Predictive Models for the Management of Vesicoureteral Reflux from the View of Statisticians

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Abstract: The management of vesicoureteral reflux (VUR) is one of the most challenging issues not only for pediatric urologists but also for pediatric nephrologists and all other related subspecialties. Urinary tract infections (UTI), pyelonephritis and renal scarring which may lead to deterioration in renal function are the common complications in a child presenting with VUR. Due to the patient heterogeneity and varying management options, patient selection for each treatment modality remains as a controversial issue. The different bio-statistical models have been used in order to disclose the factors affecting success of different management modalities and represent the incidence of possible complications. Bio-statistical models are useful to define variables which may help predict the outcome of disease during the different managements. Artificial neural networks (ANN) and regression models are popular methods employed to predict the outcome of urological abnormalities. Statistical models and ANNs provide an estimation of the probability of outcome that is of utmost importance in clinical decision. This study addresses both bio-statistical methods and ANNs employed to predict the outcome of VUR management and their clinical applications. To reach the best fit model that predicts the VUR outcome in a child, widespread knowledge regarding available bio-statistical methods is needed.

Keywords: Modeling, Vesicoureteral reflux (VUR), Regression, Artificial neural networks (ANN), Decision support.

INTRODUCTION

Vesicoureteral reflux (VUR) is defined by retrograde movement of urine into the ureters with increased risk of pyelonephritis and renal scarring [1]. For many years, it was a matter of debate that which child will benefit from the medical/surgical treatments? [2] Patient selection and counseling prior to any intervention mandate a deep insight into the factors contributing to the outcome. Here, bio-statistical models have been employed to help the urologists in decision making. The most popular models that employed widely are regression models. Regression models provide the urologist with exact odds ratio (OR) in addition to the clarification of the issue to see whether or not the factor has a significant impact on the outcome. Regression models are useful in estimating the outcome based on a linear relation and controlling for confounding variables. Logistic regression and Cox regression are two popular members belonging to the family of regression modeling [3]. Logistic regression and Cox regression are applicable in estimating the outcome of surgical and conservative management of VUR, respectively.

On the other hand, more recent tools have been developed to help physicians predict the outcome of each management approach of VUR. Artificial neural networks (ANN) as intelligence based systems are computational newer modeling tools that mimic human brain learning system [4]. They provide non-linear, robust and parallel analysis as compared with regression models. ANNs are attractive tools that can be employed in practice of clinicians [5, 6]. However the usefulness of bio-statistical models is well known in a wide variety of issues, the awareness in urology should be improved due to poor employment of modeling tools in clinical urology. Prostate cancer is the most studied issue in urology that modeling have been widely used for decision making and patient counseling [7]. VUR is another challenging issue that modeling the outcome may be helpful. This study aimed to provide a preliminary understanding regarding regression models and ANNs. Moreover, studies employed these modeling tools to predict the outcome of VUR management have been discussed.

REGRESSION MODELS

General linear model is the cornerstone of regression analysis [8]. In this type of modeling, the numerical outcome (*y*) can be easily predicted using linear predictors. In a linear predictor, the association of *n* variables (*x*) to the outcome can be determined by regression coefficients (*β*).

Formula .1) $Y= \beta_0+ \beta_1x_1+ \beta_2x_2+ \beta_3x_3+ \beta_4x_4+\ldots+ \beta_nx_n$

Regression models comply with general linear models [9]; however, there are a few differences in this type of modeling. Regression models draw the relation between independent variables with a transformation of

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dependent variable or outcome [10, 11]. With this transformation a binary outcome will be analyzed as a numerical variable. Logistic regression and Cox regression are two models that use transformation of a binary outcome for analysis. Logistic regression modeling is applicable for drawing the relation between binary outcomes and affecting variables [12, 13]. Cox regression is the model of choice for drawing the relation between the time and a binary outcome and affecting variables [12, 14]. The link function for logistic regression is logit (logarithm of odds) [15], while, the link function of Cox regression is a logarithmic function. The fitness of these regression models can be estimated using the regression coefficients. This is also called maximum likelihood estimate [16]. Indeed, the goodness of fit should be assessed to prevent from misleading and incorrect inferences [17]. This vital analysis should be noted as the first step of application of the bio-statistical methods to the dataset. Hosmer *et al* represented a brief and comprehensive methodology regarding how the goodness of fit is important and how it should be assessed [17]. Following formula shows how Logistic regression model estimates the probability of outcome (p);

