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Non-invasive parameters for the prediction of urodynamic bladder outlet obstruction: analysis using causal Bayesian networks

요역동학적 방광출구폐색의 비침습적 예측인자: 베이지안 네트워크 모델을 활용한 분석

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Master's Degree Thesis

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December 2013

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by
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Approved by Thesis Committee:

Professor ____________________Chairman
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ABSTRACT

Purpose: Numerous attempts have been made to predict urodynamic bladder outlet obstruction (BOO), however, little information exists on non-invasive parameters for BOO prediction. We aimed to identify non-invasive clinical parameters to predict BOO using causal Bayesian networks (CBN).

Methods: From October 2004 to December 2011, patients with lower urinary tract symptoms (LUTS) suggestive of BPH were included in this study. Out of the 1352 patients, 866 were selected for the analysis. Mean age, total prostate volume (TPV) and IPSS were 66.3 (±7.0, SD) years, 49.8 (±26.7) ml, and 18.0 (±7.7), respectively. Mean bladder outlet obstruction index (BOOI) was 34.0 (± 24.4), and 292 (33.5%) patients had urodynamic BOO (BOOI ≥40). Non-invasive predictors of BOO were selected using CBN. BOO prediction with selected parameters was verified using logistic regression (LR) and artificial neural networks (ANN) considering whole non-invasive parameters.

Results: CBN identified TPV, Qmax, PVR, and IPSS item 5 (slow-stream) as independent predictors of BOO. With these four parameters, sensitivity and specificity of BOO prediction were 54.1% and 86.4%, respectively, with an area under receiver operating characteristic curve (AUROC) of 0.793. LR and ANN models with the same parameters showed similar accuracy (LR: sensitivity 51.7%, specificity 90.9%, AUROC 0.797; ANN: sensitivity 43.7%, specificity 92.7%, AUROC 0.756). The AUROC of ANN was smaller than that of the other two methods (p-value range <0.001-0.005).

Conclusions: Our study demonstrated that TPV, Qmax, PVR, and IPSS item 5 (slow-stream) are independent predictors of urodynamic BOO.

Keywords: Bayes theorem; logistic model; predictive value of tests; prostatic hyperplasia; urinary bladder neck obstruction; urodynamics

CONTENTS

LEGENDS OF TABLES AND FIGURES

LISTS OF ABBREVIATIONS

Bladder outlet obstruction (BOO)

Benign prostatic hyperplasia (BPH)

Causal Bayesian networks (CBN)

Lower urinary tract symptoms (LUTS)

Prostatic specific antigen (PSA)

International prostate symptom score (IPSS)

Maximal flow rate (Qmax)

Volume of post-voided residual urine (PVR)

Logistic regression (LR)

Artificial neural networks (ANN)

Total prostate volume (TPV)

Transition zone volume (TZV)

Bladder outlet obstruction index (BOOI)

Area under receiver operating characteristic curve (AUROC)

Urodynamic study (UDS)

Prostate volume (PV)

International Continence Society (ICS)

Detrusor pressure at maximal flow rate (PdetQmax)

INTRODUCTION

The urodynamic study (UDS) is considered as the gold standard for the clinical assessment of bladder outlet obstruction (BOO) in patients with benign prostatic hyperplasia (BPH) (1-3). Patients with urodynamic BOO show higher efficacy after transurethral surgery (4, 5). In this respect, BOO is helpful in stratifying BPH patients eligible for surgical treatment. However, UDS has significant limitations in terms of invasiveness, cost, and morbidity (6).

There have been numerous attempts to substitute non-invasive parameters for UDS to predict the BOO; however, solitary parameters, including symptom score (5), prostatic specific antigen (PSA) (7), free uroflowmetry (UFM) (8), volume of post-void residual urine (PVR) (9) and prostate size (10), showed poor to weak correlation with BOO. To improve prediction ability, combinations of non-invasive parameters have been sought to predict BOO (11-15). However, these attempts had limited predictive performance. Moreover, they were too complicated for clinical application because too many parameters need to be considered for prediction.

To overcome these problems, other statistic prediction methods, such as artificial neural networks (ANN), have been introduced to predict BOO in BPH patients, and some researchers have composed the ANN by using a diversity of non-invasive parameters (16-19). However, these models, due to their 'black box' nature, could not account for non-invasive parameters that are relatively important for BOO (20).

Causal Bayesian networks (CBN) have emerged as more advanced alternative to conventional statistic models in medical fields (21, 22). The benefit of this model is that it can visualize the interaction of causes and rule out indirect causes of events (21). Hence, we aimed to identify non-invasive clinical parameters to predict BOO using CBN model.

MATERIALS AND METHODS

I. Characteristics of database

The Institutional Review Board of Seoul National University Hospital approved the protocol of this study. A database comprised 1352 patients between October 2004 and December 2011 who were older than 45 years and had lower urinary tract symptoms (LUTS) suggestive of BPH. The data were retrieved from Electronic Medical Records System of the Seoul National University Hospital. Patients with a history of previous genitourinary surgery, pelvic radiation therapy, urinary tract infection, urethral stricture, interstitial cystitis, and neuropathy suggesting neurogenic bladder or incomplete evaluations were excluded. Thus, after excluding 486 such patients (35.9%), the data from 866 patients were analyzed.

Clinical parameters of subjects, including history, physical examination, International Prostatic Symptom Score (IPSS) (23), UFM, PVR, PSA, prostate volume (PV) measured by transrectal ultrasonography, and UDS parameters were retrieved. All UDS were performed using a multichannel video system (UD-2000, Medical Measurement System, Enscheda, Netherlands) according to the International Continence Society (ICS) recommendations (24, 25). Bladder outlet obstruction index (BOOI), which is equal to detrusor pressure at maximal flow rate (PdetQmax) −2 maximal flow rate (Qmax), was used to determine BOO (26). Patients with BOOI ≥40 were considered as obstructed.

Patient demographics are shown in table 1. Mean age of patients was 66.3 (±7.0, SD) years. TPV and PSA were 49.8 (±26.7) ml and 2.77 (±3.35) ng/ml, respectively. IPSS-total, IPSS-storage, IPSS-emptying and IPSS-QoL were 18.0 (±7.7), 7.1 (±3.5), 10.9 (±5.4) and 4.0 (±1.2), respectively. Mean BOOI was 34.0 (±24.4), and 292 (33.5%) patients were classified as having BOO.

II. Statistical methods for BOO prediction

To predict the BOO, the following three statistical methods were applied.

1) Logistic regression analysis

A backward stepwise regression analysis (27) was utilized. Age, total prostate volume (TPV), transition zone volume (TZV), PSA, Qmax, PVR and IPSS were entered into LR as non-invasive parameters for BOO prediction. Relative risk (Exp(β)) of BOO was calculated, with each non-invasive parameter increasing by one unit.

2) Artificial neural networks

In the ANN (28), patients were randomly divided into two subsets: training set (614 patients, 70.9%) and testing set (252 patients, 29.1%) as previously recommended by Looney (29). The numbers of nodes in hidden layers were applied from 2 to 20. Among them, the ANN which represented the highest accuracy, was selected as the optimal condition. Input variables for ANN were the same for LR as those mentioned above.

3) Causal Bayesian networks

Figure 1 shows the structure of a simple CBN model that represents interactions among variables. The probability of event D is represented as *P (event D| event B, event C)*. This means that the probability of event D is conditional on each of the possible values of events B and C. Event A is not a direct cause of event D in the network if a prior probability is specified. These relationships are known as the causal Markov condition (30), which specifies the relationships of conditional independence. It can also be visualized by a CBN model. The causal Markov condition permits the joint distribution of the n variables in a CBN to be factored as follows (21):

$$P(x_1, x_2, ..., x_n \mid K) = \prod_{i=1}^{n} P(x_i \mid \pi_i, K)$$

where xi denotes a state of variable Xi, π_i denotes a joint state of the parents of Xi, and K denotes background knowledge.

III. Identification and verification of the independent parameters

CBN was applied to identify the independent non-invasive parameters of BOO. The causal relationships and their interaction were visualized by established CBN. The parameters that exhibited the first degree relationship with BOO are selected as the independent predictors. The weights of each selected parameter were estimated using the Spearman's correlation test. The accuracy of BOO prediction with these selected parameters was compared with that of the other two methods. To compare the predictive performance, the comparison of Receiver Operating Characteristic (ROC) curves was applied.

