

Review

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ATLAS of Nomograms, Scoring Systems and Predictive Tools to Guide Investigation or Management in Patients with Suspected or Confirmed Vesicoureteral Reflux: A Comprehensive Review of the Literature

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Review

ATLAS of Nomograms, Scoring Systems and Predictive Tools to Guide Investigation or Management in Patients with Suspected or Confirmed Vesicoureteral Reflux: A Comprehensive Review of the Literature

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Abstract

Background: Vesicoureteral reflux (VUR) contributes significantly to recurrent childhood urinary tract infections and renal scarring, yet predicting which patients will develop adverse outcomes or benefit from specific investigations or treatments remains challenging. Numerous prognostic tools have been proposed, but none have achieved widespread adoption. **Methods:** A comprehensive search of literature available on MEDLINE, PUBMED, Embase, Emcare, CINAHL, and Google Scholar was performed to identify combinations of factors, scoring systems, ratios, models, and tools relating to VUR. This included predicting spontaneous resolution of established vesicoureteral reflux, the risk of breakthrough urinary tract infections (UTIs), and guiding clinical decision making regarding the need for VCUG in patients with UTIs, continuous antibiotic prophylaxis (CAP), or surgical intervention in patients with confirmed VUR. Articles were included if they either described or validated a predictive tool that was designed to aid clinical decision making in patients with either suspected or confirmed VUR with regards to investigation or management strategies. All studies included were then analysed and the predictive tools have been summarised in a narrative format. **Results:** Seventeen predictive tools developed over 39 years were identified: six predicting spontaneous resolution, four predicting breakthrough urinary tract infection (BTUTI) on CAP, two determining which children benefit from CAP, and five estimating the probability of VUR or high-grade VUR after a first febrile UTI. Approaches ranged from radiological ratios to multifactorial clinical–radiological scores and machine-learning models. Only five tools had any external validation, and none demonstrated sufficient reliability for universal clinical use. Significant heterogeneity in design, imaging interpretation, inclusion criteria, and outcome definitions limited comparison and wider applicability. **Conclusions:** This atlas provides the first consolidated overview of prognostic tools in paediatric VUR. Future development should prioritise multicentre, prospectively validated models that integrate established clinical and radiological predictors with transparent computational methods to create practical, generalisable risk-stratification frameworks for routine care.

Keywords: vesicoureteral reflux; UTI; risk stratification; continuous antibiotic prophylaxis; machine learning

Introduction

Vesicoureteral reflux (VUR) is a leading cause of recurrent urinary tract infection in children with approximately 1-2% of the paediatric population being affected [1] and has a well-established association with the development of renal scarring [2]. Although it is postulated that approximately 1 in 3 infants presenting with urinary tract infections may have a degree of VUR [3] not all of these will go on to develop long term kidney damage [4,5]. Conventional management of children suspected of having vesicoureteral reflux has included using video cystoureterogram (VCUG) scans to confirm the diagnosis and management with continuous antibiotic prophylaxis or surgical intervention [6,7]. However, concerns regarding exposure to potentially unnecessary radiation doses and the development of antimicrobial resistance has called traditional diagnostic and therapeutic strategies into question in recent years [8,9].

It remains an ongoing challenge for clinicians to determine which children with VUR will experience spontaneous resolution, recurrent urinary tract infection, renal scarring, and potentially complications of resultant chronic kidney disease [10–15]. Multiple publications have appeared in the literature over the past 40 years that describe predictive methods, models, scores, rules, nomograms, and ratios (referred collectively hereafter as ‘predictive tools’) to stratify which children should undergo a VCUG for suspected VUR and/or guide management strategies for those with a confirmed diagnosis. Despite the variety of options, many of the tools remain relatively unknown within the field, which alongside the relative rarity of the condition may contribute to why they remain unvalidated and why no tool has thus far achieved universal adoption. This atlas is intended to serve as an easily digestible up-to-date summary of the current spectrum of predictive tools available for use and to provide a narrative appraisal of each to facilitate clinicians and researchers to easily find and evaluate the current tools.

Methods

A comprehensive search of literature available on MEDLINE, PUBMED, Embase, Emcare, CINAHL, and Google Scholar was performed to identify combinations of factors, scoring systems, ratios, models, and tools relating to predicting spontaneous resolution of established vesicoureteral reflux, the risk of breakthrough urinary tract infections, and guiding clinical decision making regarding the need for VCUG in patients with urinary tract infections, continuous antibiotic prophylaxis, or surgical intervention in patients with confirmed VUR. Search terms, including Boolean operators, included: “vesicoureteral reflux” OR “VUR” AND “prognosis” OR “predict” OR “ratio” OR “model” OR “score” OR “scoring system” OR “nomogram” to identify suitable articles. Articles were included if they either described or validated a predictive tool that was designed to aid clinical decision making in patients with either suspected or confirmed vesicoureteral reflux with regards to investigation or management strategies. All studies included were then analysed and the predictive tools have been summarised in a narrative format including details about external validation and citation count of the original published article on Google Scholar.