Formula .2) Logistic regression model; Log ($p/1\text{-}p$) = $\beta_0+ \beta_1x_1+ \beta_2x_2+ \beta_3x_3+ \beta_4x_4+\ldots+ \beta_nx_n$

The measure of independent variable effects on the outcome is OR for logistic and hazard ratio (HR) for Cox regression models [18]. Moreover, the effects linked to the outcome *via* a linear predictor are multiplicative. In a regression model, the null hypothesis is that there is no association between suggested variables and the outcome [19]. The alternate hypothesis is that there is association between suggested variables and the outcome [19]. Moreover, hypothesis testing is aimed at refining the model by examining the interactions between variables and the outcome and deciding upon variables should be included in the final model [19]. This decision is based on the Wald tests or Likelihood ratio tests [3]. This procedure is aimed at constructing a balanced model with the maximum accuracy and the least possible variance [3, 19]. Accordingly, regression modeling can be done with either of forward or backward approaches [3, 19]. In one hand, in a forward approach, only variables showing significant association with the outcome will be considered in final model [3, 19]. On the other hand, in a backward approach, all the variables are included in the model initially [3, 19]. Thereafter, all the variables do not show the significant association with the outcome will be omitted using stepwise testing to construct the final model.

LOGISTIC REGRESSION MODELING

Logistic regression is a popular method to unravel the association between multiple independent variables with a binary outcome[10]. Interpretable coefficients are of the advantages of logistic regression as compared with other models (i.e. neural networks). For *n* number of independent variables, the probability of the outcome (p) can be estimated using restatement of the formula .2 as follows;

Formula .3) $p= [exp\ (\beta_0+ \beta_1x_1+ \beta_2x_2+ \beta_3x_3+ \beta_4x_4+\ldots+ \beta_nx_n)]/ [1 + exp\ (\beta_0+ \beta_1x_1+ \beta_2x_2+ \beta_3x_3+ \beta_4x_4+\ldots+ \beta_nx_n)$

In a valid model, the estimated probability of the outcome should not differ significantly with the actual value. This may be understood only by applying the constructed model to a large body of data. Moreover, it highlights the place of studies investigating the validity of the introduced model by applying to other samples. This can be done with using the software generated based on the supposed model [20]. On the other hand, with growing knowledge regarding the affecting factors, other variables may enter into the model. Of note, this stepwise procedure may be done considering what was described for initial development of the model.

Required sample size for development (using development data set) of model and updating it (using validation data set) is of utmost importance. Using large data sets, estimated probabilities will be more close to the event, while, small data sets cause false estimation [21].

COX REGRESSION MODELING

Cox regression or proportional hazard regression is the most common model that has been used for regression analysis of time to event in different strata of affecting variables [22]. The overall approach in Cox regression is similar to the Mantel-Cox method [8]. It complies with proportional hazard assumption in which the ratio of the hazards remains constant over the time [11, 23]. However, the main assumption of survival analyses is that the hazard will be changed over the time [24]. Accordingly, hazard of the occurrence of the event at time of *t (h (t))* is needed to estimate the probability of being free from the event at time of *t (S (t)),* also called survival probability at time of *t*.