P−value <0.05 was considered significant. Statistical analysis was performed using commercial statistic program package, Genie version 2.0 (Pittsburgh, PA, USA), SPSS® version 18.0 (Chicago, IL, USA) and Medcalc® version 12.4.0 (Ostend, Belgium).

RESULTS

Identification of non-invasive BOO predictors CBN using

Based on the BPH patient data, the best network structure was sought using the CBN model (Fig. 2). TPV, Qmax, PVR and IPSS item 5 (slow stream) exhibited first-degree relationships with BOO. Therefore, those four parameters were selected as non-invasive independent predictors of BOO. The correlation coefficient was the highest for TPV ($R=0.409$, $p<0.001$), followed by Qmax ($R=-0.214$, <0.001), PVR ($R=0.213$, $p<0.001$), and IPSS item 5 ($R=0.077$, $p=0.024$).

Verification of BOO prediction

Sensitivity, specificity, and accuracy of BOO predictions with the aforementioned four parameters by CBN were 54.1%, 86.4%, and 75.6%, respectively (Table 2). In LR, Qmax ($Exp(\beta)=0.933$, $p<0.001$), PVR ($Exp(\beta)=1.003$, $p=0.006$), TPV ($Exp(\beta)=1.026$, $p=0.006$), TZV ($Exp(\beta)=1.032$, $p=0.010$), IPSS item 2 (frequency) ($Exp(\beta)=0.697$, $p<0.001$), IPSS item 5 ($Exp(\beta)=1.146$, $p=0.025$), and IPSS storage ($Exp(\beta)=1.205$, $p<0.001$) were selected as significant predictive parameters. In LR, the sensitivity, specificity, and accuracy were 51.7%, 90.9%, and 77.7%, respectively. In the setting of two hidden nodes, ANN showed the highest accuracy, reaching 77.0% of the testing set (Fig. 3). In that condition, the sensitivity, specificity, and accuracy of the BOO prediction of the testing set (N=252) were 47.1%, 92.7% and 77.0%, respectively (Table 2).

To verify the predictive power of the four selected non-invasive parameters, a comparison of ROC curves was performed (Fig. 4). The area under ROC curve (AUROC) of CBN, LR and ANN models were 0.793, 0.797 and 0.775, respectively. The AUROC of CBN was similar to that of the LR model (p=0.664); however, ANN had a smaller AUROC compared to the other two methods (p-value range <0.001-0.005).

DISCUSSION

Because single parameters have very low correlation with BOO, many researchers have built statistical prediction methods that combine multiple parameters (11−15). For this purpose, they have used diverse parameters, including Qmax, PVR, IPSS, PSA, and PV. Two methods of combination - the cumulative scoring system (11) and the construction of a formula by linear regression analysis (12−15) have been utilized. However, no one has established specific independent predictor of BOO (11−15). Some differences in detailed parameters have been suggested for prediction models. Moreover, the number of parameters used in these predictions is too high to be feasible for real−life practice with BPH patients.

Previous studies seeking to identify non−invasive predictors of BOO have encountered two major difficulties. The first is the non−linear relationship of the variables. Among the single non−processed parameters, prostate size seems to be one of the most highly correlating parameters with BOO (R range: 0.28−0.32, $p<0.001$) (10, 31). However, Eckhardt et al. (31) have found that mean PV decreased at the Schäfer grade of 5 and 6, contrary to general expectations. These non-linear conditions occur commonly in clinical medicine.

The second difficulty stems from the fact that some parameters have a co-variability, i.e., some parameters interact with each other (22), so that the established model is capable of exaggerating or underestimating the predictive power. Bell et al. (32) reported that increased PVR occurs in BOO patients. However, Eckhard et al. (31) pointed out that larger PVR may reflect detrusor underactivity rather than BOO. Yet, Kranse et al. (9) supported the findings that BOO and detrusor underactivity commonly cause a higher PVR.

ANN models are expected to be able to detect non-linear relationships and interactions between predictor variables. Sonke et al.(16) proposed the first ANN model for BOO prediction with 1903 patients. IPSS, Qmax, PVR, PV, and PSA were used as the input parameters. They reported that overall sensitivity and specificity were 71% and 69%. Wadie et al. (17) reported the superb predictive value of ANN models among 460 subjects using only IPSS, than conventional statistic models. However, same group presented that another ANN model considering average flow rate and Qmax on UFM, PVR, and PV in variable conditions showed only moderate performance with 76% of accuracy (19). Another study reported 82% and 77% sensitivity and specificity, respectively, using IPSS, PV, PSA, and UFM parameters (18). Comprehensive results show, however, that the predictive performance of ANN is not superior to that of the conventional linear models. Moreover, due to the 'black box' nature of ANN, the entire algorithm has not been fully understood yet (20). Therefore, these models do not explain the relative contribution of non-invasive parameters to urodynamic BOO.

In general, the advantage of CBNs is that they can identify conditional independence relationships and thus make it possible to confirm the only direct independent cause of the events. We expected that this advantage of the CBN model could confirm the independent parameters for the prediction of BOO. In this study, the established CBN model confirmed that TPV, Qmax, PVR, and IPSS item 5 were important predictors of BOO (Fig. 2). On the other hand, other parameters such as age, TZV, PSA, as well as other IPSS parameters had conditional independence relationships with BOO, i.e., these parameters have no additional value for the prediction of BOO. When TPV is known, the TZV, age and PSA do not improve the prediction of BOO. Moreover, with IPSS item 5, other IPSS scores do not add additional value in the prediction of BOO.

Our data showed that TPV has a moderate relationship with BOO (R=0.409), while Qmax, PVR, and IPSS item 5 have a significant but mild relationship with BOO. The current study showed that TPV, TZV, and PSA are well correlated (R range: 0.634−0.871) and that TPV is the most important and independent predictor of BOO. Our results are consistent with those of previous studies which reported that PV had a higher correlation with BOO compared to the other non−invasive parameters (12−15). These results suggest that TPV is the most important parameter for BOO prediction and that TZV and PSA do not need to be considered as predictors.

Although Qmax and PVR had a mild correlation (|R| range: 0.213−0.214), CBN confirmed that these parameters are independent predictors of BOO. Therefore, these parameters should be considered in BOO prediction. Previous studies considered various combinations of UFM parameters, such as Qmax, average flow rate (Qavg), and PVR in prediction models (11−15), but it has not yet been concluded which parameters are more important predictors of BOO. Our CBN model showed that Qmax and PVR are important for BOO prediction. It is interesting that the IPSS item 5 can represent other parameters of IPSS and independent predictor of urodynamic BOO. Previous studies excluded the IPSS from the BOO prediction model (12–15), and van Venrooij et al. (5) reported that IPSS has no statistical correlation with urodynamic obstruction grade; however, our data showed a weak correlation of IPSS item 5 with BOO (R=0.077), and the CBN model confirmed that IPSS item 5 contributes to BOO prediction independently.

To validate the performance of the BOO prediction model with these four selected independent predictors, two additional models (LR and ANN) were proposed and tested using the same dataset (Table 2). These two models showed predictive performance comparable to that of previous studies (12–19). Our BOO prediction model with only four independent parameters (TPV, Qmax, PVR, and IPSS item 5) showed predictive value similar to that of the other two models (Figure 4). These results support that our independent parameters, as confirmed by CBN, are sufficient to predict the BOO and other parameters, which in turn shows that a conditional independent relationship may not be essential for BOO prediction. Moreover, all four of these parameters are routinely evaluated as non-invasive items for BPH patients. Therefore, our findings that BOO can be predicted only with these four parameters are clinically important.

To the best of our knowledge, this study is the first to test CBN model for BOO prediction. The strength of this study is that we made our non-missing dataset of 866 patients large enough to support the construction of the CBN model. Moreover, in our study, all of the UDS were performed uniformly using the same protocol following the ICS recommendations (24, 25).

However, our current study has some limitations. First, our CBN model comprised categorized values of parameters for clarifying interactions between the parameters. In addition, our model was unable to account for the weight of each independent predictor. Therefore, the relative importance of predictors should be identified by means of indirect correlation analysis. Second, our CBN model is built from cross-sectional database; hence, in the strict sense, our model did not show cause-effect relationships between parameters but showed simple correlations or interactions. It is thus impossible to confirm parameters that precede the cause. We believe that in order to determine the true benefit of applying CBN models to BOO prediction, more well-designed and in-depth researches into the CBN model are needed.

CONCLUSIONS

Our results show that TZV, Qmax, PVR and IPSS item 5 (slow stream) are independent non-invasive predictors of BOO.

