

A clinical prediction rule for urinary tract infections in patients with type 2 diabetes mellitus in primary care

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SUMMARY

We aimed to develop a prediction rule for urinary tract infections (UTIs) in patients with type 2 diabetes mellitus (DM2). A 12-month prospective cohort study was conducted in patients with DM2 aged ≥ 45 years to predict the occurrence of recurrent UTIs in women and lower UTIs in men. Predictors for recurrent UTI in women ($n=81$, 2%) and lower UTIs in men ($n=93$, 3%) were age, number of general practitioner (GP) visits, urinary incontinence, cerebrovascular disease or dementia. In women, renal disease was an additional predictor. The optimum corrected area under the receiver-operating curve (AUC) was 0.79 (95% CI 0.74–0.83) for women and 0.75 (95% CI 0.70–0.80) for men. Using a cut-off score of 4, women with a lower risk assignment had a probability of 0.3% for the outcome. For a cut-off score of 6, women with a higher risk assignment had a probability of 5.8%. For men these figures were 0.8 and 7.1 for a cut-off score of 2 and 4, respectively. Simple variables can be used for the risk stratification of patients.

Key words: Diabetes, epidemiology, general practice, prognosis, urinary tract infection.

INTRODUCTION

Urinary tract infections (UTIs) are one of the most important community-acquired infections and recurrence is common, particularly among women. Studies show that 20–30% of women will have recurrent episodes during their lifetime [1]. Patients with

diabetes mellitus (DM) have an increased risk of UTIs [2–4].

DM may predispose patients to more severe infections and complications of the upper urinary tract [4–6]. In addition, infections in these patients may be more difficult to treat and recur often [7, 8]. However, data are lacking on individual risks of patients with DM for UTIs. Therefore, a risk assessment using an accurate, objective model of prognosis derived from population-based data could help primary-care physicians make management decisions. The aim of this study was to develop a clinical prediction rule for recurrent UTIs in women with type 2 DM (DM2) and lower UTI in men with DM2 in primary care.

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METHODS

A prospective cohort study was conducted using data from the Second Dutch National Survey of General Practice (DNSGP-2). In this survey, 195 family general practitioners (GP) were trained to register all patient visits ($n=390\,000$) for a 12-month period during the study period from May 2000 until April 2002 [9]. Patient visits were registered in computerized medical records using the International Classification of Primary Care (ICPC) codes [4, 10] for diagnoses and the codes of the Anatomical Therapeutic Chemical (ATC) classification index [4, 11] for drugs. Active medical comorbid conditions were considered present if a visit for such diseases was made in the year of registration.

Patients aged ≥ 45 years with at least one visit with an ICPC code of DM2 were included. Patients with a visit registered with ICPC codes T90.0 (diabetes not specified) or T90.3 (other diabetes) were classified on the basis of their age and medical management [4]. We excluded patients with rare diseases and malignancies requiring a specific management of infections [4].

Potential predictor variables

The selection of potential predictor variables was based on literature on DM and UTIs in general, but restricted by registered variables in the database. The following demographics were selected: age and type of health insurance as a proxy for socioeconomic status [4]. Moreover, use of medication (insulin and/or oral blood glucose lowering medication), health-care use and possibly relevant comorbidity were selected. Health-care use was defined as the number of GP visits, including regular check-ups for DM. Because we only had data for 1 year, successive visits could have been defined as a first visit. The selected comorbidity was the same as that described in a previous study by our group [4]. In addition, the following diseases were recorded: depression, chronic alcohol abuse, hypertension, cerebrovascular disease, dementia and urinary incontinence.

Outcome measure

The outcome measure was an episode of recurrent UTI (cystitis) in women and an episode of lower UTI (cystitis and prostatitis) in men, diagnosed and classified by a GP. As differentiation between cystitis and prostatitis in men is difficult in clinical practice, we combined these two diseases and called them lower

UTIs. Such a diagnosis could have been assessed in patients without documentation of bacterial cultures as is common in general practice. An episode could include one or more visits to a GP. A new episode was defined if a patient was free of complaints for 30 days after start of the treatment. A second episode after these 30 days was considered a recurrence.