Formula .4) (S (t_m)) = $s_{t1} \times s_{t2} \times s_{t3} \times s_{t4} \times \ldots . \times s_{tm}$

Where $S(t_m)$ is the probability of being free from the event at time of m. In modeling the VUR resolution $S(t_m)$ indicates the probability of being free from the VUR at follow up time of m. To find factors that significantly influence the outcome of VUR, $S(t_m)$ should be estimated for each stratum of variables using the Mantel-cox approach [25]. Other strategy that leads to the similar results is to estimate the hazards using a linear formula. Accordingly, the following formula is helpful;

Formula .5) Cox regression model; $\text{Log}(h(t)) = \log(h_0(t)) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \ldots + \beta_n x_n$

Where, $h(t)$ is the hazard at time of t and $h_0(t)$, baseline hazard. $X1$ to Xn are n variables assumed to affect the outcome. Restatement of the formula .5 gives the $h(t)$ as follows;

Formula .6) $h(t) = h_0(t) \times \exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \ldots + \beta_n x_n)$

In other words, Cox regression method represents a conditional likelihood estimation of outcome in which only the regression coefficients that significantly differ from zero will remain in the final constructed model. The procedure is similar to what happens in logistic regression analysis except that Cox regression measure of affecting variables is rate ratio [8]. As described below, this is the best type of modeling for spontaneous resolution of VUR and cohort studies [25-28]. It should be born in mind that with discovery of other variables, the model should be updated. Moreover, the stability of the model can be assessed using a bootstrap resampling procedure which is data-dependent [29, 30].

APPLICATION FOR MANAGEMENT OF VUR

The subtypes of the generalized linear models that are applicable in estimating the outcome of VUR management are logistic and Cox regression models. VUR status is a binary dependent variable with two states of presence or absence. Logistic regression is usually the best fit model to estimate the surgical correction of VUR with respect to controlling for confounders, while, Cox regression is the better option for estimating the outcome of conservative management. Conservative management of VUR is based on the spontaneous resolution of VUR during the long time conservative antibiotic prophylaxis (CAP). Time to binary event is the type of outcome variable that can be well modeled with Cox regression modeling. Cox regression model can show the association of independent variables to the time in which the outcome (i.e. VUR resolution) happened. Simple estimation of outcome of VUR resolution in each stratum can be obtained *via* the Mantel-cox analysis. As we previously demonstrated VUR grade can affect the outcome of VUR correction surgery [31]. Moreover, in consistency with other studies, it can

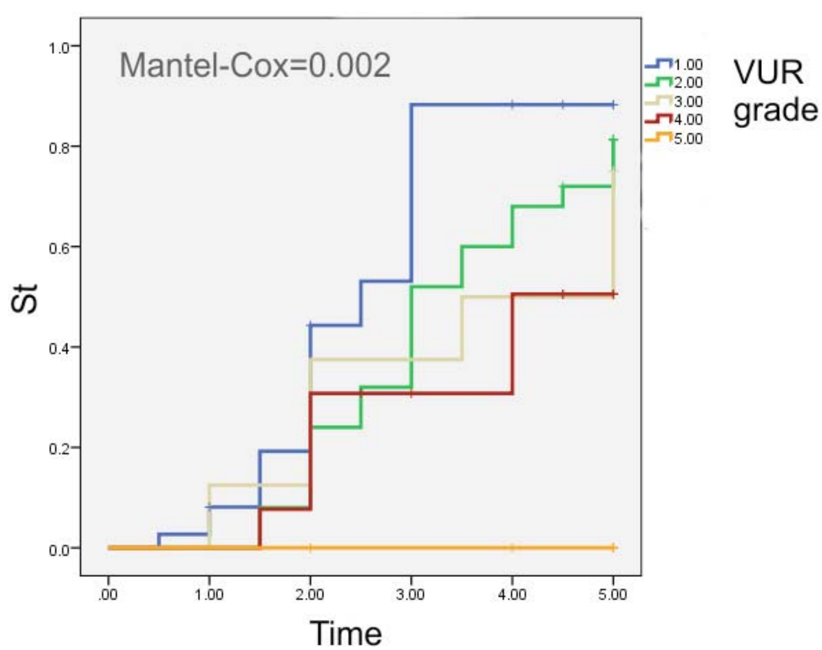

Figure 1: Spontaneous resolution of VUR using non-surgical management. The figure shows that children with grade V of VUR will not benefit from CAP, while, for the patients with lower grades of VUR spontaneous resolution will be achieved up to 86% patients. St is indicator of probability of being free from VUR.

affect spontaneous VUR resolution; Figure **1** shows the probability of VUR resolution in each grade of VUR in 88 patients with VUR who received CAP at our center. In contrast to low resolution rate in patients with higher grades of VUR (grades of IV and V), VUR was eliminated in most of the patients with the lower grades (grade of I).

