World Journal of Urology (2022) 40:593–599
https://doi.org/10.1007/s00345-021-03879-z

ORIGINAL ARTICLE

Personalized application of machine learning algorithms to identify pediatric patients at risk for recurrent ureteropelvic junction obstruction after dismembered pyeloplasty

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Received: 22 July 2021 / Accepted: 2 November 2021 / Published online: 13 November 2021

Abstract

Purpose To develop a model that predicts whether a child will develop a recurrent obstruction after pyeloplasty, determine their survival risk score, and expected time to re-intervention using machine learning (ML).

Methods We reviewed patients undergoing pyeloplasty from 2008 to 2020 at our institution, including all children and adolescents younger than 18 years. We developed a two-stage machine learning model from 34 clinical fields, which included patient characteristics, ultrasound findings, and anatomical variation. We fit and trained with a logistic lasso model for binary cure model and subsequent survival model. Feature importance on the model was determined with post-selection inference. Performance metrics included area under the receiver-operating-characteristic (AUROC), concordance, and leave-one-out cross validation.

Results A total of 543 patients were identified, with a median preoperative and postoperative anteroposterior diameter of 23 and 10 mm, respectively. 39 of 232 patients included in the survival model required re-intervention. The cure and survival models performed well with a leave-one-out cross validation AUROC and concordance of 0.86 and 0.78, respectively. Post-selective inference showed that larger anteroposterior diameter at the second post-op follow-up, and anatomical variation in the form of concurrent anomalies were significant model features predicting negative outcomes. The model can be used at https://sickkidsurology.shinyapps.io/PyeloplastyReOpRisk/.

Conclusion Our ML-based model performed well in predicting the risk of and time to re-intervention after pyeloplasty. The implementation of this ML-based approach is novel in pediatric urology and will likely help achieve personalized risk stratification for patients undergoing pyeloplasty. Further real-world validation is warranted.

Keywords Pyeloplasty · Personalized medicine · Pediatrics · Machine learning

Introduction

Pyeloplasty is the mainstay surgical intervention to manage ureteropelvic junction obstruction (UPJO) in children, with success rates exceeding 90% [1–3]. However, up to

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10% of children will require re-intervention due to recurrent obstruction [3, 4]. Several factors can potentially explain the risk of recurrence, including combinations of perioperative variables, patient characteristics, and surgeon preferences [5–7]. Nevertheless, due to the variability in improvement and resolution of hydronephrosis (HN) post-pyeloplasty, it is challenging to predict which patients, individually, are at highest risk for this outcome early in the postoperative course, thus all children are closely monitored after surgery.

Personalized medicine (PM) is gaining popularity due to its unique ability to allow providers to modify treatment plans on an individual basis by allowing the opportunity to incorporate patient-specific factors into clinical care. PM has been revolutionized by the introduction of machine learning (ML) algorithms, which consider individual patient characteristics to predict specific outcomes or to highlight treatment plan modifications tailored to an individual patient's needs. For example, ML has been used for early prediction of cardiac arrests [8], onset of sepsis [9], and effectiveness of antibiotic prophylaxis in reflux [10]. The technology could be readily applied to pediatric urology patients with a history of UPJO by considering variables such as degree of HN, anteroposterior pelvic diameter (APD), patient weight [11], length of hospital stay post-surgery and operative time [4], and use them to help determine the risk of re-obstruction on a case-by-case basis. To our knowledge, ML has not previously been used in pediatric urology to predict an individual patient's risk of recurrent obstruction after pyeloplasty, taking into account multiple factors and exposures [12].

Herein, we describe a PM UPJO cure model trained with ML to predict whether a patient will develop a recurrent obstruction and undergo re-intervention. In addition, we present a tool which can determine individual risk scores for recurrence and expected time to re-intervention by exploring the role of patient factors and their impact on post-pyeloplasty outcomes.

Materials and methods

Following Research Ethics Board approval, the institutional prospectively maintained pyeloplasty database from March 2008 to January 2020 was reviewed. The typical clinical care pathway for pyeloplasty at our institution is provided (Supplementary Fig. 1) and an 'oblique pelvi-ureteric junction' cut was generally performed [13]. A two-stage ML model was developed: (1) a logistic lasso model for binary cure model and (2) a subsequent survival model to predict the likelihood of failure after pyeloplasty.

