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ORIGINAL ARTICLE

Posterior Urethral Valves Outcomes Prediction (PUVOP): a machine learning tool to predict clinically relevant outcomes in boys with posterior urethral valves

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Abstract

Background Early kidney and anatomic features may be predictive of future progression and need for additional procedures in patients with posterior urethral valve (PUV). The objective of this study was to use machine learning (ML) to predict clinically relevant outcomes in these patients.

Methods Patients diagnosed with PUV with kidney function measurements at our institution between 2000 and 2020 were included. Pertinent clinical measures were abstracted, including estimated glomerular filtration rate (eGFR) at each visit, initial vesicoureteral reflux grade, and renal dysplasia at presentation. ML models were developed to predict clinically relevant outcomes: progression in CKD stage, initiation of kidney replacement therapy (KRT), and need for clean-intermittent catheterization (CIC). Model performance was assessed by concordance index (c-index) and the model was externally validated.

Results A total of 103 patients were included with a median follow-up of 5.7 years. Of these patients, 26 (25%) had CKD progression, 18 (17%) required KRT, and 32 (31%) were prescribed CIC. Additionally, 22 patients were included for external validation. The ML model predicted CKD progression (c-index = 0.77; external C-index = 0.78), KRT (c-index = 0.95; external C-index = 0.89) and indicated CIC (c-index = 0.70; external C-index = 0.64), and all performed better than Cox proportional-hazards regression. The models have been packaged into a simple easy-to-use tool, available at https://share.streamlit.io/jcckwong/puvop/main/app.py

Conclusion ML-based approaches for predicting clinically relevant outcomes in PUV are feasible. Further validation is warranted, but this implementable model can act as a decision-making aid.

Keywords Posterior urethral valve · Machine learning · Chronic kidney disease · Dialysis · Transplant · Catheterization

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Introduction

Posterior urethral valves (PUV) remain a frequent cause of pediatric kidney insufficiency, resulting in chronic kidney disease (CKD) in one-third of patients [1–3] and kidney failure requiring kidney replacement therapy (KRT) in one-fifth of patients [4, 5]. Due to valve bladder syndrome and inevitable myogenic failure, one quarter will require assistance with bladder emptying via clean intermittent catheterization (CIC) [6]. Determining predictors for progressive kidney and bladder deterioration, as well as an estimate for when it might occur, is of timely importance as this can help risk stratify patients and provide personalized follow-up regimens [7]. Previous studies have shown multiple risk factors for progression to CKD in PUV, including serum nadir creatinine at 1 year of life, proteinuria, vesicoureteral reflux (VUR), and abnormal ultrasound findings (loss of corticomedullary differentiation, abnormal renal cortex) [2, 8–11]. However, it remains challenging to predict individual patient outcomes from numerous risk factors in clinical practice to achieve personalized care from an early age.

Machine-learning (ML) has led to improvements in personalized medicine and can help providers individualize treatment. For example, ML has been used in pediatric urology to classify renal abnormalities [12], predict which patients with VUR may benefit from antibiotic prophylaxis [13], and predict late-presenting PUV [14]. To date, ML-based methods have not been used to predict the prognostic course of patients with PUV and personalize their longitudinal management [15].

The aim of this study was to predict progressive decline in kidney function and need for additional interventions in boys with PUV. Herein, we present a ML learning-based approach, using early clinical and imaging features to predict CKD progression-free, KRT-free, and CIC-free survival for PUV patients that is easy-to-use for clinicians.

Materials and methods

Study design and participants

Following institutional research ethics board approval, a retrospective cohort study was conducted using medical records of patients diagnosed with PUV at our institution between 2000 and 2020. At our institution, PUV patients were typically followed every 6–12 months. Patients were excluded if follow-up estimated glomerular filtration rate (eGFR) data was unavailable, if they did not have at least 1-year of follow-up, or if prenatal features and imaging were unavailable. External validation was conducted with patients treated for PUV at the Children's Hospital of Philadelphia (Philadelphia, PA).