SPONTANEOUS RESOLUTION OF VUR

Now, after a long time seeking for the best management approach for children with VUR, surgical interventions have lost their popularity and a nihilistic attitude about surgical correction of VUR has been raised [32-34]. Indeed, recently watchful waiting has been reported to be a good choice for children with low grades of VUR [34]. Moreover, the latest guidelines of American Urological Association (AUA) [1] and European Association of Urologists (EAU) [35] didn't approve any definite therapeutic modality for children with VUR and stated that the decision should be made based on affecting variables on VUR outcome such as patient's age and gender, renal function, presence or absence of lower urinary tract symptoms and bladder function [1, 35]. In this way, the role of biostatical models is highlighted since generation of valid and reliable predictive nomograms is based on such a modeling.

Of the pioneers that developed linear models to predict spontaneous resolution of VUR are Dr. Cooper and his colleagues. They developed a 1 and 2 year computational predictor model of spontaneous VUR resolution on 205 children with VUR [36]. They showed that linear modeling is more fitted for analysis rather than non-linear neural networks. The variables included in the constructed model comprised Sex with two options of male or female, presentation of VUR with 4 options of febrile UTI, afebrile UTI, antenatal hydronephrosis and others, age as a continuous variable in terms of years, laterality with two options of unilateral and bilateral, volume in which VUR started as a percent of predicted bladder capacity (ranged from 7.3% to 202.3%), VUR grade on right and left according to the international reflux study in children [37], when VUR started on right and left with 3 options of none, filling and voiding, duplication with two options of yes and no and finally voiding dysfunction with two options of yes and no. The receiver operating characteristic (ROC) curve was drawn and revealed that the model was significantly valid with the area of 0.86 [36]. Additionally, This model was also validated with a sample of Japanese patients with VUR [38]. As aforementioned, with improving the knowledge regarding the factors that can affect the outcome; the models should be updated. With suggestion of renal function as an affecting variable on VUR resolution [39], Cooper and his colleagues added this factor to previously developed model. Addition of baseline renal scan data with two options of abnormal (<=40% or renal scar) and normal improved the validity of the model in which the ROC of reconstructed model reached 0.94 [40]. One of the limitation of updated model was reconstruction based on the data of patients with primary VUR, while, the initial model was developed using the data of patients with either of primary or secondary VUR. Of utmost importance to say is that they developed the computational software with C++ and UROn++ that is applicable in other samples and it lets the physicians assess its reliability. Their computational software has been also known as university of Iowa calculator.

There are other studies that investigated the spontaneous resolution of VUR and its affecting factors in a cohort design and using linear models but none of them developed computational calculators [41, 42]. Of them, the most important application of linear models to predict the spontaneous VUR resolution was the study by Estrada *et al.* [43]. In a sample of 2462 children with VUR, application of Cox regression analysis revealed that females with bilateral VUR had the worsened prognosis regarding VUR resolution, while, in patients in whom VUR was diagnosed prior to 1 year of age, who had the history of antenatal hydronephrosis and patients with unilateral VUR resolution of VUR occurred sooner [43]. However, it was not clearly mentioned in aforementioned study, it seems that they assumed the VUR resolution as the event.