Results

In total we have found and presented 17 distinct predictive tools that have been described over a span of 39 years (Table 1-4). 6 predict spontaneous resolution of confirmed reflux, 4 predict breakthrough urinary tract infections whilst being treated with continuous antibiotic prophylaxis, 2 are designed to guide clinicians in deciding which patients to prescribe continuous antibiotic prophylaxis to, and 5 predict which patients presenting with a first febrile urinary tract infection should undergo VCUG to investigate possible VUR. 1 tool is based purely on clinical/serological factors, 2 are based purely on radiological findings, 12 utilise a combination of clinical, serological, and radiological factors that are inputted by the clinician and calculated using a formula, and 4 utilise computational or machine-learning methods. Several tools express their outcome as a percentage risk whilst others stratify patients into risk categories. Only 5 out of 17 of the predictive tools have to date undergone some form of external validation.

For the purposes of this atlas the following terminology applies:

- BBD = Bladder and bowel dysfunction, defines as issues relating to bladder and bowel function.
- VCUg = voiding cystoureterogram.
- CAP = Continuous antibiotic prophylaxis, defines as a regular low dose of prophylactic antibiotics to prevent infection.
- Spontaneous resolution = spontaneous resolution of vesicoureteral reflux, defined as a complete resolution of previously confirmed reflux on repeat VCUg.
- BTUTI = breakthrough urinary tract infection, defined as a urinary tract infection that occurred whilst on continuous antibiotic prophylaxis therapy.
- Predictive tool(s) = predictive methods, specific combinations of individual factors, models, scores, rules, nomograms, risk classification systems, and ratios whose purpose is to aid clinical decision making through quantifying possible outcomes.

1. Predictors of Spontaneous Resolution (Table 1)

1.1. Ureteral Diameter Ratio - Hellstrom et al. (1986) [16]

The ureteral diameter ratio (UDR), first described by Hellstrom et al. (1986), is a ratio calculated by measuring the largest ureteral diameter within the false pelvis (defined as the area below the most superior aspect of the ilia) in millimetres and dividing this by the distance from the bottom of the L1 vertebral body to the top of the L3 vertebral body in millimetres as seen on a voiding cystourethrogram [16].

Initially designed in the context of children diagnosed with low-risk vesicoureteral reflux this was then built upon by Cooper et al (2012) who performed a retrospective review of 79 patients treated for VUR in a single institution between 1988 and 2004 and noted that UDR outperformed reflux grade as a predictor of clinical outcomes but did not establish any numerical cut-offs for UDR to be used as a predictor of specific outcomes [17].

A cut-off value of 0.43 was suggested by Arlen et al. (2017) after finding that UDR correlated significantly with spontaneous resolution of VUR with a P value of <0.0001. No child in the cohort with a UDR of 0.43 or above experienced spontaneous resolution and only 3 (4.5%) of the patients who experienced resolution had a UDR of >0.35 [18]. In a separate publication Arlen et al. (2017) also demonstrated with statistical significance that increasing UDR correlated with an increased risk of breakthrough urinary tract infections [19].

Wong et al. (2023) further validated the prognostic utility of UDR in predicting spontaneous resolution and proposed that a cut-off value of 0.26 be used to delineate patients into high-risk of persistence (>0.26) and low risk of persistence (<0.26) [20]. Krishnan et al (2024) performed a systematic review and meta-analysis that concluded that UDR is correlated with spontaneous resolution of reflux, breakthrough urinary tract infections, persistence even after endoscopic treatment, and need for surgical intervention however concluded that optimal cut-off values could not be determined [21].

The ureteral diameter ratio is therefore a simple and easily utilised tool that requires only interpretation of a VCUg to give validated prognostic information regarding several important clinical outcomes in patients with VUR. It has been externally validated with consistent results however no cut-off values have been agreed across the literature. It has also been incorporated into other models improving predictive accuracy [22,23]. The lack of established cut-off values and validation in prospective studies remains a barrier to the UDR being used widely as a prognostic tool and these issues need to be addressed for it to be used universally.

1.2. Vesicoureteral Reflux Index - Kirsch et al. (2014) [24]

The Vesicoureteral Reflux Index (VURx) is a numerical scoring system that was developed by Kirsch et al. (2014) to predict the chance of spontaneous resolution in children under 2 years of age who have been diagnosed with vesicoureteral reflux. Derived after a retrospective analysis of all children who received a diagnosis of VUR whilst under 2 years of age over a 5-year period between the 1st of January 2006 and the 31st of December 2010 from a single centre database. A multivariate analysis demonstrated several variables that were independent predictors of delayed resolution or persistence of reflux [24].

By assigning each of the identified variables a numerical score: female sex = 1 point, presence of complete duplicate or PUD = 1 point, VUR grades 4-5 = 1 point, reflux timing: voiding only = 1 point, late filling = 2 points, mid-filling = 3 points a score was derived. The total score available is 6 points with lower scores indicating a greater probability of spontaneous resolution of reflux. The probability of resolution over 1 – 3 years can be expressed as a percentage based on the numerical scoring [24].

Externally validated through several follow up studies, including by Arlen et al. (2016) who applied the index to children under 2 years old from two institutions and demonstrated similar resolution rates as the original study [25]. Garcia-Roig et al (2017) evaluated the index in patients under 18 years of age diagnosed after 2 years old and confirmed that it can be used to predict spontaneous resolution/improvement of reflux. However, noted that improvement/resolution appears less likely as the Index score and time from diagnosis increase [26]. Arlen et al. (2020) subsequently performed a comparative analysis and demonstrated that the Vesicoureteral Reflux Index outperformed both the VUR grade and ureteral diameter ratio in predicting breakthrough urinary tract [27].

