
<td>−1.99 to −1.0</td>
<td>38 (25.8)</td>
</tr>
<tr>
<td>&gt;−1.0</td>
<td>29 (19.7)</td>
</tr>
</tbody>
</table>

CKD stage 3 at admission. Table 1 summarizes the clinical and demographic data of the patients at admission.

The median follow-up time was 53 months (IQR, 23.3–94.5 months). Of 147 patients, 72 (49%) progressed to CKD stage 5, with a median eGFR of 11.6 ml/min per 1.73 m² (IQR, 10–14 ml/min per 1.73 m²). Survival analysis estimated that the probability of CKD stage V was 12%, 35%, and 56% at 1, 5, and 10 years after admission, respectively. The estimated median renal survival time was 98.7 months (95% confidence interval [95% CI], 67.8 to 129.5 months). The laboratory evaluation at last visit revealed a median eGFR of 40.6 ml/min per 1.73 m² (IQR, 28–55 ml/min per 1.73 m²) for patients who did not progress to ESRD.

Univariate Survival Analysis

Univariate analyses suggested that the following variables were possibly associated with the progression to ESRD: nonwhite ethnicity (hazard ratio [HR], 1.67; 95% CI, 1.03 to 2.69; P=0.03), GN as primary renal disease (HR, 20.8; 95% CI, 4.6 to 93.9; P<0.001), CKD stage 4 at admission (HR, 4.82; 95% CI, 1.15 to 20.1; P=0.03), severe proteinuria (HR, 8.4; 95% CI, 3.9 to 11.8; P<0.001), uncontrolled hypertension (HR, 1.65; 95% CI, 0.98 to 2.76; P=0.07), and age at admission per 5 years (HR, 1.55; 95% CI, 1.24 to 1.94; P<0.001). Figure 1 illustrates the association between glomerular disease and progression of CKD to ESRD. In univariate analysis, the median renal survival was only 23 months (95% CI, 3.1 to 4.5 months) for patients with glomerular disease versus 122 months (95% CI, 91.2 to 152.3 months) for children with other primary diseases. The following baseline laboratory tests were also included in the unadjusted model: hemoglobin (HR, 0.92; 95% CI, 0.82 to 1.03; P=0.13), serum calcium (HR, 0.82; 95% CI, 0.66 to 1.01; P=0.06), serum albumin (HR, 0.52; 95% CI, 0.39 to 0.67; P<0.001), serum creatinine (HR, 2.33; 95% CI, 1.86 to 2.92; P<0.001), eGFR (HR, 0.97; 95% CI, 0.96 to 0.99; P=0.003), and BMI Z score (HR, 1.18; 95% CI, 0.94 to 1.48; P=0.16).

Multivariate Survival Analysis

In multivariate analysis, after adjustment by the Cox regression model, three variables remained as independent predictors of ESRD: baseline eGFR (as a continuous variable), proteinuria (as a dichotomous variable), and primary renal disease (as a dichotomous variable) (Table 2). The shrinkage factor obtained from bootstrap results was 0.9429 (Table 2).

A prognostic weighting was derived for each variable by dividing each β coefficient by the lowest β. The highest prognostic weighting for a dichotomous variable was severe proteinuria (5 points). GN had a weighting of 3 points. Basal eGFR levels were divided into six categories: 0 points (>70 ml/min per 1.73 m², reference); 1 point (59–69.9 ml/min per 1.73 m²), 2 points (48–58.9 ml/min per 1.73 m²), 3 points (37–47.9 ml/min per 1.73 m²), 4 points (26–36.9 ml/min per 1.73 m²), and 5 points (15–25.9 ml/min per 1.73 m²). Finally, a total prognostic risk score was calculated as the sum of these weightings for the three variables. A risk score was calculated for each patient by adding up these points. Risk score ranged from 0 for patients without risk factors and eGFR>70 ml/min per 1.73 m² to 13 points for patients with all risk factors and eGFR<25.9 ml/min per 1.73 m² (median, 4 points). The accuracy of the score applied to the sample was high, with a c statistic of 0.86 (95% CI, 0.79 to 0.93), 0.84 (95% CI, 0.76 to 0.91), 0.75 (95% CI, 0.65 to 0.86), and 0.73 (95% CI, 0.57 to 0.89), with a follow-up of 2, 5, 10, and 15 years, respectively (Figure 2).