Statistical analysis

Proportions or means were calculated using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA) to describe the baseline characteristics of the study population. Univariable logistic regression analysis was used to select potential predictors ($P < 0.10$), which were subsequently examined in a multivariable logistic regression model ($P < 0.05$). Odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) were assessed. For practical purposes, we presented a model with categorized predictors as well as a model with continuous predictors. Calibration of the multivariable logistic regression models was tested using the Hosmer–Lemeshow goodness-of-fit statistic. The ability to discriminate between patients with and without (recurrent) UTI was assessed by the area under the receiver-operating curve (ROC area). A ROC area of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination.

During the final stage, the regression coefficients of the model were divided by the lowest β [(age)=0.595 for women and (age)=0.583 for men] to form the scores of the predictors. Total score results were used to define clinically useful risk classes. For each class, we calculated sensitivity, specificity, positive and negative predictive value, proportion of outcomes missed ($1 - \text{sensitivity}$) and proportion of persons selected.

RESULTS

Women with recurrent UTIs

Mean age of the 3444 women included with DM2 was 69 years (s.d. = 11). The incidence of recurrent UTI was 2/100 patients followed for 1 year ($n=81$). The women with recurrent UTIs had a mean age of 72 years (s.d. = 10). Those without these infections were aged 69 years (s.d. = 11) (Table 1).

The univariable analyses showed that increasing age, number of GP visits, neurological, renal, psychiatric and thyroid disease, cerebrovascular disease or dementia and urinary incontinence were significant potential predictors of a recurrent UTI (Table 1).

Table 1. Unadjusted associations between potential predictors and urinary tract infections in patients with type 2 diabetes mellitus

Potential predictors	Women with outcome* (n=81)	Women without outcome (n=3363)	Unadjusted OR (95% CI)	P value	Men with outcome* (n=93)	Men without outcome (n=2806)	Unadjusted OR (95% CI)	P value
Demographics								
Age, yr (mean, s.d.)	72.0 (9.91)	68.9 (11.27)	1.025 (1.005–1.046)	0.016	69.4 (10.74)	65.2 (10.44)	1.039 (1.018–1.059)	< 0.001
Age ≥65 and <85 yr	59 (72.8%)	1936 (57.6%)	1.977 (1.206–3.241)	0.007	60 (64.5%)	1320 (47.0%)	2.047 (1.330–3.150)	0.001
Health insurance	69 (85.2%)	2778 (82.6%)	1.211 (0.652–2.250)	0.545	69 (74.2%)	1966 (70.1%)	1.225 (0.765–1.964)	0.398
Medication use								
Insulin	11 (13.6%)	381 (11.3%)	1.230 (0.646–2.343)	0.529	12 (12.9%)	243 (8.7%)	1.563 (0.840–2.906)	0.159
Oral medication	70 (86.4%)	2846 (84.6%)	1.156 (0.608–2.189)	0.658	83 (89.2%)	2433 (86.7%)	1.272 (0.654–2.474)	0.478
Health-care use								
No. of GP visits								
1–6	2 (2.5%)	1013 (30.1%)	—	—	9 (9.7%)	1124 (40.1%)	—	—
7–11	13 (16.0%)	1065 (31.7%)	6.183 (1.392–27.465)	0.017	25 (26.9%)	912 (32.5%)	3.423 (1.590–7.371)	0.002
≥12	66 (81.5%)	1285 (38.2%)	26.015 (6.357–106.465)	< 0.001	59 (63.4%)	770 (27.4%)	9.569 (4.717–19.413)	< 0.001
Comorbidity†								
Cardiovascular disease	46 (56.8%)	1663 (49.4%)	1.344 (0.861–2.096)	0.193	44 (47.3%)	1.194 (42.6%)	1.212 (0.801–1.834)	0.362
Pulmonary disease	6 (7.4%)	246 (7.3%)	1.014 (0.437–2.352)	0.975	13 (14.0%)	203 (7.2%)	2.084 (1.140–3.809)	0.017
Neurological disease	3 (3.7%)	20 (0.6%)	6.429 (1.871–22.085)	0.003	0 (0.0%)	10 (0.4%)	—	—
Renal disease	3 (3.7%)	10 (0.3%)	12.896 (3.481–47.776)	< 0.001	1 (1.1%)	24 (0.9%)	1.260 (0.169–9.414)	0.822
Peripheral neuropathy	0 (0.0%)	62 (1.8%)	—	—	3 (3.2%)	43 (1.5%)	2.142 (0.652–7.034)	0.209
Psychiatric disease	3 (3.7%)	20 (0.6%)	6.429 (1.871–22.085)	0.003	0 (0.0%)	9 (0.3%)	—	—
Thyroid disease	6 (7.4%)	108 (3.2%)	2.411 (1.027–5.660)	0.043	2 (2.2%)	17 (0.6%)	3.606 (0.821–15.839)	0.089
Vaginal disease	4 (4.9%)	96 (2.9%)	1.768 (0.634–4.929)	0.276	—	—	—	—
CVA or dementia	11 (13.6%)	134 (4.0%)	3.787 (1.960–7.317)	< 0.001	10 (10.8%)	107 (3.8%)	3.039 (1.534–6.022)	0.001
Urinary incontinence	11 (13.6%)	151 (4.5%)	3.343 (1.734–6.444)	< 0.001	4 (4.3%)	31 (1.1%)	4.023 (1.390–11.641)	0.010