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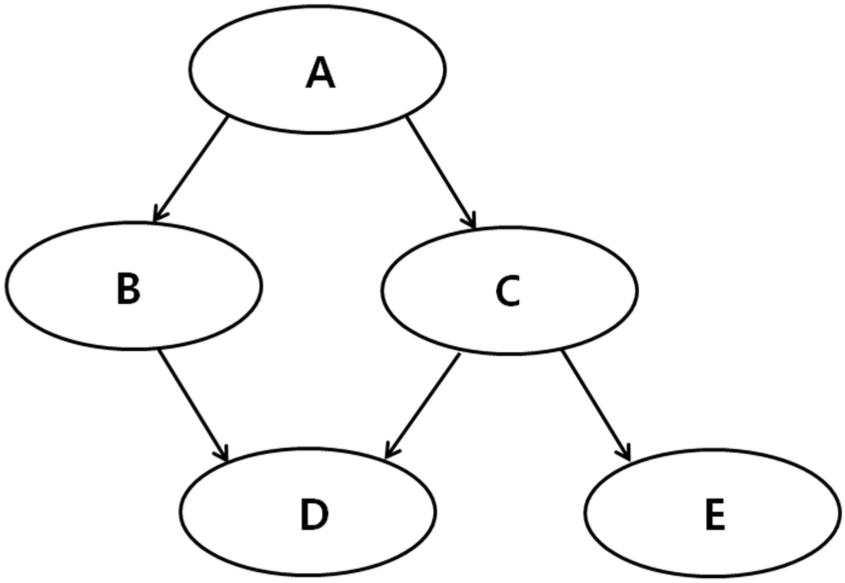

Figure 1. A simple causal Bayesian networks model

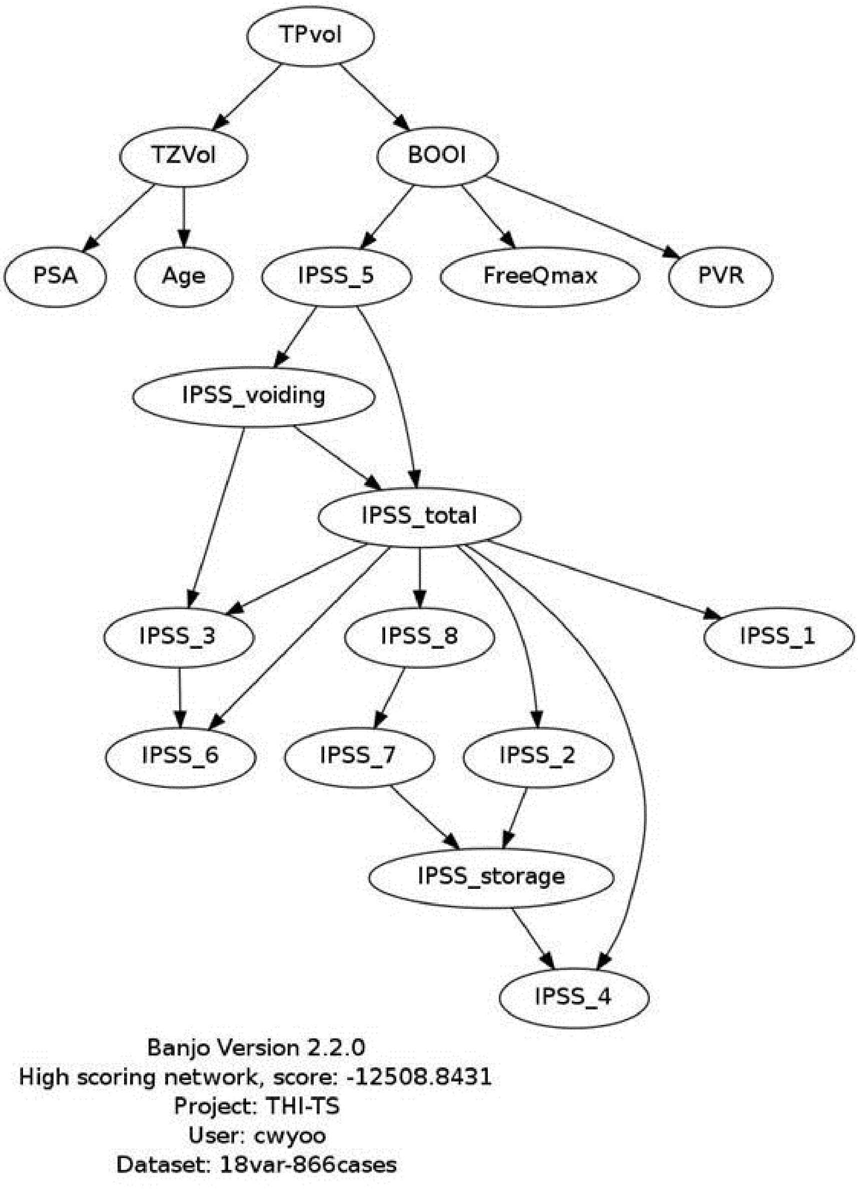

Figure 2. Causal Bayesian networks model for bladder outlet obstruction

TPvol, total prostate volume; TZVol, transition zone volume; PSA, prostatic specific antigen; BOOI, bladder outlet obstruction index; FreeQmax, maximum flow rate; PVR, post−void residual volume; IPSS, international prostatic symptom score

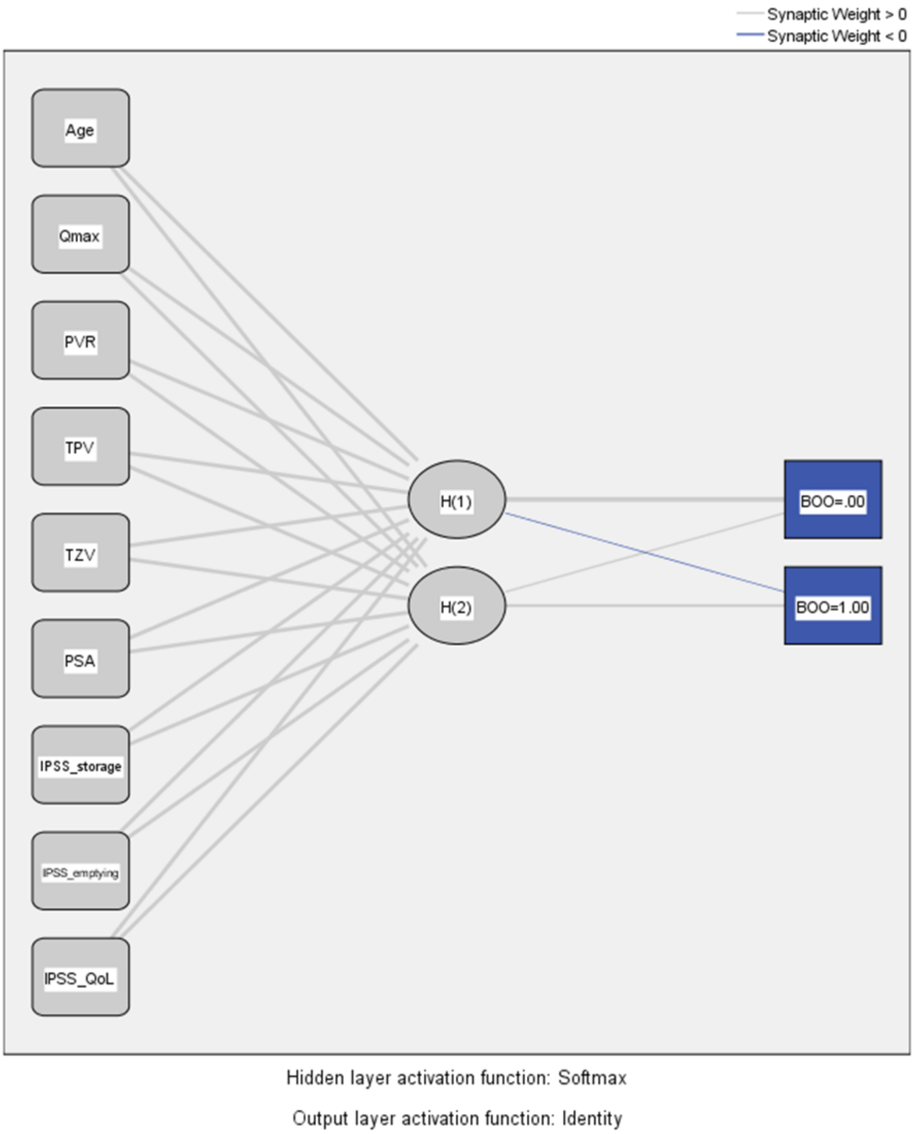

Figure 3. Optimized artificial neural networks model for bladder outlet obstruction

