

Estimation of renal scarring in children with lower urinary tract dysfunction by utilizing resampling technique and machine learning algorithms

Alt üriner sistem disfonksiyonu olan çocuklarda böbrek skarının yeniden örnekleme tekniği ve makine öğrenme algoritmaları kullanılarak tahmini

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Ethics Committee Approval: The study protocol was approved by the Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (10/9/2018-07). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Etik Kurul Onayı: Çalışma protokolü Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu (09.10.2018-07) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalarda tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 7/30/2020

Yayın Tarihi: 30.07.2020

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Published by JOSAM

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Abstract

Aim: Classical database methods may be inadequate for large data sets accumulating continuously. Machine learning (ML), one of the main subsets of artificial intelligence, may solve this problem and find the best solution for future problems by gaining experience from the present data in medical studies. A method that may show the correlation between clinical findings and renal scarring (RS) with high accuracy in patients with lower urinary tract dysfunction (LUTD) is needed. In this study, the aim is to establish a model for the prediction of RS in children with LUTD by using ML.

Methods: Patients older than three years of age (n=114) who needed urodynamic study were included in the study. There were 47 variables in the data set. Variables such as symptomatic urinary tract infection, vesicoureteral reflux, bladder trabeculation, bladder wall thickness, abnormal DMSA scintigraphy, and the use of clean intermittent catheterization were recorded. Several ML techniques (MLT) were applied to estimate RS.

Results: As a result of the comparisons, the highest accuracy rate according to the confusion matrix was obtained by the Extreme Gradient Boosting (XGB) algorithm (91.30%). In the balanced (SMOTE) data set, the highest accuracy rate was obtained by the Artificial Neural Network (ANN) algorithm (90.63%). According to the Receiver Operating Characteristic (ROC), the highest success rate was obtained by the ANN algorithm in the balanced (SMOTE) data set (90.78%).

Conclusion: High accuracy rates obtained by MLT may suggest that MLT might provide a faster and accurate evaluation process in the estimation of RS in patients with LUTD.

Keywords: Artificial intelligence, Machine learning, Renal Scar, Lower urinary tract dysfunction, Children

Öz

Amaç: Klasik veritabanı yöntemleri, sürekli biriken büyük veri kümeleri için yetersiz olabilir. Yapay zekanın ana alt kümelerinden biri olarak makine öğrenme (MÖ) bu sorunu çözebilir ve tıbbi çalışmalarda mevcut verilerden deneyim kazanarak özellik problemleri için en iyi çözümü bulabilir. Alt üriner sistem disfonksiyonu (AÜSD) olan hastalarda klinik bulgularla renal skar (RS) arasında yüksek doğrulukla korelasyonu gösterebilecek bir yöntem ihtiyacı vardır. Bu çalışmada, AÜSD'lu çocuklarda MÖ kullanarak böbrek skarının tahmini için bir model oluşturmak amaçlanmıştır.

Yöntemler: Ürodinamik çalışmaya ihtiyaç duyan üç yaşından büyük hastalar (n=114) çalışmaya dahil edildi. Veri seti 47 değişkenden oluştu. Semptomatik idrar yolu enfeksiyonu, vezikotüretal reflü, mesane trabekülasyonu, mesane duvarı kalınlığı, anormal DMSA sintigrafisi, temiz aralıklı kateterizasyon kullanımı gibi değişkenler kaydedildi. RS tahmini için farklı MÖ teknikleri (MÖT) uygulandı.

Bulgular: Karşılaştırmalar sonucunda, Karışıklık Matrisi'ne göre en yüksek doğruluk oranı (%91,30), dengesiz veri kümesinde Extreme Gradient Boosting algoritması ile elde edilmiştir. Dengeli (SMOTE) veri setinde ise, en yüksek doğruluk oranı (%90,63) Yapay Sinir Ağı (YSA) algoritması ile elde edilmiştir. Alıcı İşleme Karakteristiği'ne (ROC) göre, en yüksek başarı oranı (%90,78), SMOTE veri setinde YSA algoritması ile elde edilmiştir.

Sonuç: MÖT tarafından elde edilen yüksek doğruluk oranları, MÖT'lerin AÜSD'lu hastaların RS tahmininde daha hızlı ve doğru bir değerlendirme süreci sağlayabileceğini düşündürmektedir.