SURGICAL INTERVENTION FOR CORRECTION OF VUR

Logistic regression seems to be the model of choice to estimate the correction of VUR following anti-reflux surgery. To date, gender, age, VUR grade, voiding dysfunction, laterality of VUR, ureteral duplication as well as other causes of secondary VUR, surgical technique [44, 45], surgeon experience [46, 47] and injected volume [48] and mound appearance [49] (following injection therapy) have been suggested to affect the outcome anti-reflux surgery [31, 46, 48, 50-53]. However, the only variable that there is consensus regarding its effect on the outcome of surgery is pre-operative VUR grade. VUR grade of V seems to be resistant to injection therapy, however, with other surgical techniques such as ureteroneocystostomy and concomitant autologous blood and Dextranomer/hyaluronic injection it can be resolved with more than 80% success [54]. Yucel *et al* conducted a logistic regression analysis on 168 patients with 259 renal refluxing units (RRU). They employed injection therapy with either of subureteral or intramural techniques and found that those patients with high grade of VUR (OR = 0.46, 95% confidence interval (CI) = 0.29-0.72) and who received injected volumes more than 0.5 milliliter (OR = 0.3, 95% CI = 0.09-0.98) would experience worsened results as compared with patients with alternative features [48]. Moreover, they found that achieving a satisfactory mound was the strongest predictor of VUR resolution with OR of 11.5 and 95% CI of 5.3-25 [48]. Routh *et al* investigated the factors that can affect the outcome of anti-reflux surgery using logistic regression modeling and found that VUR grades of IV-V (OR = 5.00, 95% CI = 1.21-20.71), subureteral injection rather than hydrodistention injection technique (OR = 1.81 95% CI = 1.21-2.89) and low experience of surgeon (OR = 6.29, 95% CI = 2.38-16.60) were associated with failure of surgery on Univariate analysis. It seems that there are statistical errors in generation of OR since according to the raw data presented in the text of article OR of higher grades of VUR as well as subureteral injection technique should be 0.20 and 0.55, respectively [45]. Finally, they found that VUR grade (OR = 7.27, 95% CI = 1.51-34.94) and surgeon experience (OR = 5.17, 95% CI = 1.51-17.74) were predictive of VUR resolution on multivariate analysis [45]. Confusingly, with respect to the selected reference the final OR of aforementioned variables should be lower than 1 instead of what was presented [45].

Unfortunately, some of studies aimed at finding affecting variables on anti-reflux surgery provided neither of the exact OR nor the raw data and only stated which variables attained the level of significance [46, 47]. This reflects poor knowledge regarding the bio-statistical modeling and the need for propagating this knowledge. However OR is not as reliable as risk ratio, it is a reflection of magnitude of the affecting variable on the outcome. Moreover, OR generation is one of the advantages of logistic regression analysis over the neural networks. To combine the results of studies in a meta-analysis, provision of OR as well as the raw data is beneficial [55]. Accordingly, the authors suggest presentation of OR in future studies on the surgical outcome of VUR correction. Moreover, computational calculators with the ability to estimate the VUR correction following anti-reflux surgery are awaited.

FEBRILE URINARY TRACT INFECTIONS

The goal of management of VUR is to prevent from febrile UTIs and renal injury [1, 35] This is what noted as clinical success of VUR management rather than classic assessment of VUR correction on voiding-cystourethrogram (VCUG) [56]. Febrile UTI as the outcome can be modeled as two aspects (1) Occurrence or non-occurrence of febrile UTI as a binary outcome using logistic regression modeling, (2) Time to first febrile UTI and complementary variable of time free of febrile UTI using survival analysis and Cox regression modeling.

If a physician wants to counsel the patient regarding overall probability of febrile UTI following each management of VUR with respect to the all affecting factors, logistic regression modeling is a good choice to reach the answer. However to be clinically available and applicable, it is not enough to run a logistic regression model on a small dataset from one center. The modeling is better to be done on multicenter data with development of an online friendly user calculator. This allows the users validate the developed calculator, assess its reliability and even upgrade the current calculator *via* a worldwide cooperation. This strategy has been already carried out with successful results by Cooper and colleagues with development of Iowa calculator of spontaneous VUR resolution.