Qmax, maximum flow rate; PVR, post-void residual volume; TPV, total prostate volume; TZV, transition zone volume; PSA, prostatic specific antigen; IPSS, international prostatic symptom score; QoL, quality of life; BOO, bladder outlet obstruction

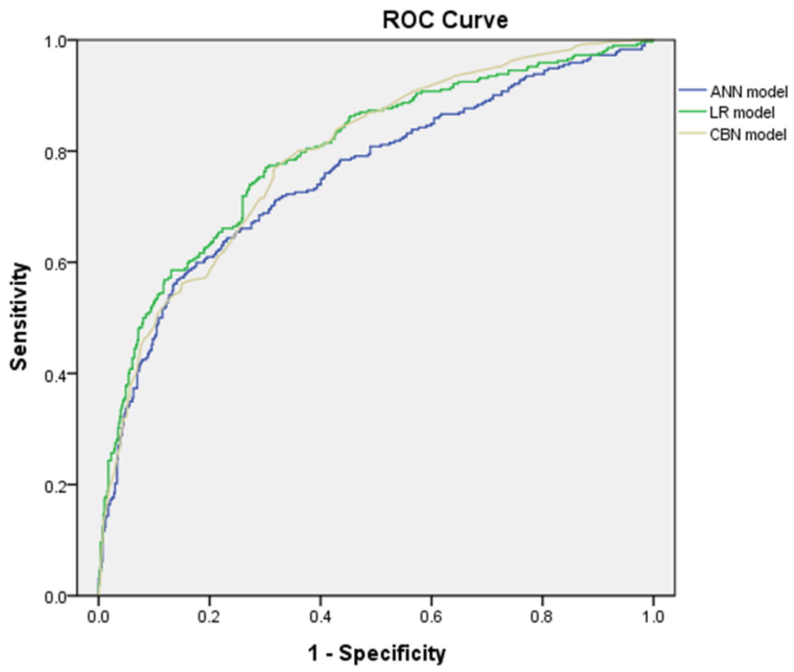

Figure 4. Receiver operating characteristic (ROC) curves of three predictive models

Logistic regression (LR): 0.797 (CI, 0.765−0.830)

Artificial Neural Networks (ANN): 0.756 (CI, 0.721−0.792)

Causal Bayesian Networks (CBN): 0.793 (CI, 0.761−0.824)

Between CBN and LR, p−value: 0.435

Between CBN and ANN, p−value: 0.005

Between LR and ANN, p−value: $<$0.001

(by comparison of ROC curve, Medcalc®)

Table 1. Baseline characteristics

Clinical parameters	Total subjects (N=866)
Age (years)	66.3 ± 7.0
Prostate volume (ml)	
Total prostate volume	49.8 ± 26.7
Transitional zone volume	23.9 ± 18.0
PSA (ng/ml)	2.77 ± 3.35
IPSS	
IPSS−total	18.0 ± 7.7
IPSS−storage	7.1 ± 3.5
IPSS−emptying	10.9 ± 5.4
IPSS−QoL	4.0 ± 1.2
Uroflowmetry parameters	
Qmax (ml/sec)	11.8 ± 5.6
Voided volume (ml)	233.7 ± 107.8
PVR (ml)	61.2 ± 79.8
Urodynamic study parameters	
MUCP(cmH_2O)	79.6 ± 26.1
Functional urethral length (mm)	71.1 ± 11.3
First desire (ml)	210.7 ± 93.6
Normal desire (ml)	295.4 ± 114.5
Strong desire (ml)	383.2 ± 119.5
Compliance (ml/cmH_2O)	70.6 ± 52.1
PdetQmax (cmH_2O)	53.6 ± 21.5
Opening pressure (cmH_2O)	54.3 ± 25.8
Bladder outlet obstruction index	34.0 ± 24.4

PSA, prostate specific antigen; IPSS, international prostatic symptom score; QoL, quality of life; Qmax, maximum flow rate; PVR, post−void residual volume; MUCP, maximal urethral closing pressure; PdetQmax, detrusor pressure at Qmax

Table 2. Predictive value of three predictive models for bladder outlet obstruction

	Predicted BOO		Urodynamic BOO (+)	Urodynamic BOO (−)	Total	Sensitivity	Specificity	Accuracy
LR	Total (N=866)	(+)	151	52	203	151/292 (51.7%)	522/574 (90.9%)	(151+522)/866 (77.7%)
		(−)	141	522	663			
		Total	292	574	866			
ANN	Training set (N=614)	(+)	113	57	170	113/205 (55.1%)	352/409 (86.1%)	(113+352)/614 (75.7%)
		(−)	92	352	444			
		Total	205	409	614			
	Testing set (N=252)	(+)	38	12	50	38/87 (41.7%)	153/165 (92.7%)	(38+153)/252 (75.8%)
		(−)	49	153	202			
		Total	87	165	252			
CBN	Total (N=866)	(+)	158	78	236	158/292 (54.1%)	496/574 (86.4%)	(158+496)/866 (75.6%)
		(−)	134	496	630			
		Total	292	574	866			

LR, logistic regression; ANN, artificial neural networks; CBN, causal Bayesian networks; BOO, bladder outlet obstruction

국문 초록

서론: 전립선비대증에서 요역동학적 방광출구 폐색을 예측하는 연구들이 있어 왔으나 신빙성 있는 지표들을 도출하기에는 부족하였다. 본 연구에서는 베이지안 네트워크를 활용하여 전립선비대증 환자에서 요역동학적 방광출구 폐색을 예측하는 비침습적 임상 지표들을 찾아 보고자 하였다.

방법: 2004 년 10 월부터 2011 년 12 월까지 전립선비대증으로 전립선증상설문 (IPSS)과 요류검사 (UFM), PSA 및 경직장전립선초음파, 요역동학검사 (UDS)를 빠짐없이 시행받은 환자들의 자료를 전자의무기록에서 추출하여 분석하였다. 요로감염, 신경인성방광 등 배뇨증상에 영향을 미칠 수 있는 다른 원인이 확인된 환자는 분석에서 제외하였다. 총 866 명 환자들의 연령은 66.3 (±7.0)세였으며, 전립선용적 (TPV)은 49.8 (±26.7)ml, IPSS 총 점수는 18.0 (±7.7)이었다. UDS 에서 확인된 방광출구폐색지수 (BOOI)는 34.0 (±24.4)이었으며, 요역동학적 폐색 (BOOI ≥40)으로 확인된 환자는 292 명 (33.5%)이었다. 베이지안 네트워크 모델을 이용하여 방광출구폐색을 유발할 수 있는 비침습적 인자들을 찾아보았으며 로지스틱 회귀분석 및 인공신경망 모델을 활용하여 선택된 임상지표들의 폐색의 예측도를 검증하였다.

결과: 베이지안 네트워크에서 TPV, UFM 에서의 최대요속 (Qmax), 잔뇨량 (PVR) 및 IPSS 설문 5 번 항목의 점수 (세뇨)가 요역동학적 폐색의 독립적인 예측인자로 확인되었다. 이 네가지 예측인자들로 만들어진 예측모델의 민감도는 54.1%, 특이도 86.4%, receiver operating characteristic (ROC) 곡선하 면적은 0.793 인 것으로 확인되었다. 로지스틱 회귀분석에서도 유사한 예측정확도와 ROC 곡선하 면적을 보였다 (민감도: 51.7%, 특이도: 90.9%, ROC 곡선하 면적: 0.797). 인공신경망 모델의 민감도는 43.7%, 특이도 92.7%, ROC 곡선하 면적 0.756 으로 확인되었다. 인공신경망 모델의 ROC 곡선하 면적은 다른 두 모델 보다 통계적으로 유의하게 작았다 (p-value 범위: <0.001-0.005).

결론: 본 연구결과 TPV, Qmax, PVR 및 IPSS 설문 5 번 항목의 점수가 요역동학적 폐색의 독립적인 비침습적 예측인자로 확인되었다.

