Management of Recurrent Cystitis in Women: When Prompt Identification of Risk Factors Might Make a Difference

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Abstract

Background: Management of recurrent urinary tract infection (rUTI) is still challenging. A better understanding of the natural history of rUTI could help us reduce antibiotic use and improve antibiotic stewardship.

Objective: To describe the effect of risk identification, stratification, and counseling on the natural course of the disease in women with rUTI.

Design, setting, and participants: A total of 373 women affected by recurrent cystitis were enrolled in this longitudinal cohort study between December 2014 and December 2019. A systematic and standardized identification of risk factors was performed.

Intervention: As intervention, risk factors were treated or removed where possible. Patients with nonremovable risk factors were included in the control group. All patients were scheduled for follow-up visits every 6 mo.

Outcome measurements and statistical analysis: The main outcome measures were the rate of symptomatic recurrences and improvement in questionnaire results from baseline to the end of the follow-up period. Reduction of antibiotic usage was regarded as a secondary outcome measure.

Results and Limitations: Finally, 353 women were analyzed: 196 in the study group and 157 in the control group. At the end of the follow-up period, a statistically significant reduction in the symptomatic recurrence rate was found between the two groups (0.9 ± 0.2 and 2.6 ± 0.5; $p < 0.001$), as well as in quality of life and anxiety according to mean questionnaire results: quality of life (0.88 ± 0.06 and 0.63 ± 0.09; $p < 0.001$) and Spielberger State-Trait Anxiety Inventory-Form Y (32.7 ± 9.3 and 47.5 ± 14.3;

Abbreviations: UTI, Urinary Tract Infections; rUTI, Recurrente Urinary Tract Infections; LUTIRE, Lower Urinary Tract Infection Recurrence risk; QoL, Quality of Life; STAI, Spielberger State-Trait Anxiety Inventory-Form Y; UDD, Used Daily Dose.

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$p < 0.001$). The use of antibiotics was significantly lower in the study group: 4410 versus 9821 ($p < 0.001$). A limitation to consider is the lack of a randomized design for the active approach in the high-risk group.
Conclusions: Identification, counseling, and removal of risk factors, where possible, are able to change the natural history of rUTI, by reducing the number of symptomatic episodes and antibiotic use and improving quality of life.
Patient summary: In this report, we analyzed a large cohort of women affected by recurrent urinary tract infections and followed for a long time period. We found that risk factor identification and counseling may change the natural history of recurrent urinary tract infections, concluding that this approach is able to reduce the number of symptomatic episodes, reduce antibiotic usage, and improve patients' quality of life.

1. Introduction

Even though uncomplicated urinary tract infection (UTI) is one of the most common infectious diseases in women, the natural history of recurrent UTI (rUTI) is not fully understood [1–3]. Owing to the important impact of rUTI on health resources and the high indirect costs related to working days lost, several authors have elaborated clinical tools to predict the recurrence risk of rUTI episodes [4]. Hooton et al [5] developed a risk prediction model by using information about the number of days with intercourse and contraceptive use to predict the risk of UTI recurrence. Cai et al [6] developed and validated an easy to use nomogram based on several parameters from the patient and the bacteria to predict the recurrence risk of UTI (the Lower Urinary Tract Infection Recurrence risk [LUTIRE] nomogram). Even though this nomogram has high accuracy and has been validated in other populations [7], it still does not provide comprehensive data about the natural history of rUTI over an extended period of time. To reduce antibiotic use and improve adherence to antibiotic stewardship programs, we need better understanding of the natural history of rUTI in women [8]. Therefore, we aim to describe the effect of the identification, counseling, and removal of risk factors, where possible, on the natural course of the disease in a large cohort of women with rUTI over a time period of 5 yr.