Recent study by Hunziker *et al* [57] aimed at finding incidence of febrile UTIs following successful correction of VUR confirmed by VCUG. Overall, 5.7% of children experienced febrile UTI following endoscopic treatment of VUR. The purpose of this study is to find the effect of different variables on the incidence of febrile UTI. They used logistic regression modeling and found that female sex (OR = 3.8, 95% CI = 1.8-7.9), Polytetrafluoroethylene injection (OR = 1.9, 95% CI = 1.1-3.3) and bladder bowel dysfunction (BBD) either before or after operation (OR = 3.5, 95% CI = 1.4-8.3 and OR = 2.9, 95% CI = 1.5-5.5) are associated with increased incidence of febrile UTI. One of the main messages of this modeling was the association of BBD with incidence of febrile UTI even with successful correction of VUR [57]. It highlights the importance of treatment of BBD to manage VUR. Accordingly, bio-statistical modeling may open new insights into the causes of failure and suggest key points to improve the practice.

ARTIFICIAL NEURAL NETWORKS (ANN)

ANNs as intelligence based systems are computational modeling tools that mimic human brain learning system [13, 58]. These expert systems use a raw database for leaning (training phase) and are developed on the basis of experience [58]. A multi-layer perceptron with interconnected neurons (nodes) in at least three layers including input, hidden and output layers construct an ANN [58]. This kind of structure makes ANNs capable of performing parallel computations *via* a non-linear approach (Figure **2**). The most prominent feature of an ANN as compared with logistic regression modeling is existence of at least one hidden layer that is vital for non-linear analysis [4, 6]. In such a way a network with sigmoid activation function that lacks a hidden layer is actually identical to a logistic regression model [58]. Moreover, logistic regression models and ANNs differ with respect to function and processing style; a logistic regression model develops and works logically with sequential processing style, while, ANN function is based on perceptual patterns and parallel data processing [58]. Indeed, the features of ANNs that make it popular are non-linearity, parallel processing style, learning, adaptivity, noise and fault tolerance and ability to handle fuzzy information [4, 6].

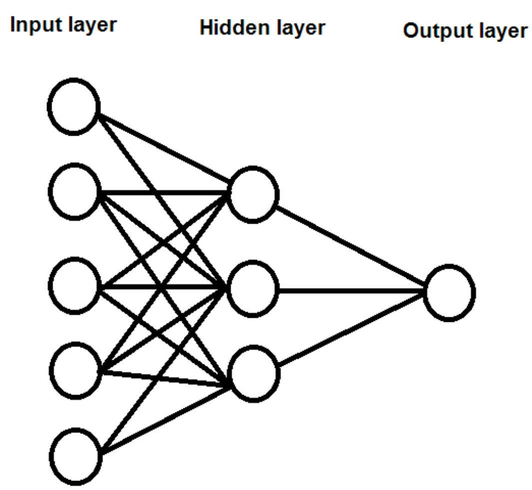

Figure 2: A three-layer feed forward neural network.

Learning rule in an ANN determines how the weights of interconnections of nodes should be updated following each training cycle [5, 59, 60]. The weight updates continue until a satisfactory error is achieved [60]. Two main phases of development an ANN are (1) training phase in which the an ANN tries to adjust the weights to fit the training data (learning) and (2) testing phase in which the performance of the network is assessed by exposing the network to untrained data and evaluation of the model response [60]. Finally, an ideal network should be validated by a distinct dataset to confirm model accuracy [61]. To come by helpful results, it necessary to reach the best fit of an ANN to address the problem changing in the number of both hidden nodes and layers. However, an ANN with only one hidden layer can be appropriate for most of medical issues. Moreover, too large number of hidden nodes may cause over-fitting (memorizing the trained data) and lacking of model generalization [5, 58, 60]. Another situation that can lead to over-fitting is too large number of training cycles. Indeed, a well fit model can be reached with using appropriate values of design parameters such as number of hidden layers and training cycles [5, 58, 60].