Anahtar kelimeler: Yapay zeka, Makine öğrenme, Renal skar, Alt üriner sistem disfonksiyonu, Çocuk

Introduction

Most healthy children achieve daytime bladder control at the age between 9 months and 5.25 years (mean of 2.4 years of age) [1]. Urinary incontinence, which is defined as involuntary urination, is a frequent problem affecting children at different ages. It has a negative effect on the quality of life of children and their families [2]. According to the International Children's Continence Society (ICCS), anatomic, neurologic, and functional conditions can cause lower urinary tract dysfunction (LUTD). Congenital anomalies of kidney and urinary tract (CAKUT) such as posterior urethral valves, and ectopic ureter can cause sphincter dysfunction and urinary incontinence [3]. The disorders involving innervation of bladder and pelvic sphincter can lead to impairment of storage and emptying functions of the bladder. Spina bifida is the most common cause of neurogenic bladder dysfunction (NBD) in children. Incomplete bladder emptying and increased intravesical pressures may cause the development of renal damage or failure [4]. Functional incontinence (FI) is defined as the involuntary loss of urine in children who do not have anatomic or structural neurologic lesions [5]. LUTD is often associated with urinary tract infections (UTI), and vesicoureteral reflux (VUR). Recurrent UTI (RUTI) may lead to the development of damage and loss of renal function in children with LUTD [6].

Machine learning (ML) is used to classify multivariate data. ML first separates the data as a training dataset and is a group of multivariate analytical methods that then define these data properties or patterns to the test dataset for data classification or estimation. ML can learn and predict from large data sets in many areas such as healthcare [7-9]. ML was applied in the emergency room for triage decisions and kidney transplantation [10]. ML is being applied increasingly in the biomedical field [11, 12]. Despite the increasing availability of data sets containing a large number of variables and patients, no study has applied machine learning techniques for predicting outcomes in children with LUTD.

In this study, we aimed to evaluate the correlations between urodynamic study, bladder ultrasound (US) and ⁹⁹Tc-dimercaptosuc-cinic acid (DMSA) scintigraphy findings in children having LUTD, using ML resampling technique. We also aimed to estimate permanent kidney damage, and the renal scar in children by investigating the risk factors via ML.

Materials and methods

The data from children older than three-years-old who needed urodynamic study between 12/1/2011 and 12/1/2016 were included in the study. Data on episodes of symptomatic UTI, the presence of VUR, bladder trabeculation, bladder wall thickness (BWT), abnormal DMSA scintigraphy, the use of clean intermittent catheterization (CIC) were recorded.

Positive urine culture was defined as one species of bacteria when 50,000 CFU (CFU) per milliliter of urine reproduced in sterile bladder catheterization, or 100,000 CFU/mL of urine reproduced in the urine collected by urinary bag [13]. RUTI was defined as two or more episodes of acute pyelonephritis or acute pyelonephritis plus one or more episode of cystitis or three or more episodes of lower urinary tract

infection. Bladder US was done in all patients. DMSA scintigraphy was performed in patients with abnormal US findings, RUTI, and small-sized kidney. A urodynamic study was performed for any clinical symptoms of lower urinary tract dysfunction refractory to urotherapy for at least 1 year and suspicion of neurogenic or non-neurogenic bladder dysfunction or infravesical obstruction.

Post voiding residual volume (PVR), trabeculation, bladder volume and wall thickness were determined in all patients by bladder US. BWT of 3 mm in filled bladder was defined as increased thickness. Detrusor hyperactivity was defined as involuntary detrusor contractions during the filling phase. Expected bladder capacity was defined as (age in years x 30+30) mL. Reduced bladder capacity was defined as <65% of the expected bladder capacity. Compliance was defined as the increase in detrusor pressure per unit of volume change in detrusor pressure (V / P) [3]. In children <6 years, post voiding residual urine volume greater than 20 mL was defined as an increased residual volume. In children >7 years, post voiding residual urine volume >10 mL was considered elevated [14]. The detrusor leak point pressure (DLPP) was defined as the lowest detrusor pressure causing leakage of urine in the absence of increased abdominal pressure [15]. The differential function of less than 40% or the presence of renal scarring and/or atrophy were considered renal damage.

Abnormal urodynamic test results were detected in 60 (80%) patients. The most frequent [n=45 (60%)] pathologic urodynamic finding was reduced bladder capacity, and median bladder capacity was 319 mL (203-384). Thirty-nine (52%) patients had elevated PVR with a median of 10 mL (0-95). Forty-five (60%) patients had hypocompliant bladder. Thirty (40%) patients had unstable detrusor contraction. VCUG was performed in 50 patients. Twenty-three (46%) patients had VUR. Renal damage was detected in 26 (34.7%) patients. Twenty-five patients (33.3%) performed clean intermittent catheterization (CIC).