Outcome definition

The two outcomes of interest were (1) a UPJO "cure", which was defined as patients who had not received any additional procedures (such as balloon dilatation, ureteric stenting, laser endopyelotomy, or redo surgery) within 30 months and (2) the time-to-event of a redo pyeloplasty or additional operation (measured in months). This two-label approach was necessary to ensure that survival models were not inappropriately used to characterize patients that would never experience the event, as well as deriving a method to predict which patients would likely benefit from a risk stratification by the survival model.

Feature generation from clinical characteristics

The assessed clinical characteristics included: age, sex, baseline and follow-up preoperative APD (described in Supplementary Information), baseline/follow-up differential renal function, concurrent anomalies, peri-operative drains, catheters, stents, analgesia type (opioid, regional analgesia, non-opioid analgesia), nausea/vomiting prophylaxis, causes of UPJO (classic intrinsic obstruction vs. concurrent abnormalities/abnormal intraoperative findings), surgery features (e.g., approach, surgeon identifiers, operation time), post-operative measures (e.g., management, length of stay). The full set of included variables can be found in Supplementary Table 1.

The entire processing pipeline is available on a publicly accessible Github page (https://github.com/goldenberg-lab/Pyeloplasty). Our cure modelling approach categorized patients into one of three categories: confirmed cured patients (successful pyeloplasty), confirmed failed patients (who experienced a re-obstruction requiring re-intervention), and patients of an unknown status. The binary cure model is used to determine whether patients of an unknown status are put into the survival model. Patients who did not require a reoperation within 30 months were considered clinically "cured".

Machine learning analysis and evaluation

Our ML analysis involved two stages: (1) fitting a cure model to predict whether redo pyeloplasty would ever occur, (2) fitting a survival model on those patients who will experience the event or are likely to (as determined by stage 1). This two-stage approach was essential to ensure that the second-stage model had an actual survival distribution. Statistical models for survival analysis assume that the probability of the event approaches one with sufficient measurement time. Since most patients will not need to undergo re-intervention,

this assumption is violated. Similar to a mixture cure modelling approach [14], we used a classification task to determine whether a patient is likely to be "cured", in the sense that they will never experience the redo pyeloplasty event.

The binary classification and survival model were fit with a logistic and Cox lasso model, respectively [15, 16]. Leave-one-out (LOO) risk scores were calculated over a range of the model complexities parameter (lambda). The value of lambda that had the highest AUROC and concordance, respectively, was chosen for the final model. Inference around the point estimate was done with the bootstrap on the empirical quantiles. Parameter inference on the model coefficients was carried out using selective inference (SI) techniques designed for the lasso model [17, 18]. Decision curve analysis was used to determine the net benefit of the binary cure model [19].

Individualized survival curves, predicting risk of re-intervention, for two patients with low (− 1SD) and high (+1SD) post-operative APD was calculated to demonstrate feature effect in a practical setting. An online web-application was developed with R.

Results

A total of 565 pyeloplasties were identified during the defined study period, and of these 157 (29%) were female patients. The median age at pyeloplasty was 16 months (IQR 90). There were more left renal units (66%, 357/543) and 11 were bilateral. Median pre-operative and post-operative APDs were 23 mm (IQR 13) and 10 mm (IQR 9), respectively. Pre-operative and post-operative differential renal functions (for 135 patients with post-operative nuclear scan) were 45% (IQR 22) and 46% (IQR 22), respectively (Table 1). In 543 patients with a median follow-up period of 22 months (IQR 35), 39 patients required re-intervention (7.6%). Of the patients included in the analysis, the 39 patients with recurrent obstruction requiring re-intervention. Included 18 patients who required ureteral stent placements, 1 patient requiring balloon dilation and laser endopyelotomy, and 20 who required redo pyeloplasties (Supplementary Table 2).