Measures and definitions

Kidney function and CKD were approximated with eGFR, calculated using the bedside Schwartz formula [16], at each study visit. For patients diagnosed before the age of one, eGFR at 1 year was used as baseline function while eGFR at presentation was used in late-presenting patients (i.e. presenting later than 1 year). Renal dysplasia was defined as radiology reporting "dysplasia" or "cortical cysts," poor corticomedullary differentiation, or increased echogenicity at the time of PUV presentation or neonatal period. VUR grade was determined at the initial voiding cystourethrogram and high-grade VUR was defined as tortuous grade 4 and above. The need for KRT, prenatal, and newborn variables were abstracted from patient medical records. Primary valve ablation is favored as the initial surgical intervention in our institution; however, if the infant is too small for instrumentation, a vesicostomy or higher diversion may be offered. Serum nadir creatinine in the first year after diagnosis (SNC1), the lowest creatinine within 1 year of diagnosis, was abstracted for all patients within 1 year of PUV presentation. SNC1 was further stratified into three groups (<0.40, 0.4–0.69, >0.70 mg/dL), in line with prior studies [6]. A sensitivity analysis was conducted between patients with PUV presentation in the first year of life vs. late presentation to assess validity. A data dictionary describing each variable is provided in Supplementary Table 1.

Outcomes and analysis

CKD progression was defined as worsening CKD stage over at least two kidney function measurements, 90 days or greater apart, than the previous stage. When height/length was missing for a given time point, it was estimated based on the height percentile curves using available heights from other visits. KRT was defined by the initiation of dialysis or kidney transplant for the patient with the earliest time used in this analysis. CIC is typically indicated when there is deterioration of kidney function, worsening hydroureteronephrosis, or incontinence.

The outcomes of interest are included as follows: (1) CKD progression-free survival, defined as a progression in CKD stage compared to baseline eGFR on initial clinic assessment around 1 year of life; (2) KRT-free survival, defined as initiation of dialysis or kidney transplantation; and (3) CIC-free survival, defined as CIC prescription. Standard statistical analysis was conducted on SPSS v.26 (IBM) and MATLAB 2020a.

Machine learning model, reference standard, and evaluation

A random survival forest model was selected for model training [17]. This is an ensemble model that builds individual survival trees using a bootstrap sample of the whole dataset. A cumulative hazard function is calculated for each tree and the final hazard function is based on the average of each survival tree. The model was built using an 80:20 train-test split, in which 80% of the data was used for training, while the remaining 20% was used for performance evaluation. Additional model details are provided in the Supplementary Materials. Feature importance was determined by a Gini impurity to identify which features had the greatest impact on model predictions.

A Cox proportional-hazards regression model using the same variables included in the machine learning model was used as the reference standard, herein referenced as the baseline model (Supplementary Materials). Model performance was assessed by concordance index (c-index).

Results

Study population

A total of 152 patients were diagnosed with PUV at our institution between 2000 and 2020, for which baseline eGFR, complete prenatal findings, and adequate follow-up were achieved in 103 patients (Table 1). Patients had follow-up over 5.7 years (IQR 2.8, 10.1) after initial kidney function assessment.

Worsening kidney function and interventions

The baseline eGFR at 1 year or at presentation was 82.0 (IQR 59, 100) with 73% of patients initially at CKD stage 3 or better. At initial VCUG, 57% of patients had high-grade VUR (i.e. grade 4 or 5) and 32% had renal dysplasia. At latest follow-up of 5.7 years (IQR 2.8, 10.1), the median eGFR increased to 91.9 (IQR 45, 114, $p = 0.17$). Initially, 27% patients had CKD stage 3 or worse. However, 26 patients (25%) had progression in CKD stage; 18 patients (17%) required KRT. Due to worsening bladder function, 32 patients (31%) were prescribed CIC.

On survival analysis, high-grade VUR was found to increase the rate of CKD progression while low baseline eGFR and renal dysplasia were not significant effectors of CKD progression (Fig. 1). Low baseline eGFR and high-grade VUR increased the rate of KRT while renal dysplasia was not significant (Fig. 2). Low baseline eGFR was associated with an increased rate of CIC while high-grade VUR and renal dysplasia were not significant (Fig. 3). Of the 58 patients with high-grade VUR, 31 had bilateral involvement and subgroup analysis did not show difference in CKD progression ($p = 0.48$), KRT initiation ($p = 0.71$), or CIC prescription ($p = 0.76$) between unilateral vs. bilateral VUR groups (Supplementary Fig. 1).