Data pre-processing

There were 106 patients and 47 features (variables) in the data set. Before the machine learning techniques were applied, the dataset was analyzed using the following steps (Table 1).

- 1- User Name was not included in the training.
- 2- Variables with more than 15% missing values were eliminated. At the end of this process, 75 (22-scar true, 53-scar false) people and 24 variables remained.
- 3- Variables with a correlation coefficient of 0.6 and above were determined and the appropriate variables were eliminated. At the end of this process, 75 people and 18 variables remained.
- 4- Machine learning algorithms were run with unbalanced data set and results were obtained.
- 5- The machine learning algorithms were run by balancing the data set with the smote technique (At the end of this process, the data set included 106 people (53-scar true, 53-scar false)) and the results were obtained.
- 6- The ratio of test and training sets was 30-70%, respectively. For Cross Validation, k value was selected as 5.
- 7- Comparing the results of three techniques.

Table 1: Outcomes of group-projects coursework

Scar	The number of cases	
	Imbalanced	SMOTE
0	53	53
1	22	53

Machine learning

Machine learning is the science of computational statistics, which based on making predictions by using computers. Machine learning focuses on estimations from the learned data based on known features [15]. In this study, Artificial Neural Networks (ANN), Decision Tree (DT), Support Vector Machine (SVM), Naive Bayes (NB), Logistic Regression (LR), k-Nearest Neighbor (KNN), Random Forest (RF) and Extreme Gradient Boosting (XGBoost) were used as MLT.

Resampling techniques

The imbalance is that the sample size of one class is much higher than the other class or classes. Therefore, data samples belonging to small classes are misclassified more often than those belonging to common classes. Some techniques have been developed to balance the unbalanced data set [13].

Synthetic minority oversampling technique

Smote is a statistical technique for increasing the number of cases in your dataset in a balanced way. The module works by generating new instances from existing minority cases that you supply as input. This implementation of Smote does not change the number of majority cases [14].

Statistical analysis

Confusion Matrix contains information about actual and predicted classifications made by a classification system. The performance of such systems is generally evaluated using the data in the matrix. The Accuracy Rate (ACC), a commonly used success evaluation method, was used in our study. The accuracy method is the rate of the sample number the system classifies as trues (True Positive (TP) and True Negative (TN)) to all sample number. Error rate is the rate of the sample number calculated false (False Positive (FP) and False Negative (FN)) to all sample number. It is expected that the accuracy rate is higher than the false rate at the end of the study. NPV means Negative Predictive Value [15]. Success scores are calculated with the help of the confusion matrix (Table 2).

Table 2: Distribution of scar variable

Scar	Actual			Total
	1	0		
Prediction	1	TP	FP	Precision Score
	0	FN	TN	NPV
Total	Recall Score, Sensitivity		Specificity	ACC

The success measures and formulas used in our study, which were calculated with the help of Confusion Matrix;

$$ACC = (TP + TN) / (TP + TN + FP + FN)$$

$$Precision = TP / (TP + FP)$$

$$NPV = TN / (TP + FP)$$

$$Recall = TP / (TP + FN)$$

$$Specificity = TN / (FP + TN)$$

There are several more accuracy scores calculated with the help of confusion matrix. In addition to the power of the study, type II error, type I error are calculated respectively via TP value, FN value and FP value.

In statistics, the ROC (receiver operating characteristic) curve is a graphical plot showing the diagnostic capability of the dual classification system. AUC (Area Under the Curve) shows the classification performance of the installed model and takes a

value between 0 and 1. AUC value close to 1 means that the classification performance of the model is high [15].

K-fold cross validation is a popular procedure for estimating the performance of a classification algorithm or comparing the performance between two classification algorithms on a data set. This procedure randomly divides a data set into k disjoint folds with approximately equal size, and each fold is in turn used to test the model induced from the other k-1 folds by a classification algorithm. The performance of the classification algorithm is evaluated by the average of the k accuracies resulting from k-fold cross validation, and hence the level of averaging is assumed to be at fold [12].

For all analysis and processing, a computer with Windows 10 64-bit operating system, quad-core Intel Skylake Core i5-6500 CPU with 3.2 GHz 6MB Cache and 8GB 2400MHz DDR4 Ram was used.