OR, Odds ratio; CI, confidence interval; CVA, cerebrovascular disease.

Values are given as number (percentage) unless otherwise indicated.

* Outcome: ≥2 episodes of cystitis in women and ≥1 episodes of lower UTI in men.

† A definition of the different groups is given in the Methods section.

Finally, our multivariable logistic regression model consisted of the following predictors: increasing age (OR, 1.01, 95% CI 1.00–1.03), number of GP visits (OR 1.06, 95% CI 1.05–1.08), urinary incontinence (OR 2.07, 95% CI 1.03–4.16), cerebrovascular disease or dementia (OR 2.23, 95% CI 1.07–4.67) and renal disease (OR 17.71, 95% CI 4.55–68.93). Table 2a shows the model with age and number of GP visits analysed as categorized variables.

The AUC of the final model, including the categorized variables age and number of GP visits, did not differ from the model with the continuous variables age and GP visits (AUC 0.79, 95% CI 0.74–0.83). The Hosmer–Lemeshow goodness-of-fit test statistic indicated an excellent calibration ($P=0.76$). Using a cut-off score of 4, patients with a lower risk assignment (score 0–3) had a probability of 0.3% and patients with a higher risk assignment (score ≥ 4) had a probability of 3.9% for a recurrent UTI. Using a cut-off score of 6, patients with a lower risk assignment had a probability of 1.1% and patients with a higher risk assignment had a probability of 5.8% for an outcome. The proportion of outcomes missed increased from 4.9% to 34.6% (Table 3a).

Men with lower UTIs

Mean age of the 2899 men included with DM2 was 65 years (s.d. = 10). The incidence of lower UTI was 3/100 patients followed for 1 year ($n=93$). The subjects with lower UTIs had a mean age of 69 years (s.d. = 11). Those without these infections were aged 65 years (s.d. = 10) (Table 1).

The univariable analyses showed that increasing age, number of GP visits, pulmonary disease, cerebrovascular disease or dementia, and urinary incontinence were significant potential predictors of a lower UTI (Table 1).

Finally, our multivariable logistic regression model consisted of the following predictors: increasing age (OR 1.02, 95% CI 1.00–1.04), number of GP visits (OR 1.06, 95% CI 1.04–1.08), urinary incontinence (OR 1.33, 95% CI 0.36–4.85) and cerebrovascular disease or dementia (OR 2.10, 95% CI 1.03–4.28). Table 2b shows the model with age and number of GP visits analysed as categorized variables.

The AUC of the final model, including the categorized variables age and number of GP visits, did not differ from the model with the continuous variables age and GP visits (AUC 0.75, 95% CI 0.70–0.80). The Hosmer–Lemeshow goodness-of-fit test statistic

indicated an excellent calibration ($P=0.42$). Using a cut-off score of 2, patients with a lower risk assignment (score 0–1) had a probability of 0.8% and patients with a higher risk assignment (score ≥ 2) had a probability of 4.7% for a lower UTI (Table 3b). Using a cut-off score of 4, patients with a lower risk assignment (score 0–3) had a probability of 1.6% and patients with a higher risk assignment (score ≥ 4) had a probability of 7.1% for a lower UTI. The proportion of outcomes missed increased from 8.7% to 34.4% (Table 3b).

DISCUSSION

We were able to derive an accurate model to predict recurrent UTI in women with DM2 and lower UTI in men with DM2 using a nationally representative large population-based database in primary care. To our knowledge this is the first population-based study on individual risks for UTIs in DM2 using a prospective design, with a sufficient sample size and taking into account a large range of potential predictors. Moreover, the diagnosed comorbidity is well registered due to the fact that in The Netherlands more than 90% of patients have their own GP who acts as a filter for specialist care. Therefore, a detailed record of each patient's ongoing medical history and characteristics were available.