주요어: 방광출구폐색, 전립선비대증, 요역동학검사, 예측 모델, 베이지안 네트워크, 로지스틱 회귀분석

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Non-invasive parameters for the prediction of urodynamic bladder outlet obstruction: analysis using causal Bayesian networks

요역동학적 방광출구폐색의 비침습적 예측인자: 베이지안 네트워크 모델을 활용한 분석

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Non–invasive parameters for the prediction of urodynamic bladder outlet obstruction: analysis using causal Bayesian networks

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Non–invasive parameters for the prediction of urodynamic bladder outlet obstruction: analysis using causal Bayesian networks

by
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Approved by Thesis Committee:

Professor ____________________Chairman
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ABSTRACT

Purpose: Numerous attempts have been made to predict urodynamic bladder outlet obstruction (BOO), however, little information exists on non-invasive parameters for BOO prediction. We aimed to identify non-invasive clinical parameters to predict BOO using causal Bayesian networks (CBN).

Methods: From October 2004 to December 2011, patients with lower urinary tract symptoms (LUTS) suggestive of BPH were included in this study. Out of the 1352 patients, 866 were selected for the analysis. Mean age, total prostate volume (TPV) and IPSS were 66.3 (±7.0, SD) years, 49.8 (±26.7) ml, and 18.0 (±7.7), respectively. Mean bladder outlet obstruction index (BOOI) was 34.0 (± 24.4), and 292 (33.5%) patients had urodynamic BOO (BOOI ≥40). Non-invasive predictors of BOO were selected using CBN. BOO prediction with selected parameters was verified using logistic regression (LR) and artificial neural networks (ANN) considering whole non-invasive parameters.

Results: CBN identified TPV, Qmax, PVR, and IPSS item 5 (slow-stream) as independent predictors of BOO. With these four parameters, sensitivity and specificity of BOO prediction were 54.1% and 86.4%, respectively, with an area under receiver operating characteristic curve (AUROC) of 0.793. LR and ANN models with the same parameters showed similar accuracy (LR: sensitivity 51.7%, specificity 90.9%, AUROC 0.797; ANN: sensitivity 43.7%, specificity 92.7%, AUROC 0.756). The AUROC of ANN was smaller than that of the other two methods (p-value range <0.001–0.005).

Conclusions: Our study demonstrated that TPV, Qmax, PVR, and IPSS item 5 (slow-stream) are independent predictors of urodynamic BOO.

Keywords: Bayes theorem; logistic model; predictive value of tests; prostatic hyperplasia; urinary bladder neck obstruction; urodynamics

CONTENTS

LEGENDS OF TABLES AND FIGURES

LISTS OF ABBREVIATIONS

Bladder outlet obstruction(BOO)

Benign prostatic hyperplasia (BPH)

Causal Bayesian networks (CBN)

Lower urinary tract symptoms (LUTS)

Prostatic specific antigen (PSA)

International prostate symptom score (IPSS)

Maximal flow rate (Qmax)

Volume of post-voided residual urine (PVR)

Logistic regression (LR)

Artificial neural networks (ANN)

Total prostate volume (TPV)

Transition zone volume (TZV)

Bladder outlet obstruction index (BOOI)

Area under receiver operating characteristic curve (AUROC)

Urodynamic study (UDS)

Prostate volume (PV)

International Continence Society (ICS)

Detrusor pressure at maximal flow rate (PdetQmax)

INTRODUCTION

The urodynamic study (UDS) is considered as the gold standard for the clinical assessment of bladder outlet obstruction (BOO) in patients with benign prostatic hyperplasia (BPH) (1-3). Patients with urodynamic BOO show higher efficacy after transurethral surgery (4, 5). In this respect, BOO is helpful in stratifying BPH patients eligible for surgical treatment. However, UDS has significant limitations in terms of invasiveness, cost, and morbidity (6).

There have been numerous attempts to substitute non-invasive parameters for UDS to predict the BOO; however, solitary parameters, including symptom score (5), prostatic specific antigen (PSA) (7), free uroflowmetry (UFM) (8), volume of post-void residual urine (PVR) (9) and prostate size (10), showed poor to weak correlation with BOO. To improve prediction ability, combinations of non-invasive parameters have been sought to predict BOO (11-15). However, these attempts had limited predictive performance. Moreover, they were too complicated for clinical application because too many parameters need to be considered for prediction.

To overcome these problems, other statistic prediction methods, such as artificial neural networks (ANN), have been introduced to predict BOO in BPH patients, and some researchers have composed the ANN by using a diversity of non-invasive parameters (16-19). However, these models, due to their 'black box' nature, could not account for non-invasive parameters that are relatively important for BOO (20).

Causal Bayesian networks (CBN) have emerged as more advanced alternative to conventional statistic models in medical fields (21, 22). The benefit of this model is that it can visualize the interaction of causes and rule out indirect causes of events (21). Hence, we aimed to identify non-invasive clinical parameters to predict BOO using CBN model.

MATERIALS AND METHODS

I. Characteristics of database

The Institutional Review Board of Seoul National University Hospital approved the protocol of this study. A database comprised 1352 patients between October 2004 and December 2011 who were older than 45 years and had lower urinary tract symptoms (LUTS) suggestive of BPH. The data were retrieved from Electronic Medical Records System of the Seoul National University Hospital. Patients with a history of previous genitourinary surgery, pelvic radiation therapy, urinary tract infection, urethral stricture, interstitial cystitis, and neuropathy suggesting neurogenic bladder or incomplete evaluations were excluded. Thus, after excluding 486 such patients (35.9%), the data from 866 patients were analyzed.

Clinical parameters of subjects, including history, physical examination, International Prostatic Symptom Score (IPSS) (23), UFM, PVR, PSA, prostate volume (PV) measured by transrectal ultrasonography, and UDS parameters were retrieved. All UDS were performed using a multichannel video system (UD−2000, Medical Measurement System, Enscheda, Netherlands) according to the International Continence Society (ICS) recommendations (24, 25). Bladder outlet obstruction index (BOOI), which is equal to detrusor pressure at maximal flow rate (PdetQmax) −2 maximal flow rate (Qmax), was used to determine BOO (26). Patients with BOOI ≥40 were considered as obstructed.

Patient demographics are shown in table 1. Mean age of patients was 66.3 (±7.0, SD) years. TPV and PSA were 49.8 (±26.7) ml and 2.77 (±3.35) ng/ml, respectively. IPSS−total, IPSS−storage, IPSS−emptying and IPSS−QoL were 18.0 (±7.7), 7.1 (±3.5), 10.9 (±5.4) and 4.0 (±1.2), respectively. Mean BOOI was 34.0 (±24.4), and 292 (33.5%) patients were classified as having BOO.

II. Statistical methods for BOO prediction

To predict the BOO, the following three statistical methods were applied.

1) Logistic regression analysis

A backward stepwise regression analysis (27) was utilized. Age, total prostate volume (TPV), transition zone volume (TZV), PSA, Qmax, PVR and IPSS were entered into LR as non-invasive parameters for BOO prediction. Relative risk (Exp(β)) of BOO was calculated, with each non-invasive parameter increasing by one unit.

2) Artificial neural networks

In the ANN (28), patients were randomly divided into two subsets: training set (614 patients, 70.9%) and testing set (252 patients, 29.1%) as previously recommended by Looney (29). The numbers of nodes in hidden layers were applied from 2 to 20. Among them, the ANN which represented the highest accuracy, was selected as the optimal condition. Input variables for ANN were the same for LR as those mentioned above.

3) Causal Bayesian networks

Figure 1 shows the structure of a simple CBN model that represents interactions among variables. The probability of event D is represented as *P (event D| event B, event C)*. This means that the probability of event D is conditional on each of the possible values of events B and C. Event A is not a direct cause of event D in the network if a prior probability is specified. These relationships are known as the causal Markov condition (30), which specifies the relationships of conditional independence. It can also be visualized by a CBN model. The causal Markov condition permits the joint distribution of the n variables in a CBN to be factored as follows (21):

$$P(x_1, x_2, \ldots, x_n \mid K) = \prod_{i=1}^{n} P(x_i \mid \pi_i, K)$$

where xi denotes a state of variable Xi, π_i denotes a joint state of the parents of Xi, and K denotes background knowledge.

III. Identification and verification of the independent parameters

CBN was applied to identify the independent non-invasive parameters of BOO. The causal relationships and their interaction were visualized by established CBN. The parameters that exhibited the first degree relationship with BOO are selected as the independent predictors. The weights of each selected parameter were estimated using the Spearman's correlation test. The accuracy of BOO prediction with these selected parameters was compared with that of the other two methods. To compare the predictive performance, the comparison of Receiver Operating Characteristic (ROC) curves was applied.