Results

In this study, we used machine learning to retrospectively analyze data from patients with LUTD. The records of 114 patients who underwent urodynamic study were retrospectively investigated in this study. The data of 39 patients were excluded from the study due to the missing information.

The mean age of 75 patients [48 (64%) girls, 27 (36%) boys] was 8.7 (3.78) years. Of 75 patients, 24 (32%) had NBD, 25 (33.3%) FI and 26 (34.7%) CAKUT. Fifty-one (68%) patients had RUTI (22 patients with UTI due to extended-spectrum beta-lactamase-producing Enterobacteriaceae). There was renal parenchymal thinning in 6 (8%) patients on US examination. Hydronephrosis was detected in 19 (25.3%) patients. US examination showed bladder wall thickening in 26 (34.7%) patients. The trabeculated bladder was present in 15 (20%) patients. Table 3 shows the results obtained by MLT. Table 4 shows the best scores of the study. Figure 1 shows ROC AUC Graphs for Imbalanced and Smote Dataset.

Table 3: The results obtained by MLT

(%)	Alg.	LR	KNN	SVM	NB	DT	RF	XGB	ANN
Specificity	Smote	80.00	66.67	76.19	76.19	88.24	88.24	93.33	93.75
	Imb.	100.0	28.57	100.0	57.14	50.00	50.00	100.0	80.0
Sensitivity	Smote	91.67	58.87	90.91	90.91	86.67	86.67	82.35	87.50
	Imb.	80.95	75.00	80.95	87.50	82.35	85.00	89.47	88.89
NPV	Smote	94.12	58.82	94.12	94.12	88.24	88.24	82.35	88.24
	Imb.	33.33	33.33	33.33	66.67	50.00	50.00	66.67	66.67
Precision	Smote	73.33	66.67	66.67	66.67	86.67	86.67	93.33	93.33
	Imb.	100.0	70.59	100.0	82.35	82.35	100.0	100.00	94.12
ROC AUC	Smote	83.73	62.75	80.39	80.39	87.45	87.45	87.84	90.78
	Imb.	66.67	51.96	66.67	74.51	66.18	75.00	83.33	80.39
ACC	Smote	84.38	62.50	81.25	81.25	87.50	87.50	87.50	90.63
	Imb.	82.61	60.87	82.61	78.26	73.91	86.96	91.30	86.96
Cross Validation	Smote	75.27	72.82	75.18	73.55	75.55	80.45	78.27	81.27
	Imb.	(6.92)	(6.94)	(12.42)	(4.74)	(8.72)	(10.39)	(9.94)	(9.82)
		78.42	61.19	63.87	74.13	68.88	66.38	73.06	79.93
		(5.75)	(5.8)	(7.52)	(9.21)	(10.86)	(10.08)	(8.42)	(9.94)

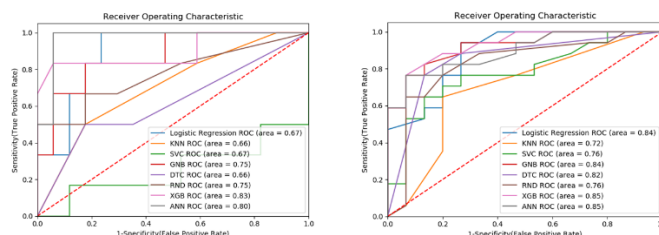


Figure 1: ROC AUC Graphs for Imbalanced and Smote Dataset

Table 4: The best scores of the study

(%)	Imbalanced (ANN)			Imbalanced (XGB)			Smote (ANN)			Smote (XGB)		
Predict/Actual	1	0	ACC	1	0	ACC	1	0	ACC	1	0	ACC
1	16	1	94.12	17	0	100.00	14	1	93.33	14	1	93.33
0	2	4	66.67	2	4	66.67	2	15	88.24	3	14	82.35
ACC	88.89	80.00	86.96	89.47	100.00	91.30	87.50	93.75	90.63	82.35	93.33	87.50
Cross Validation Score	79.93 (6.12)			73.06 (8.42)			81.27 (9.82)			78.27 (9.94)		
ROC AUC	80.39			83.33			90.78			87.84		

Discussion

The highest success rate according to the ACC value in the Confusion Matrix was obtained by the XGB algorithm in the unbalanced data set (91.30%). However, the Cross-Validation method and ROC AUC results are more reliable, especially because of the small number of data. When the ROC AUC values were examined, the highest success rate was obtained by ANN algorithm (90.78%). When cross-validation results (k=5) were examined, it was found that it supports ROC AUC results and the highest success rate was achieved with ANN algorithm (81.27%). In addition, by performing smote the data set, the number of samples (data) was increased and the data was balanced, the result was higher than the balance of the data.