Several studies described risk factors for the development of UTIs [2, 5, 12] and different results have been found regarding age [13, 14]. Urinary incontinence has been described as a risk factor [3, 15]. In contrast to some earlier studies, we did not find insulin therapy to be a predictor for UTIs [15, 16]. Dementia in relation to UTIs has been described in the elderly [17, 18]. However, according to Ginde *et al.* [19] dementia may not be as important as previous studies have suggested, although this retrospective cohort study had a relatively small sample size.

Several limitations of the present study should be noted. The power was not adequate to choose more distinct categories of comorbidity and to enable analysis of specific subgroups of patients. Therefore, we were not able to use hospitalization or death as an outcome, two measures that are frequently used in prognostic research. In addition, laboratory biochemical data were not registered. Taking a small sample size into account, Ginde *et al.* [19] showed that laboratory data were helpful in determining risks in geriatric patients. However, our prediction rule permits GPs to avoid ordering laboratory tests and

Table 2a. Adjusted associations between potential predictors and recurrent urinary tract infections in women with type 2 diabetes mellitus

Potential predictors*	Women with outcome† (n=81)	Women without outcome (n=3363)	Adjusted OR (95% CI)	P value	Regression coefficient (β)	Score
Demographics						
Age ≥ 65 and < 85 yr	59 (72.8%)	1936 (57.6%)	1.813 (1.093–3.007)	0.021	0.595	1
Health-care use						
No. of GP visits						
0–6	2 (2.5%)	1013 (30.1%)	—	—	—	—
7–11	13 (16.0%)	1065 (31.7%)	6.243 (1.399–27.867)	0.016	1.831	3
≥ 12	66 (81.5%)	1285 (38.2%)	23.434 (5.695–96.423)	<0.001	3.154	5
Comorbidity						
Urinary incontinence	11 (13.6%)	151 (4.5%)	2.399 (1.222–4.708)	0.011	0.875	1
CVA or dementia	11 (13.6%)	134 (4.0%)	2.771 (1.409–5.449)	0.003	1.019	2
Renal disease	3 (3.7%)	10 (0.3%)	17.266 (4.059–73.445)	<0.001	2.849	5

OR, Odds ratio; CI, confidence interval; CVA, cerebrovascular disease.

Values are given as number (percentages) unless otherwise indicated.

* Potential predictors with $n \geq 5$.

† Outcome: ≥ 2 episodes of cystitis in women.

Table 2b. Adjusted associations between potential predictors and lower urinary tract infections in men with type 2 diabetes mellitus

Potential predictors*	Men with outcome† (n=93)	Men without outcome (n=2806)	Adjusted OR (95% CI)	P value	Regression coefficient (β)	Score
Demographics						
Age ≥ 65 and < 85 yr	60 (64.5%)	1320 (47.0%)	1.791 (1.153–2.782)	0.010	0.583	1
Health-care use						
Number of GP visits						
0–6	9 (9.7%)	1124 (40.1%)	—	—	—	2
7–11	25 (26.9%)	912 (32.5%)	3.247 (1.506–7.001)	0.003	1.178	4
≥ 12	59 (63.4%)	770 (27.4%)	8.597 (4.216–17.527)	<0.001	2.151	—
Comorbidity						
Urinary incontinence	4 (4.3%)	31 (1.1%)	2.403 (0.802–7.202)	0.117	0.877	2
CVA or dementia	10 (10.8%)	107 (3.8%)	1.854 (0.916–3.753)	0.086	0.618	1
Renal disease	1 (1.1%)	24 (0.9%)	0.975 (0.125–7.587)	0.981	–0.025	0

OR, Odds ratio; CI, confidence interval; CVA, cerebrovascular disease.

Values are given as number (percentages) unless otherwise indicated.

* Potential predictors with $n \geq 5$.