The Vesicoureteral Reflux Index can be easily applied and provides a numerical predictor of spontaneous resolution and potentially breakthrough infections thus can be useful in counselling patients and their families. Although it has been evaluated across a range of age ranges the index has predominantly been validated in children under 2 years of age and its reliance on VCUG findings introduces a risk of interobserver heterogeneity in interpretation and differences in imaging techniques limiting its generalisability. It has also not been prospectively validated, and this will be required to make it universally applicable.

1.3. Nomograms – Estrada et al. (2009) [28]

Estrada et al. (2009) described the derivation of several nomograms that can be used to predict spontaneous resolution of vesicoureteral reflux after a retrospective analysis of 2462 children referred to a single high-volume unit between 1998 and 2006. Through univariate and multivariate analysis the following variables: age at presentation, sex, grade of reflux, laterality (unilateral vs. bilateral), ureteral anatomy (single vs. duplex ureter), and mode of clinical presentation (e.g., postnatal evaluation for prenatal hydronephrosis or sibling screening) were identified as independently predictive of VUR resolution. Cox proportional hazards regression was then performed to model time to VUR resolution and nomograms were developed using every combination of the identified factors. The nomograms can be used to provide a cumulative probability of resolution of reflux at annual intervals of 1 to 5 years expressed as a percentage of presenting cases.

Although no external validation has been published for these nomograms which limits their reliability and generalisability, they offer distinct advantages as decision making and counselling aids for Paediatric Urologists. The fact that a unique nomogram has been developed for each combination of predictive factors allows for a relatively individualised approach for each patient. The nomograms also offer an easy-to-use tool and the expression of probability as a percentage is easily understood and explained to patients and their families which means these have potential to be useful clinical tools to aid decision making and patient counselling [28].

1.4. Scoring System - Sjöström et al. (2020) [29]

The Sjöström scoring system was originally published in 2020. It is a points based scoring system with a score range between 0 to 14 points available derived from 4 variables: sex (male = 0, female = 4), presence of breakthrough urinary tract infections (no = 0, yes = 3), presence of renal damage (none = 0, focal = 2, generalized = 4), and glomerular filtration rate (normal = 0, subnormal = 3). In the study renal damage was assessed through DSMA or MAG3 scans [29].

The score can be used to predict the likelihood of downgrading of VUR from grade 4/5 to grade 2 or below. The variables included in the scoring system were identified through a prospective analysis of 89 infants with VUR grade 4 or 5 diagnosed at median age 2.5 months and followed to 39 months; the risk variables were collected at 12 months of age. Univariate analysis and subsequently multivariate analysis were used to identify factors that were independently predictive of the described outcome and incorporated into the above score.

Sjöström et al. (2020) defined that those with a score of 0-4 being classed as high probability of VUR being less than or equal to 2 at final follow up, scores between 4-8 being intermediate probability of VUR less than or equal to 2, and scores between 8-14 being low probability of VUR less than or equal to 2 at final follow up. The authors attempted to generate a score to predict absolute resolution of VUR however due to the rarity of this even in their cohort they could not do so. The scoring system was internally validated using a bootstrapping technique using 5000 samples drawn with replacement from the original population, sampling 5,000 studies of the same size as the original sample (n = 89) [29]. No external validation has been published to date.

The Sjöström Scoring system provides a simple numerical scoring system using information gathered early in life to aid in clinical decision making and patient/family counselling. However, due to the requirement for multiple different imaging studies to be performed as well as blood tests, and the relatively small sample size coupled with a lack of external validation studies it is not currently able to be used universally in clinical practice.

1.5. Computational Model – Knudson et al. (2007) [30]

Knudson et al. (2007) built a computational model based on a retrospective analysis of 205 children with primary vesicoureteral reflux treated at a single institution in Iowa between 1988 and 2004. Clinical data extracted included: age, gender, presenting symptom, reflux grade, laterality, whether reflux occurred during filling or voiding, initial bladder volume at onset of reflux, and complete ureteral duplication. Using spontaneous resolution or unresolved reflux if the patient underwent surgery or had persistent reflux on follow up cystogram 1 and 2 years after diagnosis as designated outcomes, the team set to create a computational model to predict the above outcomes. Two data sets were created and randomly assigned to a modelling set of 155 patients for training and a cross-validation set of 50 patients for internal validation. Multiple computational models were built and a linear support vector machine was chosen due to having the best predictive accuracy. The final model utilises reflux grade, age at diagnosis, bladder volume at reflux onset, and history of prenatal hydronephrosis and modelled the outcomes for 1 and 2 years after diagnosis. The ROC curve area of the final model was 0.819 and 0.86 for the 1 and 2-year models respectively. The model was inputted into JavaScript to enable clinicians to easily input patient specific data and get individualised predictions through an online platform [30].

A re-evaluation to the initial model was described by the team that developed the initial model in Nepple et al. (2008). On this iteration the team included renal scan data on renal scarring or decreased relative renal function (40% or less in the refluxing kidney) and tested the new model on data from 161 children. The data sets were randomly assigned to either the modelling set (111 children) and a cross-validation set (50 children). A linear regression model was selected as the superior predictive model both in this publication and when compared to the previous model with a ROC area of 0.945 for predicting reflux resolution in the 2-year model [31].