Finally, the prognostic risk score was divided into three categories: low risk (≤4 points), medium risk (5–7 points), and high risk (8–13 points) for progression to ESRD. Of 147 patients, 82 (56%) were classified as low risk, 40 (27%) were classified as medium risk, and 25 (17%) were classified as high risk. Figure 3 shows calibration plots for the model of risk prediction according to follow-up time (2, 5, 10, and 15 years). The model demonstrated better calibration for 2 and 5 years of follow-up for all risk categories, while plots for 10 and 15 years had larger deviations between the observed and predicted probabilities with a systematically overrated renal survival for all risk categories (Figure 3). Model calibration was also assessed by survival analysis (Figure 4). The median renal survival was estimated at 135 months (95% CI, 110 to 159 months), 80 months (95% CI, 26.7 to 133.3 months), and 16.3 months (95%, 5.2 to 27.3 months) for patients assigned to the low-risk, medium-risk, and high-risk groups, respectively (P<0.001). By survival analysis it was estimated that at
10 years after admission, the probability of renal survival was about 63% for patients in the low-risk group and 43% for patients in the medium-risk group; all patients assigned to the high-risk group were in CKD stage 5 ($P < 0.001$).

**Discussion**

In this retrospective cohort study, we investigated possible predictive factors associated with the progression of CKD in a series of pediatric patients after enrollment in the PDIMP. In addition, we have developed a risk prediction model for the occurrence of ESRD in this population. Of particular interest, we were able to develop a model with good accuracy and satisfactory calibration, especially for the first 5 years after admission to our program.

Our sample is similar to several published series of pediatric patients with CKD. As expected, the most prevalent primary renal disease was CAKUT. Harambat *et al.* (1), in a comprehensive review, showed that the main causes of pediatric CKD included CAKUT (48%), hereditary kidney diseases (10%), and GN (14%). CAKUT and hereditary disorders predominate among younger patients, and GN is more prevalent in patients older than age 12 years. A similar distribution of causes of pediatric CKD was registered in European countries, such as Italy and Belgium (38,39). However, as Harambat *et al.* point out (1), children with CAKUT present a slower progression of CKD than those with glomerular diseases, resulting in a lower proportion of CAKUT in the population of children with ESRD. Of particular interest, our findings illustrate this point because GN as primary renal disease was an independent predictor of ESRD. Moreover, the median renal survival for patients with nonglomerular diseases was about five times greater than for children with GN.

According to our univariate analysis, patients who progressed significantly faster to ESRD were older children of nonwhite ethnicity, with glomerular diseases, who were at CKD stage 4 at admission, and with severe proteinuria. Among the continuous variables, age, baseline serum albumin, and eGFR were significantly associated with the outcome. In addition, hemoglobin, serum calcium, and BMI Z score at admission were also included in multivariate analysis. After adjustment by the Cox proportional hazard model, only three variables remained as predictors of outcome: eGFR, severe proteinuria, and GN as primary kidney disease. Few studies have investigated predictive factors of progression of CKD in the pediatric population (40,41). Interestingly, our findings agree with those of a recent study by Staples *et al.* (17) that evaluated a larger series of 4166 pediatric patients from the North American Pediatric Renal Trials and Cooperative Studies CKD database. These investigators showed that the factors, which independently correlated with the progression of CKD, were age at admission, CKD stage, primary renal disease, hypertension,
anemia, hypoalbuminemia, hyperphosphatemia, hypocalcemia, and the use of erythropoietin and growth hormone. These factors are quite similar to our findings in univariate analysis, in which most of these variables were also associated with the emergence of ESRD. Possibly, the variation in the magnitude of the samples accounts for the difference in variables, which remained significant after adjustment by the proportional hazard model. For instance, uncontrolled hypertension did not remain in the final model, although our patients with uncontrolled hypertension have a double risk of progression to ESRD. It should be emphasized that controlled studies have shown that strict control of BP, with around 50th percentile values, has a strong effect on the delay of deterioration of renal function, especially in patients with GN (42).