P-value <0.05 was considered significant. Statistical analysis was performed using commercial statistic program package, Genie version 2.0 (Pittsburgh, PA, USA), SPSS® version 18.0 (Chicago, IL, USA) and Medcalc® version 12.4.0 (Ostend, Belgium).

RESULTS

Identification of non-invasive BOO predictors CBN using

Based on the BPH patient data, the best network structure was sought using the CBN model (Fig. 2). TPV, Qmax, PVR and IPSS item 5 (slow stream) exhibited first-degree relationships with BOO. Therefore, those four parameters were selected as non-invasive independent predictors of BOO. The correlation coefficient was the highest for TPV ($R=0.409$, $p<0.001$), followed by Qmax ($R=-0.214$, <0.001), PVR ($R=0.213$, $p<0.001$), and IPSS item 5 ($R=0.077$, $p=0.024$).

Verification of BOO prediction

Sensitivity, specificity, and accuracy of BOO predictions with the aforementioned four parameters by CBN were 54.1%, 86.4%, and 75.6%, respectively (Table 2). In LR, Qmax ($Exp(\beta)=0.933$, $p<0.001$), PVR ($Exp(\beta)=1.003$, $p=0.006$), TPV ($Exp(\beta)=1.026$, $p=0.006$), TZV ($Exp(\beta)=1.032$, $p=0.010$), IPSS item 2 (frequency) ($Exp(\beta)=0.697$, $p<0.001$), IPSS item 5 ($Exp(\beta)=1.146$, $p=0.025$), and IPSS storage ($Exp(\beta)=1.205$, $p<0.001$) were selected as significant predictive parameters. In LR, the sensitivity, specificity, and accuracy were 51.7%, 90.9%, and 77.7%, respectively. In the setting of two hidden nodes, ANN showed the highest accuracy, reaching 77.0% of the testing set (Fig. 3). In that condition, the sensitivity, specificity, and accuracy of the BOO prediction of the testing set (N=252) were 47.1%, 92.7% and 77.0%, respectively (Table 2).

To verify the predictive power of the four selected non-invasive parameters, a comparison of ROC curves was performed (Fig. 4). The area under ROC curve (AUROC) of CBN, LR and ANN models were 0.793, 0.797 and 0.775, respectively. The AUROC of CBN was similar to that of the LR model ($p=0.664$); however, ANN had a smaller AUROC compared to the other two methods (p-value range $<0.001-0.005$).

DISCUSSION

Because single parameters have very low correlation with BOO, many researchers have built statistical prediction methods that combine multiple parameters (11−15). For this purpose, they have used diverse parameters, including Qmax, PVR, IPSS, PSA, and PV. Two methods of combination - the cumulative scoring system (11) and the construction of a formula by linear regression analysis (12−15) have been utilized. However, no one has established specific independent predictor of BOO (11−15). Some differences in detailed parameters have been suggested for prediction models. Moreover, the number of parameters used in these predictions is too high to be feasible for real−life practice with BPH patients.

Previous studies seeking to identify non−invasive predictors of BOO have encountered two major difficulties. The first is the non−linear relationship of the variables. Among the single non−processed parameters, prostate size seems to be one of the most highly correlating parameters with BOO (R range: 0.28−0.32, $p<0.001$) (10, 31). However, Eckhardt et al. (31) have found that mean PV decreased at the Schäfer grade of 5 and 6, contrary to general expectations. These non-linear conditions occur commonly in clinical medicine.

The second difficulty stems from the fact that some parameters have a co-variability, i.e., some parameters interact with each other (22), so that the established model is capable of exaggerating or underestimating the predictive power. Bell et al. (32) reported that increased PVR occurs in BOO patients. However, Eckhard et al. (31) pointed out that larger PVR may reflect detrusor underactivity rather than BOO. Yet, Kranse et al. (9) supported the findings that BOO and detrusor underactivity commonly cause a higher PVR.

ANN models are expected to be able to detect non-linear relationships and interactions between predictor variables. Sonke et al.(16) proposed the first ANN model for BOO prediction with 1903 patients. IPSS, Qmax, PVR, PV, and PSA were used as the input parameters. They reported that overall sensitivity and specificity were 71% and 69%. Wadie et al. (17) reported the superb predictive value of ANN models among 460 subjects using only IPSS, than conventional statistic models. However, same group presented that another ANN model considering average flow rate and Qmax on UFM, PVR, and PV in variable conditions showed only moderate performance with 76% of accuracy (19). Another study reported 82% and 77% sensitivity and specificity, respectively, using IPSS, PV, PSA, and UFM parameters (18). Comprehensive results show, however, that the predictive performance of ANN is not superior to that of the conventional linear models. Moreover, due to the 'black box' nature of ANN, the entire algorithm has not been fully understood yet (20). Therefore, these models do not explain the relative contribution of non-invasive parameters to urodynamic BOO.

In general, the advantage of CBNs is that they can identify conditional independence relationships and thus make it possible to confirm the only direct independent cause of the events. We expected that this advantage of the CBN model could confirm the independent parameters for the prediction of BOO. In this study, the established CBN model confirmed that TPV, Qmax, PVR, and IPSS item 5 were important predictors of BOO (Fig. 2). On the other hand, other parameters such as age, TZV, PSA, as well as other IPSS parameters had conditional independence relationships with BOO, i.e., these parameters have no additional value for the prediction of BOO. When TPV is known, the TZV, age and PSA do not improve the prediction of BOO. Moreover, with IPSS item 5, other IPSS scores do not add additional value in the prediction of BOO.

Our data showed that TPV has a moderate relationship with BOO (R=0.409), while Qmax, PVR, and IPSS item 5 have a significant but mild relationship with BOO. The current study showed that TPV, TZV, and PSA are well correlated (R range: 0.634–0.871) and that TPV is the most important and independent predictor of BOO. Our results are consistent with those of previous studies which reported that PV had a higher correlation with BOO compared to the other non-invasive parameters (12–15). These results suggest that TPV is the most important parameter for BOO prediction and that TZV and PSA do not need to be considered as predictors.

Although Qmax and PVR had a mild correlation (|R| range: 0.213–0.214), CBN confirmed that these parameters are independent predictors of BOO. Therefore, these parameters should be considered in BOO prediction. Previous studies considered various combinations of UFM parameters, such as Qmax, average flow rate (Qavg), and PVR in prediction models (11–15), but it has not yet been concluded which parameters are more important predictors of BOO. Our CBN model showed that Qmax and PVR are important for BOO prediction. It is interesting that the IPSS item 5 can represent other parameters of IPSS and independent predictor of urodynamic BOO. Previous studies excluded the IPSS from the BOO prediction model (12–15), and van Venrooij et al. (5) reported that IPSS has no statistical correlation with urodynamic obstruction grade; however, our data showed a weak correlation of IPSS item 5 with BOO (R=0.077), and the CBN model confirmed that IPSS item 5 contributes to BOO prediction independently.

To validate the performance of the BOO prediction model with these four selected independent predictors, two additional models (LR and ANN) were proposed and tested using the same dataset (Table 2). These two models showed predictive performance comparable to that of previous studies (12–19). Our BOO prediction model with only four independent parameters (TPV, Qmax, PVR, and IPSS item 5) showed predictive value similar to that of the other two models (Figure 4). These results support that our independent parameters, as confirmed by CBN, are sufficient to predict the BOO and other parameters, which in turn shows that a conditional independent relationship may not be essential for BOO prediction. Moreover, all four of these parameters are routinely evaluated as non-invasive items for BPH patients. Therefore, our findings that BOO can be predicted only with these four parameters are clinically important.

To the best of our knowledge, this study is the first to test CBN model for BOO prediction. The strength of this study is that we made our non-missing dataset of 866 patients large enough to support the construction of the CBN model. Moreover, in our study, all of the UDS were performed uniformly using the same protocol following the ICS recommendations (24, 25).

However, our current study has some limitations. First, our CBN model comprised categorized values of parameters for clarifying interactions between the parameters. In addition, our model was unable to account for the weight of each independent predictor. Therefore, the relative importance of predictors should be identified by means of indirect correlation analysis. Second, our CBN model is built from cross-sectional database; hence, in the strict sense, our model did not show cause-effect relationships between parameters but showed simple correlations or interactions. It is thus impossible to confirm parameters that precede the cause. We believe that in order to determine the true benefit of applying CBN models to BOO prediction, more well-designed and in-depth researches into the CBN model are needed.