A wide variety of models have been introduced that each helps solving a specific problem. Hopefield, adaptive resonance theory (ART), Kohonen, back-propagation, recurrent, counter-propagation and radial basis function (RBF) networks are examples of introduced methods. They are differed based on the problem designed to solve, direction of flow of information, the way that weights are updated including the learning rule and algorithm and the degree of connectivity of the neurons [5, 58, 60]. Though, there are general issues in the development of an ANN including application of appropriate database size to reach a general model, data preprocessing to accelerate convergence, assigning appropriate initial values for the thresholds and weights to avoid premature neuron saturation and determining appropriate learning rate (η) and momentum coefficient (μ) to accelerate training and avoiding overshooting the solution. Finally, an important part of the ANN development is to choose convergence criteria. As mentioned before, training usually continues to reach a satisfactory error. The practical synonym of this statement is the sum of squared errors (SSE) [62, 63];

Formula .7) $SSE = (1/n)\sum_{p=1}^{n}\sum_{i=1}^{m}(t_{pi} - o_{pi})^2$

Where “*p*” denotes to training examples with “1” to “*n*” numbers, *“I”* denotes to output nodes with “1” to “*m*” numbers and t_{pi} and o_{pi} are corresponding actual and target solutions [62, 63]. With this criterion the point to terminate training that yields an optimized network can be determined [62, 63].

APPLICATION FOR MANAGEMENT OF VUR

A wide variety of problems can be solved by application of ANNs including pattern classification, clustering, forecasting, association (image completion) and function approximation (modeling) [64-66]. The main application in medical research is function approximation ability of an ANN [58]. Despite the wide employment in management of prostate disease [7], data upon ANNs in management of pediatric urological anomalies such as VUR is very poor. Serrano-Durba *et al* [67] created a back-propagation ANN to predict the outcome of VUR with anti-reflux surgery. From 261 RRUs, 183 were cured and inputs included cause of VUR, number of the treatments ranged from one to three times, the affected ureter with 4 possible types of right, left, upper pole, lower pole, endoscopic findings and the type of cystography with conventional VCUG or radio-nucleotide cystourethrogram (RNC). Initial weights were (-0.5, 0.5) and various values were tested to reach the appropriate learning rate (0.2) and momentum coefficient (0.4). Number of nodes in input, hidden and output layers was 10, 6 and 1, respectively. Five hundred training cycles (epochs) with respect to the least SSE was selected. ROC of developed model for prediction of VUR resolution was 0.77. They also found that ANN was better predictor of VUR resolution as compared with logistic regression modeling [67]. Another study by Seckiner *et al* on 95 children with 145 RRUs showed that ANN can predict VUR status following different management approaches with 98.5% sensitivity, 92.5% specificity, 97% positive predictive value, and 96% negative predictive value [68].

CONCLUSION

With respect to the controversies regarding how to manage a child with VUR and diverse therapeutic modalities that encompass watchful waiting, CAP and surgical correction of VUR, patient selection and counseling remain challenging. Bio-statistical modeling is an appropriate solution for this problem. Moreover, it paves the roads for an individualized based medicine. Artificial neural networks and regression models are popular methods employed to predict the outcome of urological abnormalities in pediatric population. Statistical models and generated calculators based on them provide an estimation of the probability of outcome that is of utmost importance in clinical decision. To develop a well fit model, deep insight to statistical and computational basis of regression and ANN models is essential.

Non-linearity, parallel processing style, learning, adaptivity, noise and fault tolerance and ability to handle fuzzy information make the ANNs popular methods for function estimation (modeling) of medical issues (for instance VUR outcome). On the other hand, regression analysis such as logistic and Cox regression modeling are older linear statistical tools with logical function and sequential processing style. However, these old tools are better predictors of VUR outcome in some studies [36]. Generally speaking, both of the regression models and ANNs may be appropriate to model VUR outcome but their fitness should be tested prior to application in decision making.

CONFLICT OF INTEREST

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