Table 1 Baseline characteristics of study population

		Toronto, ON (n = 103) [training]		Philadelphia, PA (n = 22) [external validation]	
		N, median	%, IQR	N, median	%, IQR
Age at diagnosis (days)		13	3, 67	6	2, 265
Late presentation of PUV (> 1 year)		16	16%	5	23%
Age at baseline eGFR (years)		1.0	0.9, 1.2	1.0	0.9, 1.8
Follow-up duration (years)		5.7	2.8, 10.1	4.5	3.2, 9.2
Baseline eGFR (mL/min/1.73 m^2)		82.0	59, 100	66.5	32.6, 107.8
eGFR at follow-up (mL/min/1.73 m^2)		91.9	45, 112	79.5	36.8, 110.2
SNC1 (mg/dL)	< 0.40	64	62%	10	45%
	0.40–0.69	24	23%	8	36%
	> 0.70	15	15%	4	18%
CKD stage 3 or better at baseline		75	73%	9	41%
Maximum VUR Grade	No VUR	37	36%	-	-
	Grade 1–3 (Low)	8	2%	-	-
	Grade 4–5 (High)	58	57%	9	41%
Renal dysplasia at presentation/neonatal period		33	32%	21	95%
CKD progression (≥ 1 stage change)		26	25%	2	9%
Initiation of kidney replacement therapy (dialysis or transplant)		18	17%	3	14%
Need for clean intermittent catheterization		32	31%	2	9%

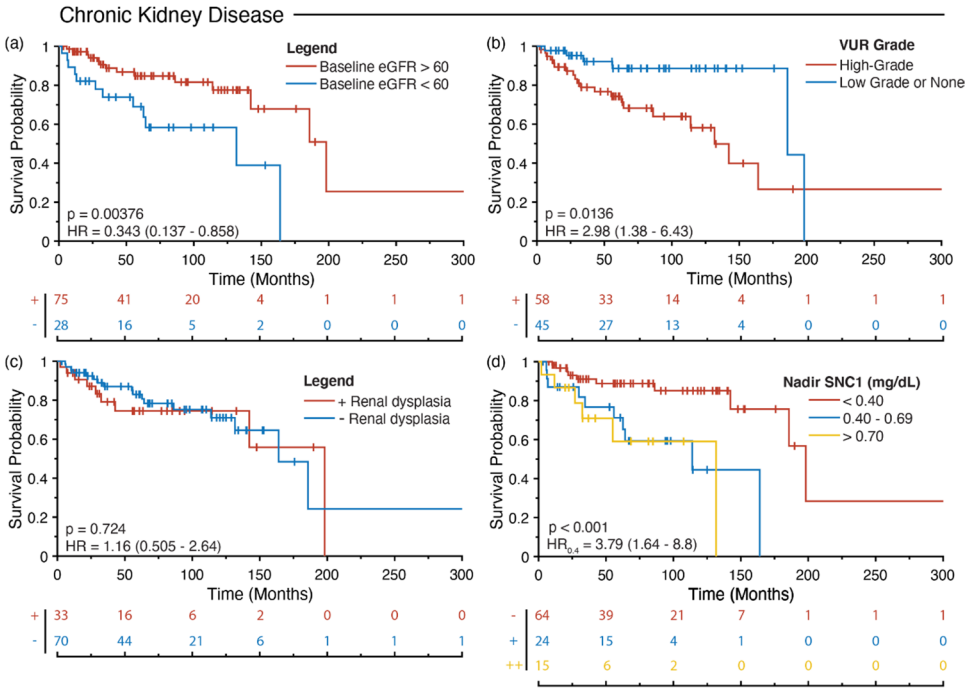

Fig. 1 Kaplan–Meier plots for chronic kidney disease progression compared between groups by (**a**) baseline eGFR, (**b**) high vs. low/no VUR grade, (**c**) renal dysplasia, and (**d**) SNC1 (*p* value given for two-group comparison)