CONCLUSIONS

Our results show that TZV, Qmax, PVR and IPSS item 5 (slow stream) are independent non-invasive predictors of BOO.

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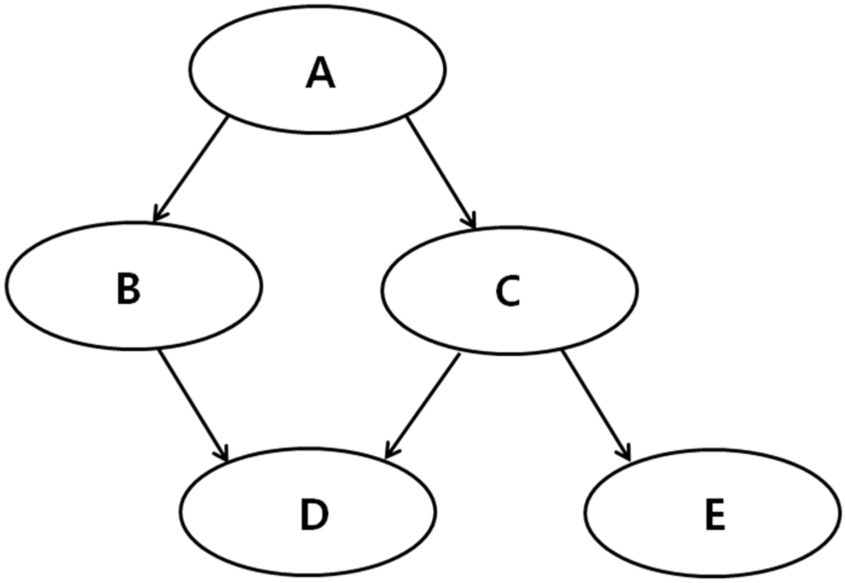

Figure 1. A simple causal Bayesian networks model

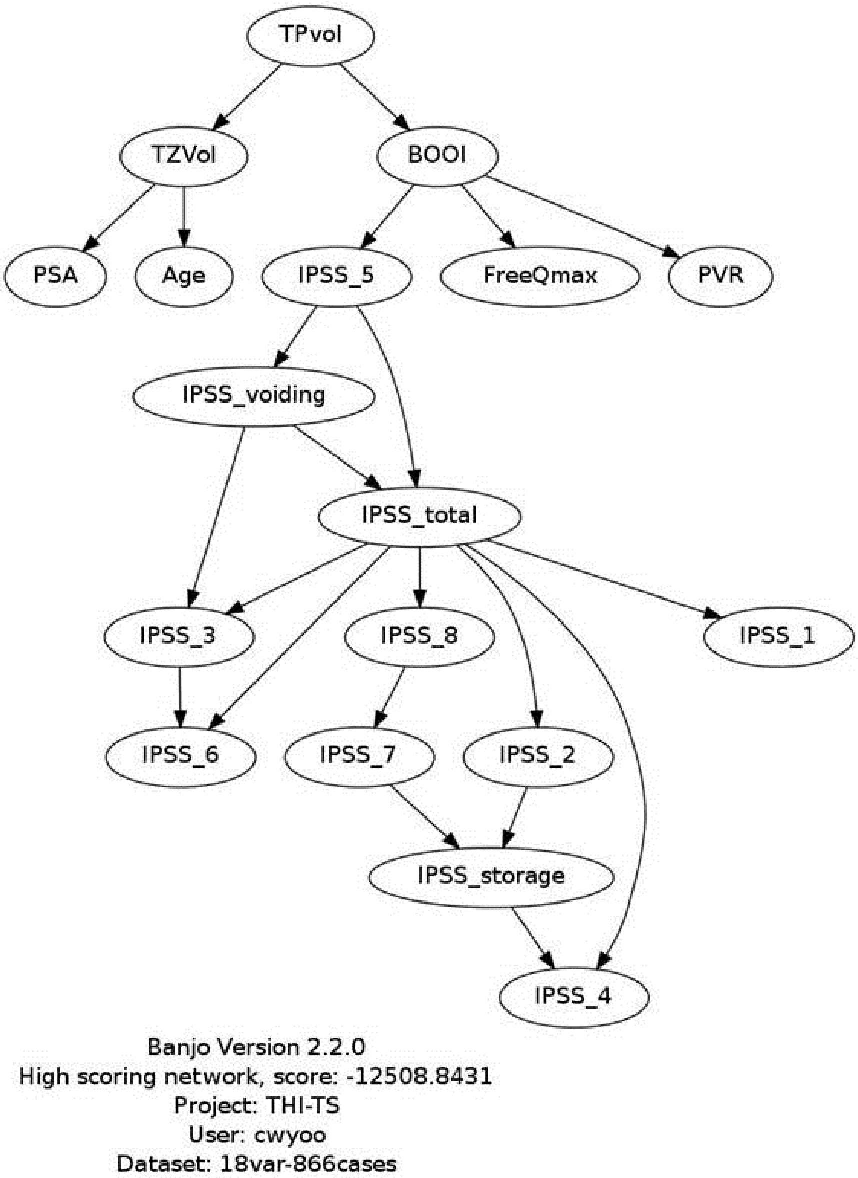

Figure 2. Causal Bayesian networks model for bladder outlet obstruction

TPvol, total prostate volume; TZVol, transition zone volume; PSA, prostatic specific antigen; BOOI, bladder outlet obstruction index; FreeQmax, maximum flow rate; PVR, post−void residual volume; IPSS, international prostatic symptom score

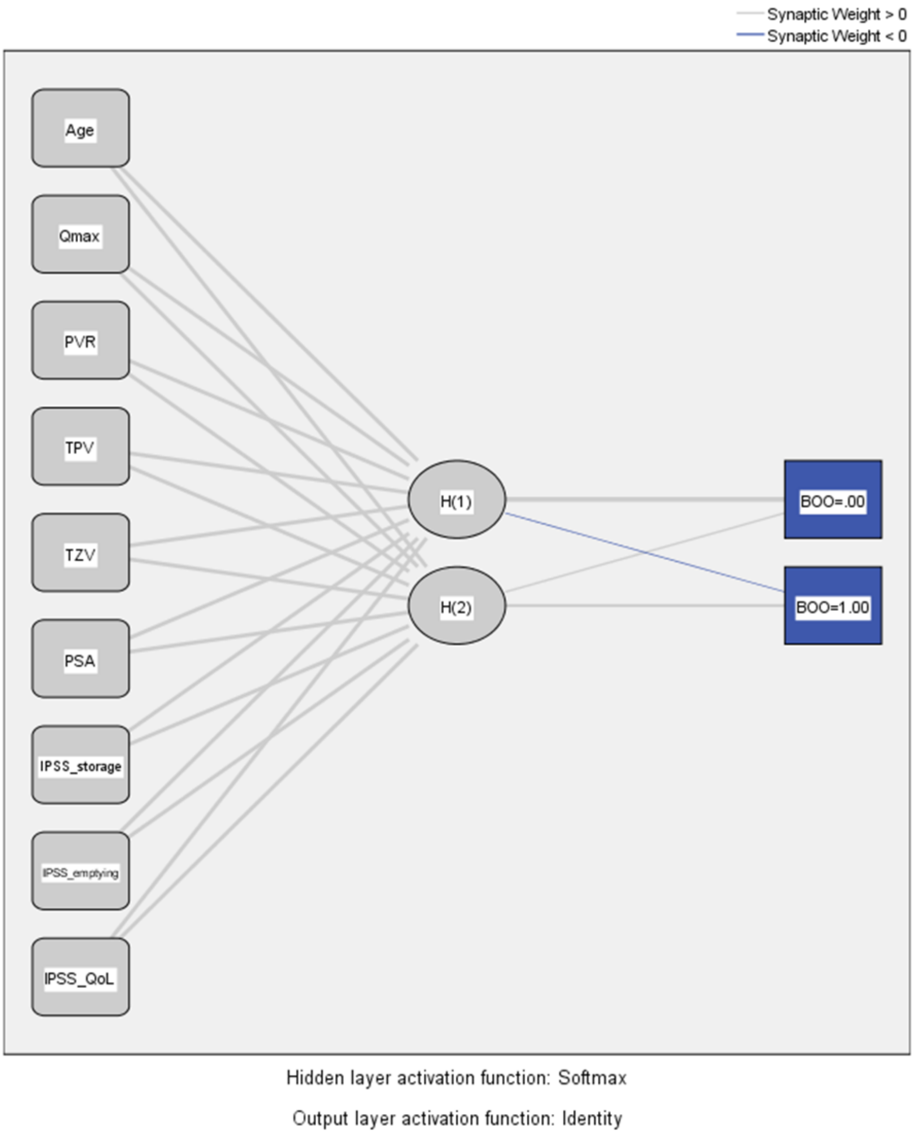

Figure 3. Optimized artificial neural networks model for bladder outlet obstruction