2. Patients and methods

2.1. Study design and participants

This is an interventional comparative cohort study embedded in a long-term observational single-center registry study. A total of 373 women with uncomplicated cystitis, who were included in our database for the internal validation of the LUTIRE nomogram (number of partners, bowel function, type of pathogens isolated [Gram positive/negative], hormonal status, number of UTI recurrences, and previous treatment of asymptomatic bacteriuria) [6], were enrolled in this longitudinal cohort study between December 2014 and December 2019. At the time of enrollment, accurate risk factor identification was performed, in line with the LUTIRE nomogram [6] and the European Association of Urology (EAU) guidelines [9]. All patients were encouraged to remove all risk factors related to the recurrence of UTI. Patients in whom removal of risk factors was not possible were allocated to the control group. Risk factor elimination and/or active strategies, where indicated, were implemented from enrollment. All patients were scheduled for follow-up visits every 6 mo with dedicated questionnaires and a microbiological analysis (urine culture before antibiotic use) in case of symptoms related to UTI. In all enrolled patients, the mean follow-up period for the entire study was 59.3 mo (ranging from 14 to 71 mo). The study schedule is shown in Figure 1. Recurrent UTI refers to two or more infections in 6 mo or three or more infections in 1 yr [9].

2.2. Inclusion and exclusion criteria

We enrolled women aged >18 yr who were affected by clinically and microbiologically diagnosed recurrent cystitis. Only women who tested positive for uropathogens in two or more consecutive cultures (colony-forming unit $\geq 10^5$/ml) were included [5,10]. The exclusion criteria were major concomitant diseases such as uncontrolled diabetes mellitus, liver and/or renal failure, malignancy in the urinary tract, polycystic kidney disease, upper urinary tract stones, bladder stones, and foreign bodies. Women who tested positive for sexually transmitted diseases were also excluded.

2.3. Outcome measures

The main outcome measures were the rate of symptomatic recurrences over the whole follow-up period and the improvement in questionnaire results on quality of life (QoL) and anxiety from baseline to the end of the follow-up period. The reduction in antibiotic usage was considered a secondary outcome measure. For the evaluation of antibiotic consumption, the actual dose administered per person and in the observation period was applied (used daily dose [UDD] and total number of antibiotic tablets used in all patients in the follow-up period), in line with the study by Cai et al [8]. To obtain comparable results, we analyzed UDDs from baseline to the end of the follow-up period among the groups.

2.4. Assessment of risk factors

Two urologists (T.C. and I.T.) analyzed all patients in terms of clinical, microbiological, and anamnestic characteristics [6]. In line with the LUTIRE nomogram [6], all women were stratified into one of the following three risk groups:

1. Low risk (total probability of recurrence ranging from 0.20 to 0.45, over a period of 1 yr)
2. Moderate risk (total probability of recurrence ranging from 0.46 to 0.70, over a period of 1 yr)
3. High risk (total probability of recurrence ranging from 0.71 to 0.99, over a period of 1 yr)

In each group, standardized counseling about rUTI risk factors, during the urological visit, was carried out and accurate information about risk factor removal was given. Risk factors related to rUTI development included hygiene, clothing, diet, activities, and medications in line with