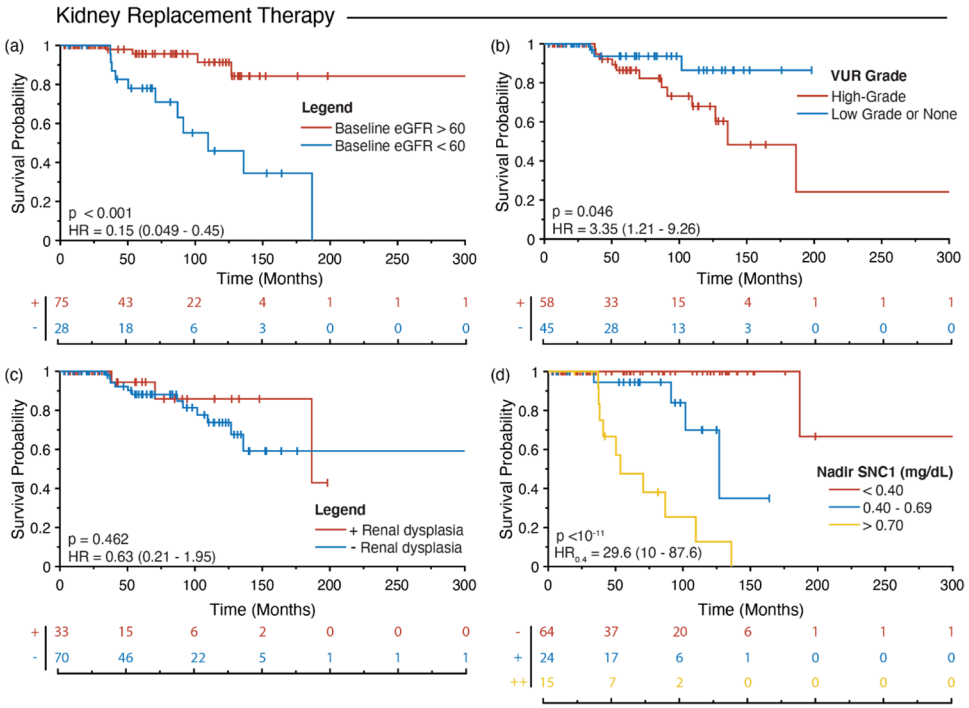

Fig. 2 Kaplan–Meier plots for initiation of kidney replacement therapy compared between groups by (**a**) baseline eGFR, (**b**) high vs. low/no VUR grade, (**c**) renal dysplasia, and (**d**) SNC1 (*p* value given for two-group comparison)

For the SNC1, there was a significant difference in the rate of CKD ($p = 0.001$), KRT ($p < 0.001$), and CIC ($p = 0.001$) comparing groups based on SNC1 (Fig. 1–3d). When excluding 28 patients with SNC1 after the age of one for sensitivity analysis, the between-group difference was still significant for CKD progression ($p < 0.001$), KRT ($p < 0.001$), and CIC ($p = 0.036$).

Final model and model performance

The survival models were based on baseline eGFR, presence of high-grade VUR, presence of renal dysplasia, and SNC1 (Table 2).

For CKD progression-free survival, the ML model achieved a c-index of 0.765 compared to 0.714 for the