The modified model was externally validated by Shiraishi et al. (2009) using a retrospective cohort of 82 Japanese children and found that it predicted resolution by 2 years post diagnosis with

overall accuracy of 80.5%, sensitivity of 82.5%, specificity of 78.6%, positive predictive value of 78.6%, and negative predictive value of 82.5% [32].

In summary, The Knudson/Nepple computational model seems to be a potentially useful model however further prospective external validation will be required to ensure reliability. Being available through the internet makes it openly accessible however it does rely on knowledge of bladder and renal status obtained through advanced tests that may not be universally available.

1.6. Machine-Learning Model – Tafazoli et al. (2025) [33]

Tafzoli et al. (2025) developed a machine-learning model for predicting several clinical outcomes in children with confirmed vesicoureteral reflux who are being treated with continuous antibiotic prophylaxis (CAP). The outcomes defined in the original study include breakthrough urinary tract infections, renal scarring, and persistence of reflux.

They performed a retrospective analysis of data for 225 children under 2 years of age taken from two separate units, 115 children treated with continuous antibiotic prophylaxis at a paediatric nephrology clinic were used for model development and 110 children who were treated at a paediatric surgery unit with endoscopic injection of dextranomer/hyaluronic acid copolymer were used as a comparator group. Data gathered included: sex, age at diagnosis, medications, VUR laterality, dimercaptosuccinic acid (DMSA) differential renal function, VUR grade, dilating or non-dilating reflux in ultrasonography, and presence of febrile UTI, prenatal hydronephrosis, ureteral anomaly, bladder dysfunction, neuropathic bladder, failure to thrive, and renal scarring [33].

After multivariate analysis it was demonstrated that only renal scarring was significantly associated with post-treatment febrile UTIs and/or renal scarring (p-value: 0.007) and bladder dysfunction was the only factor significantly associated with post-treatment VUR persistence (p-value: 0.004) [33]. Thus, these were used for model derivation.

The final model was trained using 75% of the data from the CAP group and 25% was used for internal validation. The final model reported an overall predictive accuracy of between 72% and 75% for VUR persistence/resolution and breakthrough UTI/renal scarring respectively [33].

This machine-learning model serves as a potentially useful tool to discriminate between children who can be trialled on continuous antibiotic prophylaxis versus those who should be considered for a surgical intervention. The fact that it utilises only two clinical variables makes it relatively simple to apply, however acquisition of these variables does require interpretation radiological assessments that may not be universally available. The Machine-learning technology is also potentially a limiting factor in different economic and technological environments, and the model does not facilitate any decision making that does not involve active treatment which precludes its use in mild cases where observation might be considered.

Prospective external validation on larger cohorts would be necessary to demonstrate widespread applicability and alongside the reliance on variables that may be inconsistently reported represents the greatest limitation of this model at this stage.

2. Predictors of Breakthrough Urinary Tract Infections (Table 2)

2.1. Risk Prediction Model – Dias et al. (2010) [34]

Dias et al. (2010) developed a risk prediction model for the development of breakthrough urinary tract infection in paediatric patients with primary vesicoureteral reflux. The authors reviewed retrospective data derived from patients treated in a single tertiary renal unit in Brazil between 1970 and 2008. 740 patients were identified and included. Binary logistic regression was used to identify independent predictors of recurrent UTIs, defined by as more than 1 episode of febrile UTI during follow-up [34].

5 variables were found to be independently predictive of the defined outcome: UTI as the initial presenting problem, female sex, age < 6 months at presentation, presence of dysfunctional elimination syndrome, and reflux grade 4-5 [34].

A numerical weighting was calculated for each of the independently predictive variables and a total score for each patient was derived from summing the weightings present. The total score range therefore is between 0 – 9.05. The prognostic risk score was presented as: <4.25 = low-risk, 4.25 - 5.05 = intermediate-risk, and 5.05 – 9.05 = high-risk. The overall accuracy of the scoring was found to be acceptable with a C statistic of 0.68 and a Hosmer-Lemeshow goodness-of-fit test P value = 0.97. The calculated UTI incidence rate per 1000 person-months for each risk group which were 4.3 (95% CI, 3.2, 5.6), 7.9 (95% CI, 6.7, 9.1), and 11.3 (95% CI, 9.9, 12.8) for the low-risk, intermediate-risk, and high-risk groups, respectively [34].

This risk-prediction model offers a simple and easily applied tool using patient information that is likely to be readily available in most contexts however to date no external validation has been published and thus it cannot be confidently said to apply outside of its derivation cohort. External prospective validation studies will be necessary to ensure its reliability across a range of patient populations.

2.2. Risk Prediction Model – Hidas et al. (2015) [35]

Another risk prediction model developed to predict breakthrough urinary tract infections was published by Hidas et al. (2015). They performed a retrospective analysis of clinical and demographic data from 252 children with vesicoureteral reflux treated as a single unit between June 2008 and December 2010 to identify independent risk factors for breakthrough urinary tract infections. Variables were initially evaluated for associations with breakthrough UTIs using Fisher exact test and those that demonstrated association in the unadjusted bivariate analysis were included in an initial multivariate logistic regression model. Subgroup analysis was subsequently performed comparing variable associations in patients with lower grade VUR (grades 1-3) and those with higher grade VUR (grades 4-5) [35].