Table 1 Summary of clinical characteristics

	All pyeloplasties ($n=565$)	
	N, median	%, IQR
Age at surgery (months)	16	90
Sex (male)	397	70.3%
Side (left)	357	63.2%
Anomalies		
Horseshoe kidney	11	1.9%
Solitary kidney	2	0.4%
Duplex	8	1.4%
Polyp	6	1.1%
Other	3	0.5%
Approach[a]		
Laparoscopic	184	32.6%
Robotic	13	2.3%
Lap-assisted	35	6.2%
Open	333	58.9%
OR time (min)	147	69
Baseline function (differential %)	45	22
Post-operative function (differential %)	46	22
Pre-operative AP diameter (mm)	23	13
Post-operative AP diameter (mm)	10	9
Follow-up duration (months)	22	35

[a]Lap-assisted surgery (whole dissection with laparoscopy, small flank incision to complete the anastomosis to permit external stent)

Model workflow

Of the 565 pyeloplasties included in the study, 543 procedures were included in the analysis (Fig. 1a) and data cleaning is described in Supplementary Information. Each observation fell into one of three categories: cured (193), failed (39), and unknown status (311 not yet at 30-month follow-up). The cured and failed patients were combined into a data set, and a model was first trained to predict which group they would be assigned based on their clinical variables. The probability scores from this first-stage model were used to assign the remaining 311 censored patients into either an assumed cured (100) or "persistent unknown status" (211) category. Given the small sample size, a generous cutoff of a cure probability less than or equal to 95% was determined to be clinically relevant to ensure sufficient variation in the clinical covariates of the survival mode (Supplementary Fig. 2). In addition, there was a large jump in the number of patients with probabilities above 95%, suggesting a natural breakpoint in the distribution. The failed and "persistent unknown status" patients were combined into a final survival data set (250).

Model performance

In the first stage cure model, 39 of 232 patients required re-intervention within 30 months of their initial pyeloplasty. The logistic lasso model performed well with a AUROC = 0.86 [95% CI: 0.80, 0.91] on LOO cross validation, as shown in Fig. 1b. The post-selection inference procedure showed significant results for two features: the cause for obstruction (classic intrinsic obstruction vs. UPJO with concurrent anomalies or abnormal intraoperative finding) and the second postoperative APD (see Fig. 1c). A larger