When all these findings are evaluated together, it can be said that ANN algorithm with (90.63%), Cross Validation score (81.27%) and ROC AUC value (90.78%) can give high results in estimating renal scar in children with lower urinary tract dysfunction. In this case, patients with truly scarring are estimated correctly (93.33%) and in fact, non-scar patients are more accurately estimated (82.35%). However, higher number of data (sample size) would lead to a better result.

Abnormalities of the bladder wall by muscular hypertrophy and abnormal collagen in the detrusor muscle could result in bladder wall thickness and trabeculation in LUTD. The children with LUTD have an increased risk for RUTI infections due to the presence of PVR and other alterations of lower urinary tract dynamics. The incidence of breakthrough infection is higher in LUTD than in patients without voiding dysfunction [16]. The adequate blood flow of the bladder is very important for the host defense mechanism. Bladder ischemia due to over-distension or poor compliance may lead to an increased risk of UTI. PVR urine is especially important in the diagnosis of LUTD dysfunction. There is a positive association between elevated PVR and an increased risk of UTI [17]. The disorders of bladder emptying and drainage of the pelvicalyceal system may lead to the development of renal scarring by UTI. Also, elevated PVR may increase the risk for upper urinary tract damage [18]. Upper urinary tract deterioration and renal scarring are the most threatening problems in patients with lower urinary tract dysfunction (LUTD), occurring in 5–50% [19].

Follow-up studies of children with LUTD defined a subset at risk for urinary tract deterioration focused on disadvantageous urodynamic parameters, which include dyssynergia between the detrusor and the external urethral sphincter, detrusor pressure at maximal cystometric capacity (PMCC) greater than 40 cm water, and decreased bladder compliance [20].

Sonography is an important imaging modality with some remarkable advantages to follow the renal scar. It can be performed rapidly and in multiple settings, costs less, and saves patients from ionizing radiation and anesthesia. Major

disadvantages are its lower resolution and inter- and intra-operator variability. Normal USG could not exclude the renal parenchymal lesion [21]. However, previous reports have proven a low correlation between RBUS and renal scarring, compared to the gold standard DMSA scintigraphy, with sensitivity ranging from 5 to 47% [22, 23]. It can substitute Tc-DMSA scintigraphy, especially in patients requiring follow-up scanning and, accordingly, remarkable radiation exposure [24].

Hydronephrosis is thought to cause renal functional deterioration. DeLair et al. [25] reported that hydronephrosis did not correlate with kidney damage. Vega et al. [21] reported that the reduced bladder capacity was the most frequent finding in children with RUTI and bilateral renal damage. Arora et al. [26] showed that the frequency of decreased bladder capacity was higher in patients with renal scarring. They had greater leak pressures compared to patients without renal damage.

It is particularly important to protect kidney function in patients with LUTD. Clean intermittent catheterization is one of the treatment methods in patients with difficulty emptying their bladder due to neurogenic and non-neurogenic causes. The majority of patients to whom CIC was performed are at an increased risk for RUTI. The use of urine catheters can lead to increase the risk of UTI due to decreased protective effect of urethral length, chronic inflammation, and alterations in defense mechanisms [25]. CIC has been performed to decrease hydronephrosis, VUR, bladder trabeculation, and renal scarring. In recent years, controversial results have been reported regarding the benefit of CIC to decrease renal scarring, trabeculated bladder, and VUR. DeLair et al. [26] reported that delayed initiation of CIC was associated with renal cortical deterioration, but there was no statistically significant difference in their study. In another study, it was shown that early CIC might not prevent renal scarring in children with NBD. Moreover, early initiation of CIC was associated with the development of abnormal findings on DMSA scintigraphy. Also, the performing of CIC is one of the most important risk factors for UTI in patients with LUTD [27]. CIC facilitates the entry of bacteria into the bladder. Also, bacteria can reach the kidney more easily in patients VUR.

Limitations

There are several limitations in our study. Firstly, this is a retrospective analysis. Secondly, the numbers of patients are small. Nevertheless, the first time, the estimation model for renal scarring in children was tested by using ML.

Conclusion

In conclusion, our data may suggest that ML is a useful method of predicting a diagnosis of renal damage in children with LUTD. In addition, the use of ML method could be helpful to prevent unnecessary DMSA scintigraphy and radiation exposure.

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