The final model was based on the following factors deemed to be significant for prediction: sex, primary presentation as a urinary tract infection, grade 4-5 reflux, and presence of bladder and bowel dysfunction. The individual factors were multiplied by their individual beta-coefficients (the natural log of the odds ratio) and then summed to give a total score. This score was evaluated based on the 2-year probability of a breakthrough UTI and presented as a percentage risk. The authors were then able to categorise patients based on their score as low, intermediate, or high-risk of having a breakthrough UTI during that 2-year period [35].

The model demonstrated good overall accuracy with the area under a ROC curve of 0.76 on the original derivation cohort and 0.8 of a prospective cohort of 56 children evaluated within the original study by way of validation [35].

Hidas et al. (2015) used their model to develop a web-based scoring system that presented the overall risk of breakthrough UTI as a percentage. The score is called the iReflux score and can be readily accessed online. Of note the current iteration of the score includes details regarding patient age, laterality of reflux, and circumcision status despite these not affecting the probability outcome. The inclusion of circumcision in the online calculator is addressed in the original publication by justifying that, like bladder and bowel dysfunction, circumcision status has been linked in other studies to UTIs in children and is a modifiable factor.

To date no external validation is available in the literature for this risk prediction score which is the major limitation. Given that the score was derived from a relatively small cohort from a single centre; prospective, large cohort external validation will be required to ensure that the score can be used in widespread clinical practice. The stratification of patients into risk categories, expression or risk in the form of a simple percentage, and inclusion of easily accessible clinical and demographic variables does make this an attractive option if it is demonstrated reliable through external validation.

2.3. Prediction Model – Yang et al. (2025) [36]

Yang et al. (2025) developed a risk prediction model and nomogram for breakthrough urinary tract infections in children being treated for primary vesicoureteral reflux after a retrospective

analysis of 193 patients treated between January 2019 to August 2021 from a single specialist centre in China. Data was extracted from clinical records and VCUG scans and subjected to univariate and multivariate analysis to identify independent predictors and developed a model which they compared to two other established predictors, urethral diameter ratio and the vesicoureteral index [36].

Multivariate logistic regression analysis revealed that: sex, high-grade VUR, and ureterovesical junction diameter were independent predictors of breakthrough UTIs ($P < 0.05$) and thus were used to construct the risk prediction model and nomogram [36].

The performance of the model was assessed for discrimination, calibration, and clinical benefit. The calibration curve was then used to compare between the observed and predicted outcomes. The receiver operating characteristic (ROC) curve was used to evaluate the model's discriminative ability. The optimal threshold probability was based on the Youden index from the model's ROC analysis. A decision curve analysis (DCA) was used to assess the clinical net benefit of the nomogram [36].

Yang et al. (2025) performed internal validation of the nomogram using 1,000 bootstrap sample corrections. The optimism-corrected concordance index (C-index) was 0.73 after corrections, with a calibration slope of 0.93, and the area under the curves for Yang et al.'s model, the UDR, and the VURx in predicting the occurrence of breakthrough infections were 0.736, 0.680, and 0.546, respectively [36].

This prediction model and nomogram show promise for being a simple, user-friendly tool that can be applied easily in a clinic setting. The clinical and radiological variables included are generally easily available and the simplicity in interpretation makes it an attractive option. The primary limitation of the models use at present is the lack of any external validation limiting generalizability. Future prospective studies with larger populations across a diverse background are necessary to bring this model into mainstream practice.

2.4. Computational Model – Troesch et al. (2021) [37]

Troesch et al. described their development of a computation model to predict early breakthrough urinary tract infections in children with vesicoureteral reflux. Retrospective records were reviewed from 864 children treated for primary vesicoureteric reflux in a single centre in Iowa between 1988 and 2018 with the intention of developing a model to predict breakthrough urinary tract infections. 136 children were included due to data availability. Using logistic regression and multiple neural network architectures through neURON++ and C++ programs, multiple predictive models utilising a range of variable were developed and assessed. The best performing model computational model was one that utilised all the variables and was demonstrated to have an area under the curve of 0.802 [37].

This computational model demonstrates high predictive accuracy which shows that if externally validated in diverse prospective cohorts it may prove to be a useful tool in clinical practice. The main limitations are that the outcome duration was limited to breakthrough UTIs within 13 months of VUR diagnosis. This was due to concerns about the relevance of clinical data changing through development thereby limiting its current usefulness to predicting UTIs in the first 13 months. It is also noteworthy that the model's reliance on a large amount of clinical data and access to advanced computational technology disadvantages it when compared to some of the other predictive tools available.

3. Predictors of Those Who Benefit from Continuous Antibiotic Prophylaxis (Table 3)

3.1. Risk Classification System – Wang et al. (2018) [38]

Wang et al. (2018) sought to identify which patients with vesicoureteral reflux were at greatest risk of breakthrough infections by re-evaluating the data from the RIVUR trial [38]. The RIVUR trial

was a multisite, randomized, placebo-controlled trial involving 607 children with vesicoureteral reflux to evaluate antimicrobial efficacy, renal scarring, and antimicrobial resistance [39].