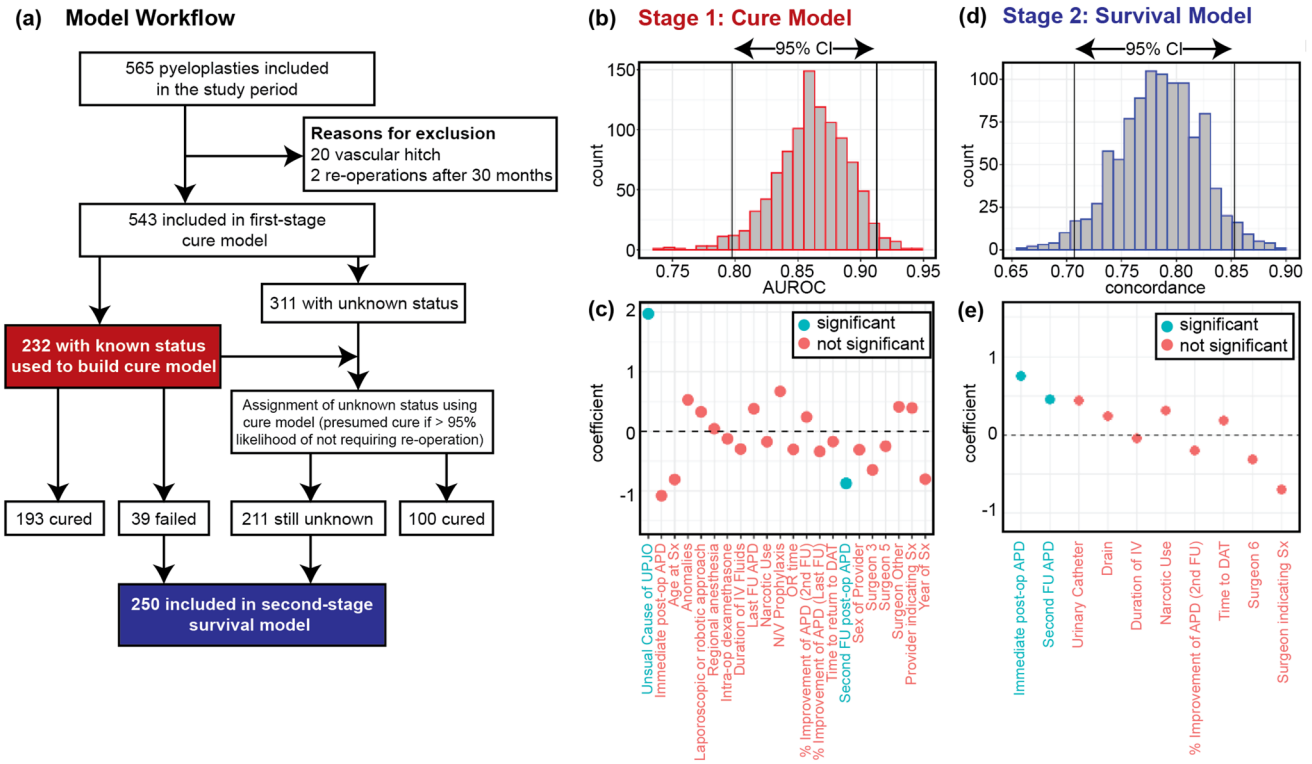

Fig. 1 **a** Flowchart of patients included in ML model and exclusions, **b** bootstrap distribution LOO-AUROC for all included patients in the cure model, and **c** significance of model input variables from post-selection inference in the cure model. **d** Bootstrap distribution LOO-concordance for patients included in the survival model, and **e** significance of model input variables from post-selection inference in the survival model

second APD measurement (coefficient = − 0.9) was associated with a decreased likelihood of being "cured", and "classic" causes of obstruction (coefficient = 2.0) was associated with a higher likelihood of being cured.

The model had a higher net benefit than a treat-all strategy for clinically relevant probability cutoffs for UPJO cure between 80 and 95% (Supplementary Fig. 3). For example, using a cutoff of 90% probability of cure, this strategy results in 28 more patients who can safely avoid intervention per 100 patients compared to a treat-all strategy. The model also demonstrated excellent discrimination when stratified based on year of surgery, gender, age, kidney laterality, surgeon, and surgical approach (Supplementary Table 3).

A total of 250 patients with less than a 95% probability of cure were included in the second-stage survival model. The survival model predicted the time to re-intervention with a concordance of 0.78 [95% CI 0.71, 0.86], as shown in Fig. 1d, on LOO cross validation. A larger APD immediately post-operatively and at second follow-up (coefficient = 0.5) was associated with a reduced likelihood of cure, and the latter was associated with quicker time to re-intervention.

We developed an R-shiny web application which estimates individualized survival from features in this work, freely available at https://sickkidsurology.shinyapps.io/PyeloplastyReOpRisk/. This web-applications integrates APD measurements and clinical features described in this work and source code is openly available (https://github.com/goldenberg-lab/Pyeloplasty).

Discussion

The high success rate of pyeloplasty has been well documented, but it is important to determine predictors for failure in the approximately 5–10% of patients who require re-intervention [1–3]. Risk factors for recurrent UPJO requiring re-interventions have been previously suggested in observational studies and include unique anatomical findings of crossing vessels, long ureteral strictures, ureteral kink, kidney laterality, post-operative adhesions, and markedly redundant renal pelvis [3, 5, 20]. Patient characteristics such as patient age [21], weight, or length of hospital stay also play a role [4]. However, small sample size and limited number of available variables make it difficult to recognize which child is at higher risk of failed pyeloplasty. Two recent studies used multivariable regression to show low weight, intraoperative complications, and comorbidities were associated with increased postoperative complications [6]. However,

these studies do not attempt to predict pyeloplasty failure. Our ML model defined risk factors and emphasized interactions between them which reaches toward personalized risk stratification for the clinically relevant outcome of pyeloplasty success.

Proof of concept with anteroposterior diameter

Artificial intelligence is gaining popularity in pediatric urology [12]. ML approaches have been used to classify different kidney diseases, predict renal abnormalities, and to predict the likelihood of surgical intervention [12, 22, 23]. Zheng et al. used transfer and deep learning to classify congenital kidney abnormalities from ultrasound findings and our institution has published the use of neural networks to predict surgical intervention and the likelihood of obstruction in children [12, 23, 24]. In pediatric urology, ML-based models have been used to predict outcomes at different timepoints, but the work here is the first combination of an ML-based binary cure and forecasted survival model for pyeloplasty [25]. However, due to the inherent issues with explainability in ML, and the expertise required to develop and train models, the usability and interoperability have limited their translation into clinical practice [26]. The technique described in the present study is unique in that we used a two-stage model to predict which patients will have recurrent UPJO and the individual time to failure using routinely collected clinical variables. For example, Supplementary Fig. 4 shows the likelihood of redo pyeloplasty over 30 months after initial surgery for two individual patients, with low (6 mm) vs. high (30 mm) post-operative APD (fixing all other variables to be equal), respectively, which emphasizes the association of post-operative APD and the risk of re-intervention. This can readily be used by clinicians for patients via the developed web-application. The authors acknowledge that ML-based prediction should be considered in the context of surgeon and clinical judgement.