Severe proteinuria was a predictor of deterioration of renal function in our analysis, even in patients with nonglomerular diseases, thus confirming its importance as an independent factor in the progression of CKD. Interestingly, studies focused on children with nonglomerular diseases also observed that the level of proteinuria at baseline was associated with ESRD (40,43,44). Our finding is also in agreement with those of previous studies in adult and pediatric populations, in which proteinuria levels at baseline were consistently associated with progression of CKD (43,45). For instance, in 1997, Wingen et al. (46) reported that high-grade proteinuria at baseline was associated with a faster decline in renal function. In a cross-sectional study including 366 children with CKD, Wong et al. (47) reported that the prevalence of proteinuria increased with CKD severity.

Figure 2. | Receiver-operating characteristic curves estimated for evaluating the capacity of discrimination of the risk score to predict ESRD. (A) Up to 2-year follow-up (134 patients, 27 events, c=0.86). (B) Up to 5-year follow-up (116 patients, 46 events, c=0.84). (C) Up to 10-year follow-up (87 patients, 62 events, c=0.75). (D) Up to 15-year follow-up (75 patients, 70 events, c=0.73). The dotted lines represent the 95% confidence intervals.
Recently, they have shown that the level of proteinuria tended to be higher as the level of iohexol-based GFR decreased, irrespective of the cause of CKD (48). In a study of 176 children with CKD secondary to renal dysplasia and CAKUT, González Celedón et al. (40) found that patients with a Up/Uc ratio > 200 mg/mmol deteriorated faster than those with a Up/Uc ratio < 50 mg/mmol.
Our study has proposed the development of a clinical predictive model of progression to ESRD in a selected pediatric population. These patients were then classified into low-, medium- and high-risk groups, with the median time for progression to ESRD of about 16, 80, and 135 months, respectively. Recently, in a Canadian study with a large adult population with moderate to severe CKD, Tangri et al. (16) developed a predictive model of risk for ESRD. In their analysis, the model with better accuracy included the following variables: age, sex, eGFR, albuminuria, serum calcium, phosphorus, bicarbonate, and albumin (c statistics of 0.92). In this context, it is important to point out that the causes of CKD in adults are very different from those observed in children and can account for model differences.

Our study has some limitations, and several methodologic considerations should be taken into account in evaluating our findings. First, we did not validate this risk prediction instrument in an independent cohort. Second, our relatively small sample consisted of a pediatric population followed up at a tertiary center. Therefore, our conclusions should be applied to similar samples. In addition, we were not able to systematically analyze time-dependent variables, such as hypertension and proteinuria, that might contribute to the prediction of renal outcome (17,19,49). Finally, in our study, we were only able to estimate the survival times. Despite the long follow-up time of our cohort, this period was shorter than the median survival time reported for many groups. However, some features of the study can increase the strength of our survival time reported for many groups. However, some features of the study can increase the strength of our findings, such as the large set of data collected over many years, the number of events, and the long-term follow-up by an interdisciplinary team with a well established protocol.

In conclusion, we have developed a predictive model for ESRD in children with CKD (27,29,36). Our model uses routinely available clinical, laboratory, and imaging data and can predict the long-term risk for renal impairment with accuracy. Furthermore, our predictive model may assist professionals involved in the care of these patients, who may possibly establish appropriate measures for each risk group. External validation in large prospective cohorts is clearly needed.

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Disclosures
None.

References