After retrospectively re-evaluating the trial data from all 607 patients. Wang et al. (2018) performed a multivariable analysis to determine factors that were independent predictors of breakthrough urinary tract infections. They concluded that VUR grade (high vs. low), presence of bladder and bowel dysfunction, history of urinary tract infection recurrence, and presence of renal scarring were all significant predictors and developed a risk classification model utilising these variables. The model stratifies patients into low-risk (circumcised males or females with grade 1-3 reflux AND no evidence of bladder and bowel dysfunction/constipation) and high-risk (uncircumcised males with VUR Grade I-III ± BBD/Constipation OR females with VUR Grade I-III and BBD/Constipation OR females and males with VUR Grade IV ± BBD/Constipation). Wang et al. calculated that the number needed to treat for low-risk patients was 18 and for high-risk patients was 5 with regards to treatment with prophylactic antibiotics to prevent breakthrough urinary tract infection. All outcomes reported has p values of <0.05 [39].

This risk model provides an insight into whether patients benefit from continuous antibiotic prophylaxis which is a pertinent clinical question considering concerns regarding antimicrobial resistance. It is easily applied in clinical practice as the categorisation is binary however currently it has not been externally validated so cannot be reliably applied outside of its original cohort.

3.2. Machine Learning Model – Bertsimas et al. (2021) [40]

Another attempt to generate a predictive model through re-evaluation of the RIVUR trial data was undertaken by Bertsimas et al. (2021). In this case the investigating team used the following variables: VUR grade, serum creatinine, race, gender, prior UTI symptoms (fever, dysuria), and weight percentiles to develop a machine-learning model to predict which patients would benefit from continuous antibiotic prophylaxis [40].

Two models were constructed in parallel using a randomly selected 80% of the trial data, one to predict the risk of recurrent urinary tract infection whilst being treated with antibiotic prophylaxis, and one without treatment with antibiotics. The final prediction model of recurrent urinary tract infection (continuous antibiotic prophylaxis/placebo) achieved an area under the curve of 0.82 indicating high predictive accuracy [40].

By assigning a risk reduction cutoff of 10% for recurrent urinary tract infection, it was found that the minimal recurrent urinary tract infection per population level was achieved by giving continuous antibiotic prophylaxis to 40% of patients with vesicoureteral reflux instead of everyone. In a test set the incidence of recurrent urinary tract infection in this group was significantly lower when compared to those whose continuous antibiotic prophylaxis assignment differed from model suggestion (7.5% vs 19.4%, $p=0.037$) [40].

In summary, Bertsimas et al. (2021) created a machine-learning model that appears to be able to accurately differentiate which patients will achieve the greatest benefit from continuous antibiotic prophylaxis. Whilst this is an attractive option thus far it has not been externally validated and cannot therefore be reliably applied across paediatric urology practice. This combined with the technological limitations of making this model widely accessible are preclusive to general use.

4. Predictors of Those who Benefit from VCUG After a First Febrile UTI (Table 4)

4.1. Oostenbrink Multivariate Model – Oostenbrink et al. (2000) [41]

The Oostenbrink Multivariate Model was described after a retrospective analysis of 140 children who presented aged <5 years old to hospital with a first episode of febrile urinary tract infection between September 1993 and September 1996. Data was collected from 3 large hospitals in The Netherlands. The purpose of the model was to predict which children presenting with their first

febrile urinary tract infection may have vesicoureteral reflux and thus should be investigated with a VCUG [41].

After using a stepwise approach to include variables and refine predictive models they concluded from their analysis that sex, age, family history of uropathology, serum C reactive protein, and ureteral dilation on ultrasound scan were all independent predictors of VUR [41].

The final clinical prediction model achieved an area under the ROC curve of 0.78 and a risk prediction score was produced that consists of a summation of points attracted for each of the positive findings. Oostenbrink et al. (2000) concluded that the risk score showed promise but required prospective validation before being applicable in clinical practice [41].

Several studies have gone on to externally validate the Oostenbrink model. Leroy et al (2006) tested the model using a retrospective cohort of 149 children and concluded that although the sensitivity was high the specificity was low at 3% for VUR of all grades and 13% for VUR of grade 3 or higher [42]. Sánchez Bayle et al. (2008) concluded after a review including 267 infants that the score did not effectively predict VUR [43], and Verhola et al. (2010) concluded after applying the model in 406 patients that the sensitivity was 24% for identifying reflux of grade 3 or higher [44]. The external validation therefore suggests that this tool is not widely applicable to clinical practice.

4.2. Leroy Clinical Decision Rule – Leroy et al. (2012) [45]

Leroy et al. (2012) derived a clinical decision rule to predict which children presenting with a first febrile urinary tract infection will go on to be diagnosed with grade 3 or higher vesicoureteral reflux and therefore would benefit from cystography [45].

The authors performed a reanalysis of data from 8 institutions gathered from previously published prospective cohort studies. They considered all children from 1 month to 4 years old who presented with a first febrile UTI to hospital; 494 children were included. Procalcitonin, CRP, pelvicalyceal dilatation, and ureteral dilatation were all statistically significant for high-grade VUR on univariate analysis.

All these variables were then entered into a predictive model, and after a stepwise reduction procedure revealed only serum procalcitonin and ureteral dilatation on ultrasound scan remained significantly associated with VUR grade 3 or higher thus contributed to the prediction according to a maximum likelihood ratio estimate. The final fit of the model was good with a P value = 0.2 and its area under the ROC curve being 0.75 [45].

The final rule recommended that cystography should be performed in cases with a serum procalcitonin level ≥ 0.17 ng/mL and ureteral dilation on ultrasound scan, or without ureteral dilatation when the serum procalcitonin level ≥ 0.63 ng/mL. The publishing team found that the rule yielded an 86% sensitivity with a 46% specificity [45].