Machine learning and personalized medicine

PM will lead to more accurate diagnoses and the development of individualized long-term treatment plans which will improve patient care [27]. The use of patient-specific risk scores in the context of a survival model allows for the generation of individualized survival curves with our developed web-application. For example, any provider can input a patient's APD measurements and clinical features after follow-up to determine that patient's risk of pyeloplasty failure based on our ML model. Such visualization schemes can provide clinicians with a sense of how the survival trajectory of a patient compares to the "average" as well as providing a range of uncertainty for the patient. In addition, the creation of a web-based application for public use and access to our code in a repository improves transparency, explainability, and generalizability while offering the opportunity for true personalized medicine for pediatric pyeloplasty patients.

Examples of well-implemented PM approaches include selecting therapy with reference to patient genotype [28], predicting individual patient-risk and follow-up in uro-oncology [29], or predict which patients with vesicoureteral reflux would benefit from antibiotic prophylaxis [10]. While pyeloplasty has evolved over the years to become a very successful surgery for most patients, the few who require additional interventions are potentially exposed to not only recurrent symptoms but also additional general anesthesia and procedural complications. Hence, individualizing risk factors for each patient who undergoes pyeloplasty can allow us to utilize patient factors to predict those at risk of re-obstruction, while also recognizing those who can be safely discharged without risk of re-presenting later with symptoms and potential decline in renal function. Moreover, this risk stratification will help to determine which patients should be investigated with more invasive tests, such as diuretic renography, and decrease repeated ultrasounds for those who are unlikely to require additional procedures. These outcomes result in less clinical congestion, more efficient use of diagnostic tests, less cost for the institution, and faster access to additional procedures for those deemed likely to experience a recurrent obstruction.

Limitations of the model

While the present study represents promising early work in PM for pediatric urology, it does have some limitations. First, this study represents data from a single institution, and while it is a large, tertiary referral centre, the current data set is still to be considered small by ML standards. Although the data set is clean and prospectively collected, this limits generalizability to pyeloplasty outcomes at other institutes which commonly use robot-assisted pyeloplasty, routinely perform reduction pyeloplasties, or have different follow-up standards. Moreover, there are still a proportion of patients who may experience the event after the current timepoint. Finally, using reoperation as an outcome may be considered a limitation as indications vary between institutions and clinicians, depending on follow-up schedule, and the definition of a failed pyeloplasty is contentious in the literature. The use of ultrasound and clinical assessment for failed pyeloplasty limits our ability to correlate the model split function or renogram assessment. This further limits comparison with previous models and generalizability to other institutions. Most studies use different definitions based on institutional practices which can vary the success rate in previous studies by up to 20% [30, 31]. Here, our follow-up routine is similar to

established standards and pyeloplasty failure was determined from ultrasound assessment which is in line with best practices [31].

Despite these limitations, we propose our study adds valuable methodology, tools, and resources to the body of literature on pediatric pyeloplasty by providing an ML trained application to allow for individual risk stratification. In addition, by offering access to other researchers by employing Github and R shiny, we aim to increase transparency and aid in the use of this technology for other urological conditions.

Conclusion

Using ML algorithms to determine who is at risk of early recurrent obstruction appears feasible. Here, we present a freely available model which enables clinicians to determine an individual patient's risk of requiring re-intervention from their clinical and ultrasound findings during pyeloplasty. Conducting this risk stratification on an individual patient basis allows for the introduction of PM into the hydronephrosis population. Further evaluation may allow for monitoring strategies tailored to each patient's risk profile, potentially minimizing unnecessary tests, decreasing costs, and maximizing satisfaction with care.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-021-03879-z.

Author contributions ED, AK, JJK, JCCK, LE, MC, DTK, ML, JDS, GT, MR, and AJL: project development, data collection, data analysis, manuscript writing.

Funding This research was supported by the Hospital for Sick Children, and the Urology Care Foundation. A.K. is the recipient of an AUA Summer Medical Student Fellowship (Herbert Brendler, MD, Research Fund; ID: 839859). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Code availability All code used in this study is publicly available at https://github.com/goldenberg-lab/Pyeloplasty.

Declarations

Conflict of interest None.

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.

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