† Outcome: ≥ 1 episode of lower UTI in men.

enhance the possibility of risk calculation immediately. Unfortunately, diagnostic tests such as the routine measurement of glycaemic control were not validly registered or available for analysis. Thus far, data regarding this potential predictor is not conclusive [12, 20, 21]. Since this study concerns a computerized database study it was necessary to make use of the ICPC coding system for the registration of

medical encounters. In such records, a detailed description of sexual habits is not available, let alone being valid. Although, this might be a very important predictor, we were not able to use it for our analysis using routine medical care data. Furthermore, it might be argued that we missed some patients with DM2. First, we could have missed them by taking a cut-off of age 45 years. For example, it has recently

Table 3a. Recurrent urinary tract infections in women with type 2 diabetes mellitus (DM2) in different risk classes

Risk class	Women with DM2 (n = 3444)	Women with outcome* (%) (n = 81)	Cut-off point	SE (%)	SP (%)	PPV (%)	NPV (%)	OM (%)	Selection (%)
0-1	973	2.5	0	100	0	2.4	0	0	100
2-3	484	2.5	2	97.5	28.9	3.2	99.8	2.5	71.7
4-5	1073	29.6	4	95.1	43.2	3.9	99.7	4.9	57.7
≥6	914	65.4	6	65.4	74.4	5.8	98.9	34.6	26.5

SE, Sensitivity; SP, specificity; PPV, positive predictive value for an outcome among subjects having a score greater or equal to the cutoff point; NPV, negative predictive value; OM, outcomes missed; Selection, the percentage of the cohort having a score greater or equal to the indicated cut-off point.

* Outcome: ≥2 episodes of cystitis in women.

Table 3b. Lower urinary tract infections in men with type 2 diabetes mellitus (DM2) in different risk classes

Risk class	Men with DM2 (n = 2899)	Men with outcome* (%) (n = 93)	Cut-off point	SE (%)	SP (%)	PPV (%)	NPV (%)	OM (%)	Selection (%)
0-1	1116	9.7	0	100	0	3.2	0	0	100
2-3	927	24.7	2	90.3	39.5	4.7	99.2	8.7	61.5
≥4	856	65.6	4	65.6	71.7	7.1	98.4	34.4	29.5

SE, Sensitivity; SP, specificity; PPV, positive predictive value for an outcome among subjects having a score greater or equal to the cut-off point; NPV, negative predictive value; OM, outcomes missed; Selection, the percentage of the cohort having a score greater or equal to the indicated cut-off point.

* Outcome: ≥1 episode of lower UTI in men.

been described that a growing number of children and adolescents are developing DM2. However, this especially concerns ethnic minority populations [22, 23]. Second, the onset of DM might have been after the date of the UTI. However, we do not believe that this has biased our results, because the incidence of new patients with DM is about ten times lower than the prevalence (26.3 cases/1000 patients). By far the majority of patients with DM2 are aged ≥45 years and most cases of UTI occur in this age group.

Our prediction rule can be used in all patients with DM2 aged ≥45 years. The choice of the optimum cut-off level of the prediction rule may be chosen depending on the acceptability of the proportion of missed outcomes. For example, a higher cut-off point, in favour of a higher specificity, may be chosen in case of intensive and costly treatment strategies. Choosing a cut-off level of 4 points, the proportion of selected women is 58% and a low number of complications would be missed. Choosing a cut-off level of 6 points increases the probability of a recurrent UTI in women (from 3.9% to 5.8%), but the proportion of outcomes missed increases accordingly (from 4.9% to 34.6%). For patients at increased risk for (recurrent) UTI,

GPs can take accompanying preventive measures. GPs may recommend that these patients should visit their practice as soon as possible when symptoms of UTI occur. People could be educated about risk factors and signs indicating a UTI. For example, they should pay attention to indicators of UTI in the early stage and visit their GP for advice. Moreover, these patients could use self-diagnosis strategies that can simplify the required care for UTIs. For example, the study by Gupta *et al.* [1] provides strong evidence for a safe and feasible strategy for recurrent UTIs in women. GPs could consider further options to manage cases of recurrent UTI [24]. In the future, *E. coli* vaccination might be a potential method of preventing UTIs in women with DM [25], particularly as there are important concerns about the possible future global implications associated with the overuse of antibiotics [26, 27].

In conclusion, we were able to derive an objective model with acceptable discriminatory ability to predict recurrent UTIs in women with DM2 and lower UTIs in men with DM2. Simple variables can be used for the risk stratification of patients. Future prospective trials should focus on cost-effectiveness and safety

of application of the rule by GPs. Importantly, further studies are needed to verify whether the same predictors are relevant to predict the prognosis once a patient with DM2 has been diagnosed with a UTI. Whether or not the GP should treat more aggressively or for a longer period should be established in further studies.

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DECLARATION OF INTEREST

None.

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