The clinical rule was validated by the original publishing team soon after republication of the original manuscript using a separate cohort of 413 children. They reported that the specificity of 46%, unchanged from the original publication, however sensitivity dropped to 64%. This difference was speculated to be related to the timing of procalcitonin evaluation. In this cohort 34% of the patients with high-grade VUR were misdiagnosed by the rule [46].

This clinical decision rule is simple to apply and requires minimal specialist information making it an attractive option for clinical practice however currently it has not been demonstrated in external validation studies to be reliable and therefore is not currently appropriate for use in general clinical practice.

4.3. Lertdumrongluk Score – Lertdumrongluk et al. (2021) [47]

The Lertdumrongluk score was developed after retrospective analysis of 260 children under 72 months of age who presented to a tertiary hospital in Thailand between January 2008 and December 2019 with a first febrile urinary tract infection, and underwent renal ultrasound scanning and voiding cystourethrography during their admission. The authors performed a multivariate logistic regression analysis to identify variables that were significantly associated with an ongoing diagnosis of

vesicoureteral reflux and concluded that the following factors were significant: age >6 months at presentation, white blood cell count of greater than or equal to 15,000/mm³, presence of sepsis, and abnormal renal ultrasound findings [47].

Lertdumrongluk et al. assigned points for the presence of each variable, and used the total summed score was used to develop a binary scoring system. Patients with a score of 0-2 were stratified as low-risk and those with a score of > 2 were stratified as high-risk. By categorising the patients with a score of >2 as high risk and using this to facilitate the decision to perform a VCUG to diagnose VUR Lertdumrongluk et al. were able to reduce the number of patients undergoing unnecessary VCUG with a reported predictive accuracy of 70% [47].

The main advantages of the Lertdumrongluk score are that it relies on simple and readily available information early in the clinical course and is easy to calculate. However, to date no external validation has been published and therefore the score is not currently applicable outside of its derivation cohort.

4.4. Kurokawa Predictive Score – Kurokawa et al. (2022) [48]

Kurokawa et al. (2022) developed a predictive scoring system to attempt to improve stratification of patients under 2 years of age presenting with a first febrile urinary tract infection secondary to an E coli infection. Data was collected retrospectively regarding all children who presented with a first febrile E coli UTI between within two distinct timeframes: January 2007 – March 2014 and January 2016 – December 2019. All the patients were treated at a single large teaching hospital in Japan. The specific timeframes given were chosen due to a policy change whereby between 2007 and 2014 every patient presenting with a first febrile UTI underwent a VCUG whereas between 2014 and 2019 only patients who had abnormal renal ultrasound findings, complications of bacteraemia, non-E-coli induced febrile UTI, or acute focal bacterial nephritis. Kurokawa thus dubbed the 2007 – 2014 cohort the 'non-selective' group and the 2014 – 2019 group the 'selective' cohort. The non-selective cohort consisted of 111 patients and the selective cohort consisted of 102 patients [48].

The authors utilised the factors that they identified as being significantly predictive of diagnosing VUR and formulated a predictive score. They then applied the score to patients from the selective and non-selective cohorts and refined the predictive factors based on their results. The final score consisted of age <5 months at presentation (1 point), female sex (2 points), duration of fever >3 days (1 point), serum total protein of <6.6g/dl (2 points), serum sodium <136mEq/L (1 point), and serum glucose >100mg/dl (2 points). The maximum score is 9 and a value of ≥5 had 80.7% sensitivity, 62.9% specificity, a positive predictive value of 49.0% and a negative predictive value of 88.0%. The overall area under the ROC curve was 0.8 [48].

The Kurokawa predictive score is a simple tool that utilises data that is readily available in patients being investigated for a febrile urinary tract infection. This makes it a promising way to stratify who needs to undergo further investigations with a dose of radiation. The primary limitation is at this stage that no external validation has been published making it difficult to confidently say that the score is useful outside of its original cohort.

4.5. Prediction Model for High Grade VUR – Laleoğlu et al. (2025) [3]

Laleoğlu et al. (2025) sought to improve prediction of which children presenting a urinary tract infection and/or hydronephrosis to strategise who is likely to have an underlying diagnosis of severe vesicoureteral reflux (VUR grade 4 or greater) and thus would benefit from a voiding cystourethrogram [3].

The authors performed a retrospective analysis of 1044 patients who underwent VCUG due to a urinary tract infection or dilated urinary tract on ultrasonography and developed a predictive model using variables that they determined were significantly associated (P<0.05) with VUR grades 4 or above. The variables were selected using the chi square test. The odds ratio for each chosen variable was determined and divided by the lowest odds ratio to simplify the score. Cut-off values for each variable were then established the evaluating the sensitivity and specificity values, and

Youden's Index. The variables chosen for inclusion in the model included: age <2 years, male sex, non-E. coli uro-pathogen, hydronephrosis classified as UTD-P3 urinary tract dilatation on ultrasound, and multiple kidney scars on DMSA scintigraphy with 1 point assigned for the presence of all variables except for hydronephrosis on ultrasound and multiple kidney scars which were assigned 2 points when present [3].

The total score therefore was between 0-7 points, patients were classified as low-risk if they scored 0-2 points, moderate-risk if they scored 3-4 points, and high risk if they scored 5-7 points. The rate of severe VUR among children with a score 5 was 37.5%, while it was only 1.8% in children with a score ≤ 4 ($p < 0.001$). Sensitivity, specificity, PPV, NPV and OR of score 5 for predicting severe VUR were 50.0%, 97.1%, 37.5%, 98.2% and 33.6, respectively [3].