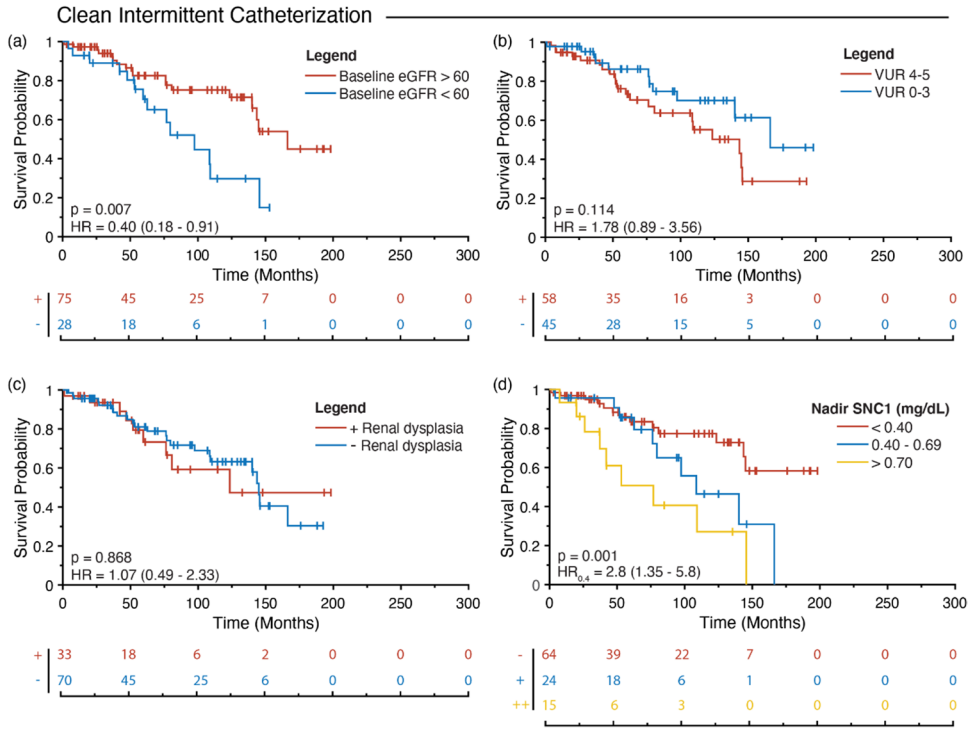

Fig. 3 Kaplan–Meier plots for treatment with clean intermittent catheterization compared between groups by (**a**) baseline eGFR, (**b**) high vs. low/no VUR grade, (**c**) renal dysplasia, and (**d**) SNC1 (*p* value given for two-group comparison)

Table 2 Feature importance for chronic kidney disease progression, kidney replacement therapy, and clean intermittent catheterization-free survival models. The hazard ratios (HR) and *p* values are listed for the Cox proportional hazards regression model, while the percent importance by Gini impurity is provided for the machine learning model

Feature	HR (95% CI)	p value for HR	Percent importance
Chronic kidney disease progression			
Baseline eGFR	0.99 (0.97–1.00)	0.10	0.19
High-grade VUR	2.48 (0.96–6.41)	0.06	0.00
Renal dysplasia	1.51 (0.64–3.57)	0.35	0.81
Serum nadir creatinine at 1 year of follow-up	1.23 (0.45–3.34)	0.68	0.00
Kidney replacement therapy			
Baseline eGFR	0.99 (0.96–1.01)	0.37	0.28
High-grade VUR	3.02 (0.57–16.06)	0.19	0.00
Renal dysplasia	1.21 (0.29–5.06)	0.80	0.00
Serum nadir creatinine at 1 year of follow-up	6.06 (1.76–20.90)	< 0.01	0.72
Clean intermittent catheterization			
Baseline eGFR	1.00 (0.98–1.01)	0.58	0.28
High-grade VUR	1.54 (0.69–3.44)	0.29	0.05
Renal dysplasia	1.30 (0.57–2.95)	0.53	0.13
Serum nadir creatinine at 1 year of follow-up	1.83 (0.71–4.72)	0.21	0.54

eGFR, estimated glomerular filtration rate; *HR*, hazard ratio; *VCUG*, voiding cystourethrogram; *VUR*, vesicoureteral reflux

baseline model. Renal dysplasia and baseline eGFR were the most important features for the ML model, although none reached statistical significance for the baseline model. For KRT-free survival, the ML model achieved a c-index of 0.952 compared to 0.894 for the baseline model. SNC1 was the most important feature for both the ML and baseline model. For CIC-free survival, the ML model achieved a c-index of 0.700 compared to 0.647 for the baseline model. SNC1 was the most important feature for the ML model, although none reached statistical significance for the baseline model.

External validation was conducted on available data from 22 patients treated for PUV at the Children's Hospital of Philadelphia (Philadelphia, PA) meeting the same inclusion

criteria (Table 1). The model achieved a c-index of 0.784 for CKD progression-free survival, 0.887 for KRT-free survival, and 0.639 for CIC-free survival which are in strong agreement with the achieved c-index from holdout validation.

All survival models were packaged into a simple-to-use tool, available at https://share.streamlit.io/jcckwong/puvop/main/app.py

Discussion

Predicting worsening kidney function and need for CIC in patients with PUV is critical in providing appropriate and timely management, as well as when counselling families. Although risk factors for CKD have been well-established, they are difficult to apply in clinical practice for individualized care. Given that the degree of obstruction in PUV is variable, the effects on renal reserve and bladder function fall within a spectrum. For some boys with PUV, both CIC and worsening kidney function may be inevitable; therefore, being able to provide an estimate of when these outcomes may occur provides the opportunity for individualized family discussions and expectant management. Here, we demonstrate the feasibility of a ML-based model in predicting decline in kidney and bladder function in an easily implementable tool to aid in decision-making and family counselling.