Qmax, maximum flow rate; PVR, post-void residual volume; TPV, total prostate volume; TZV, transition zone volume; PSA, prostatic specific antigen; IPSS, international prostatic symptom score; QoL, quality of life; BOO, bladder outlet obstruction

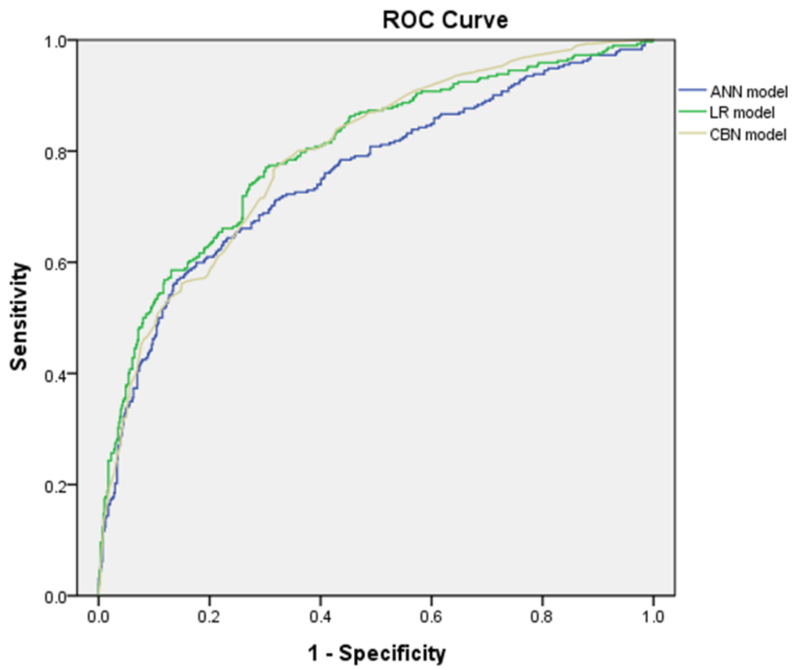

Figure 4. Receiver operating characteristic (ROC) curves of three predictive models

Logistic regression (LR): 0.797 (CI, 0.765–0.830)

Artificial Neural Networks (ANN): 0.756 (CI, 0.721–0.792)

Causal Bayesian Networks (CBN): 0.793 (CI, 0.761–0.824)

Between CBN and LR, p-value: 0.435

Between CBN and ANN, p-value: 0.005

Between LR and ANN, p-value: <0.001

(by comparison of ROC curve, Medcalc®)

Table 1. Baseline characteristics

Clinical parameters	Total subjects (N=866)
Age (years)	66.3 ± 7.0
Prostate volume (ml)	
Total prostate volume	49.8 ± 26.7
Transitional zone volume	23.9 ± 18.0
PSA (ng/ml)	2.77 ± 3.35
IPSS	
IPSS−total	18.0 ± 7.7
IPSS−storage	7.1 ± 3.5
IPSS−emptying	10.9 ± 5.4
IPSS−QoL	4.0 ± 1.2
Uroflowmetry parameters	
Qmax (ml/sec)	11.8 ± 5.6
Voided volume (ml)	233.7 ± 107.8
PVR (ml)	61.2 ± 79.8
Urodynamic study parameters	
MUCP(cmH_2O)	79.6 ± 26.1
Functional urethral length (mm)	71.1 ± 11.3
First desire (ml)	210.7 ± 93.6
Normal desire (ml)	295.4 ± 114.5
Strong desire (ml)	383.2 ± 119.5
Compliance (ml/cmH_2O)	70.6 ± 52.1
PdetQmax (cmH_2O)	53.6 ± 21.5
Opening pressure (cmH_2O)	54.3 ± 25.8
Bladder outlet obstruction index	34.0 ± 24.4

PSA, prostate specific antigen; IPSS, international prostatic symptom score; QoL, quality of life; Qmax, maximum flow rate; PVR, post−void residual volume; MUCP, maximal urethral closing pressure; PdetQmax, detrusor pressure at Qmax

Table 2. Predictive value of three predictive models for bladder outlet obstruction

	Predicted BOO		Urodynamic BOO (+)	Urodynamic BOO (−)	Total	Sensitivity	Specificity	Accuracy
LR	Total (N=866)	(+)	151	52	203	151/292 (51.7%)	522/574 (90.9%)	(151+522)/866 (77.7%)
		(−)	141	522	663			
		Total	292	574	866			
ANN	Training set (N=614)	(+)	113	57	170	113/205 (55.1%)	352/409 (86.1%)	(113+352)/614 (75.7%)
		(−)	92	352	444			
		Total	205	409	614			
	Testing set (N=252)	(+)	38	12	50	38/87 (41.7%)	153/165 (92.7%)	(38+153)/252 (75.8%)
		(−)	49	153	202			
		Total	87	165	252			
CBN	Total (N=866)	(+)	158	78	236	158/292 (54.1%)	496/574 (86.4%)	(158+496)/866 (75.6%)
		(−)	134	496	630			
		Total	292	574	866			

LR, logistic regression; ANN, artificial neural networks; CBN, causal Bayesian networks; BOO, bladder outlet obstruction

국문 초록

서론: 전립선비대증에서 요역동학적 방광출구 폐색을 예측하는 연구들이 있어 왔으나 신빙성 있는 지표들을 도출하기에는 부족하였다. 본 연구에서는 베이지안 네트워크를 활용하여 전립선비대증 환자에서 요역동학적 방광출구 폐색을 예측하는 비침습적 임상 지표들을 찾아 보고자 하였다.

방법: 2004 년 10 월부터 2011 년 12 월까지 전립선비대증으로 전립선증상설문 (IPSS)과 요류검사 (UFM), PSA 및 경직장전립선초음파, 요역동학검사 (UDS)를 빠짐없이 시행받은 환자들의 자료를 전자의무기록에서 추출하여 분석하였다. 요로감염, 신경인성방광 등 배뇨증상에 영향을 미칠 수 있는 다른 원인이 확인된 환자는 분석에서 제외하였다. 총 866 명 환자들의 연령은 66.3 (±7.0)세였으며, 전립선용적 (TPV)은 49.8 (±26.7)ml, IPSS 총 점수는 18.0 (±7.7)이었다. UDS 에서 확인된 방광출구폐색지수 (BOOI)는 34.0 (±24.4)이었으며, 요역동학적 폐색 (BOOI ≥40)으로 확인된 환자는 292 명 (33.5%)이었다. 베이지안 네트워크 모델을 이용하여 방광출구폐색을 유발할 수 있는 비침습적 인자들을 찾아보았으며 로지스틱 회귀분석 및 인공신경망 모델을 활용하여 선택된 임상지표들의 폐색의 예측도를 검증하였다.

결과: 베이지안 네트워크에서 TPV, UFM 에서의 최대요속 (Qmax), 잔뇨량 (PVR) 및 IPSS 설문 5 번 항목의 점수 (세뇨)가 요역동학적 폐색의 독립적인 예측인자로 확인되었다. 이 네가지 예측인자들로 만들어진 예측모델의 민감도는 54.1%, 특이도 86.4%, receiver operating characteristic (ROC) 곡선하 면적은 0.793 인 것으로 확인되었다. 로지스틱 회귀분석에서도 유사한 예측정확도와 ROC 곡선하 면적을 보였다 (민감도: 51.7%, 특이도: 90.9%, ROC 곡선하 면적: 0.797). 인공신경망 모델의 민감도는 43.7%, 특이도 92.7%, ROC 곡선하 면적 0.756 으로 확인되었다. 인공신경망 모델의 ROC 곡선하 면적은 다른 두 모델 보다 통계적으로 유의하게 작았다 (p-value 범위: <0.001-0.005).

결론: 본 연구결과 TPV, Qmax, PVR 및 IPSS 설문 5 번 항목의 점수가 요역동학적 폐색의 독립적인 비침습적 예측인자로 확인되었다.

주요어: 방광출구폐색, 전립선비대증, 요역동학검사, 예측 모델, 베이지안 네트워크, 로지스틱 회귀분석
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