This prediction model shows promise for being a simple scoring system using variables that are generally easy to obtain although ultrasound scanning and DSMA scanning do require a level of specialist investigation that might not be universally available. To date no external validation of this predictive model has been published and this will be necessary to demonstrate its widespread validity.

Discussion

Vesicoureteral reflux remains a clinical challenge both to streamline exposure to diagnostic modalities and to predict short and long-term outcomes. Numerous scoring systems, nomograms, predictive tools/models, ratios, and computational models have been developed over the past 4 decades to aid clinicians in predicting which patients should be investigated for potential reflux and of those with a confirmed diagnosis who is likely to experience spontaneous resolution, persistent disease requiring surgical intervention, or recurrent infections. The persistence in publications suggests that there remains an uncertainty surrounding the best method to predict disease progression and treatment response. To our knowledge this ATLAS serves as the first document to provide a comprehensive summary of current tools that have been developed to predict outcomes for patients with suspected or confirmed vesicoureteral reflux.

The predictive tools described in the literature demonstrate of a range of methodologies - from early anatomical or radiographic ratios to advanced machine learning and computational models. This progression demonstrates the evolving evidence regarding individual predictive factors but also the technological advancements that have become available to individualise prognostic assessments. Whilst early assessments tended to focus on radiological parameters that can be reproduced with relative reliability to provide categorical risk stratification, more modern multifactorial indices and computer-based models often use a wide range of radiological, clinical, and biochemical data points to produce individualised numerical scores which can be applied either as they are or then categorised into risk groups. Recent tools have leaned heavily into automated data processing and pattern recognition to enhance predictive accuracy. Despite the relatively large number of predictive tools that have now been published none has demonstrated sufficient reliability, accessibility, and generalizability to achieve widespread clinical use in paediatric urology.

Several limitations consistently recur across the available tools, most notably the fact that most tools were derived using relatively small, single centre retrospective data sets often collected over extensive time periods. This introduces challenges both with the acquisition of data for analysis such as missing data points and variability in the methods used to initially gather, store, and present data points, and changes in diagnostic standards and management strategies over time. In combination the heterogeneity in imaging practices/interpretation, reflux grading, and treatment standards make it difficult to validate and compare different tools for clinical use. Even tools such as the vesicoureteral reflux index and nomograms published by Estrada et al. (2009) which were developed using relatively large data sets remain constrained by a lack of prospective external validation and inherent variability in interpretation of voiding cystourethrograms.

Another significant challenge is heterogeneity in inclusion criteria, outcome measurement, and statistical analysis even when comparing tools with similar outcomes. Alongside the issue of small

data sets and challenges in extracting meaningful information this makes meta-analytic synthesis and the formation of universal recommendations or cut-off values challenging.

The transition towards computational and machine-learning models represents a promising new era of prognostic modelling. Several of these methods have demonstrated superior discriminatory ability when compared to earlier publications of regression-based tools. However, their reliance on detailed and complete data sets containing diverse clinical information, complex computational capabilities, and imaging data with potential heterogeneity in interpretation and availability between patients and clinical settings serves as a current barrier to widespread real-world application.

Despite the variability in design, methodology, and defined outcomes across the predictive tools described here, several factors have consistently demonstrated prognostic value. Ureteral morphology, reflux grade, bladder dysfunction, and presence of renal scarring have been widely found to have consistent prognostic significance in patients with confirmed or suspected vesicoureteral reflux suggesting that these may prove valuable focal points for future development of predictive tools.

Ultimately, the field remains limited by a lack of multicentre, prospective validation of many of these predictive tools. Collaborative studies designed to evaluate and compare existing tools using uniform definitions of predictors and outcomes are essential. Incorporating advanced statistical methods and artificial intelligence technologies offers an opportunity to compare and combine current published methods to develop a universal, evidence-based risk-stratification model that can be used to guide both diagnostic decision making and management strategies in patients with vesicoureteral reflux. This will require a balance of technological sophistication and clinical practicality to ensure that the predictive tool is a useful adjunct to clinical practice rather than complicating everyday clinical work.

Conclusion

This ATLAS provides the first consolidated overview of current predictive tools designed to aid clinicians prognosticate when considering investigative and treatment pathways for paediatric patients with suspected or confirmed vesicoureteral reflux. Across 17 described tools ranging from traditional anatomical ratios to modern machine-learning models a consistent goal emerges: to improve risk-stratification, reduce unnecessary invasive or potentially harmful investigations, and provide individualised treatment plans to optimise patient care. However, despite decades of research and progress, no predictive tool has demonstrated to be universally applicable. The principal limitations are the reliance on retrospective, single centre datasets, variability in definitions, and lack of prospective validation. The convergence of simple clinical predictors and advanced computational modelling represents a promising direction however rigorous multicentre validation across a diverse population will be required to translate these advances into practical clinical tools.

We suggest therefore that future work includes developing a standardised, multicentre, and prospectively validated predictive framework that incorporates established clinical variables and the analytical power of artificial intelligence. Such a model could provide the necessary transparency, accessibility, and precision to achieve universal adoption – transforming risk evaluation and personalisation of care for patients with vesicoureteral reflux.

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