In the present study, we found that 25, 17, and 32% of PUV patients developed CKD progression, required KRT, and initiated CIC, respectively, which is in keeping with previous studies [6, 18]. Most literature has shown serum creatinine and derivatives thereof to be the most robust predictors of worsening function, which agrees with our ML-model. Serum nadir creatinine within the first year of life is a well-established prognostic factor for adverse kidney outcomes [6, 10, 19]. This is reflected well in our study, in which SNC1 was among the strongest predictors for all three ML-models. Previous studies have also shown VUR [10] and renal dysplasia [2, 8] to be predictors for worsening kidney function. In our ML-model, VUR and renal dysplasia were important model features in the survival models outside of regular kidney function measures. This further stresses the role of careful imaging in the context of PUV to determine potential early risk factors for intervention. Here, with the use of clinically relevant outcomes in our model, this provides an estimation of need for intervention which can further risk-stratify patients for personalized care [20]. For example, our model suggests a patient with high-grade VUR, 0.5 mg/dL SNC, positive renal dysplasia, and eGFR of 60 mL/min/1.73 cm^2 will have a 3.8% risk of CKD progression, 0.2% risk of needing KRT, and 4.3% risk of being prescribed CIC within 3 years. As a decision-aid, a clinician could utilize ML-models to modify follow-up schedules for individual patients with significant risk of requiring additional therapy, as well as to guide discussions with families about long-term outcomes.

Personalized medicine will result in more accurate diagnoses and the development of individualized treatment regimens, and with the use of patient-specific risk factors, these models can be implemented in clinical practice. Easy-to-use ML tools provide a first step towards individualized care and can offer practical decision-aid compared to other clinical models. For example, Abdovic et al. (2019) developed an accurate ML-model which predicts late-presenting PUV with an easily accessible web tool [14]. Examples of fully implemented ML-based personalized medicine approaches in pediatric urology are still limited, but with the growing popularity and convincing results of ML in pediatric urology, there is great promise for future models [13, 15].

The findings of this study should be interpreted in the context of certain limitations. First, patients without adequate follow-up or baseline kidney function were excluded to ensure homogeneity in ML training, which limits the applicability of the findings to the true population where patients may be retained with worsening function while lost-to-follow up with symptom resolution. Additionally, the reporting of "renal dysplasia" is subjective to specific findings found in radiology reports which is not standardized across institutions, while the prescription of CIC is an outcome susceptible to care provider variation rather than strict clinical thresholds. Together, the subjective nature of some variables and outcomes may influence the generalizability of our model. Moreover, our final model was trained on 103 and tested on 22 unique patients, which is small for ML applications; however, this allowed for the identification of individual risk factors which would not be available in larger administrative datasets. Models trained on smaller datasets have a risk of overfitting and generalizability to the overall patient population, missing relevant features, and are prone to bias, especially towards patients included in the study [21]. Here, we do show strong agreement between two included institutions, but further external validation is warranted for more robust model predictions with multiple centers to ensure generalizability. Lastly, the use of eGFR, estimated from serum creatinine, as the measure of kidney function is contentious with improved GFR equations, cystatin-C based metrics, or other biomarkers of kidney dysfunction in pediatric patients [22, 23]. The aim of this model was to provide risk estimation of disease progression with information readily available in medical records, and we acknowledge that the accuracy can be improved with more sophisticated clinical inputs and larger datasets. For example, the use of kidney size and bladder wall thickness could be strong covariates that correlate with long-term outcomes and should be considered in future work [24, 25]. While we acknowledge the limitations of this model, this

work further establishes the predictive capacity of SNC1, VUR, and renal dysplasia as risk factors for PUV-associated symptoms and shows the first year after PUV diagnosis is a critical window. Without additional training, our ML-based model may improve family counselling and management for boys with PUV.

Conclusion

Use of ML algorithms to predict worsening kidney function and need for additional interventions in PUV patients is feasible. Our model was able to accurately predict CKD progression, initiation of KRT, and CIC prescription and can be freely accessed at https://share.streamlit.io/jcckwong/puvop/main/app.py. Further validation is warranted, but the use of ML-based approaches can help risk-stratify patients and individualize patient care.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-021-05321-3.

Author contribution All authors contributed to project development, data collection, data analysis, and manuscript writing.

Code availability Code used in this study is available upon request to the corresponding author.

Declarations

Research involving human participants This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Research and Ethics Board of The Hospital for Sick Children approved this study.

Informed consent Due to the retrospective nature of this study, informed consent was not required.

Competing interests The authors declare no competing interests.

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