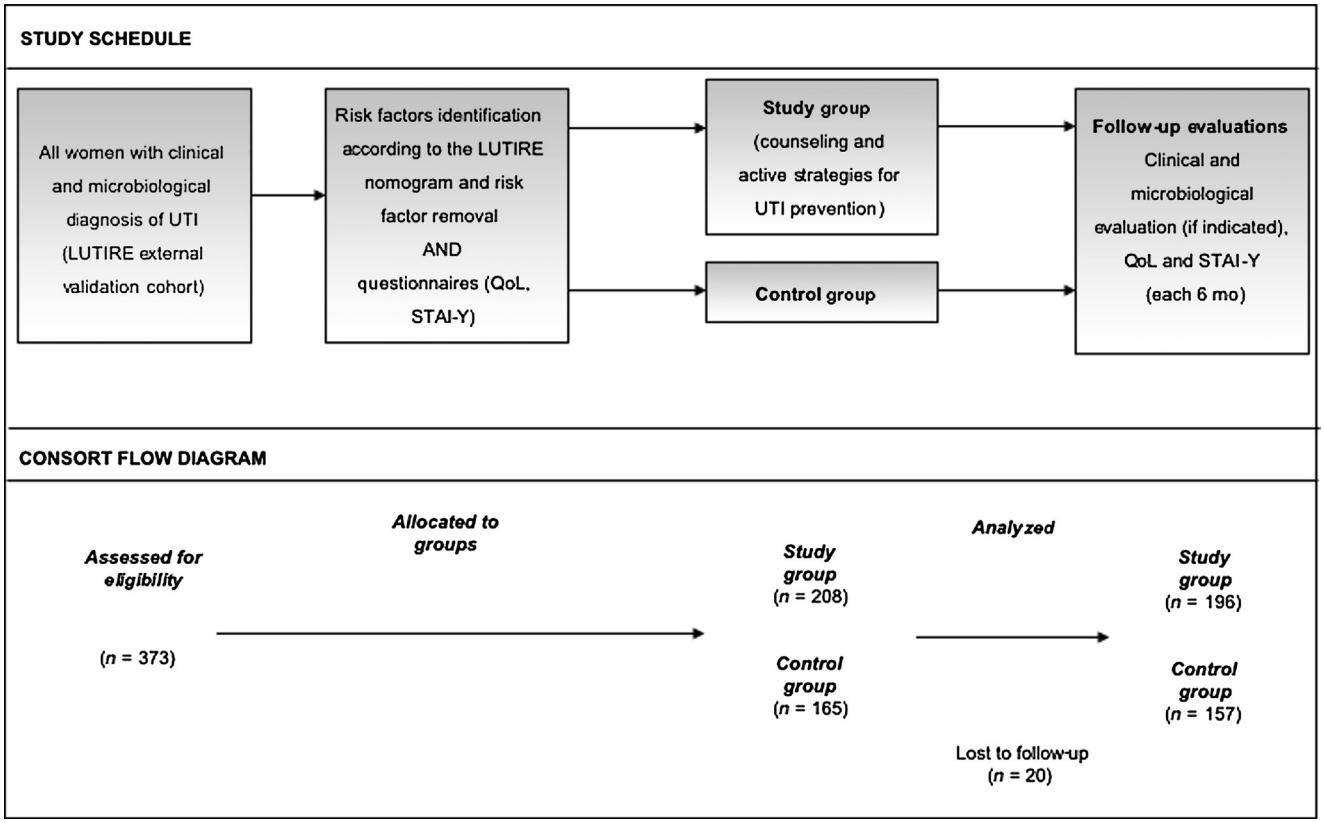

Fig. 1 – The figure shows the flow diagram adapted from "Consolidated Standards of Reporting Trials". LUTIRE = Lower Urinary Tract Infection Recurrence risk; QoL = quality of life; STAI-Y = Spielberger State-Trait Anxiety Inventory-Form Y; UTI = urinary tract infection.

the EAU guidelines [9]. We considered the following risk factors as removable: diet (bowel function regulation, water intake increase, and physical activity), sexual activity (use of spermicides and/or diaphragm, lack of postcoital urination, number of sexual partners, and frequency), vulvovaginal atrophy, urinary incontinence (when removable), and regular treatment of asymptomatic bacteriuria. Moreover, we considered the following risk factors as nonremovable: congenital diseases of the urological tract, neurological bladder dysfunction, prolapse of the anterior vaginal wall, and increased postvoid residual urine volume (not fit for the surgical treatment). All patients were requested to modify their lifestyle in terms of rUTI risk factors and/or were treated for risk factors, where possible and appropriate. All women in whom risk factors could be removed successfully were included in the study group. All other women, in whom risk factor removal was not feasible for whatever reason, were allocated to the control group (Fig. 1 and the Supplementary material).

2.5. Counseling and active strategies for avoiding exposure to rUTI risk factors

All patients underwent specific and standardized counseling, discussing with the patients the impact of UTI on their QoL and the need for evaluating risk factors in order to change the rUTI natural history. In addition to the related rUTI risk factors, all physicians asked about the previous use of antibiotics and the previous nonantibiotic strategies for preventing rUTI. On the basis of a recurrence risk, all patients in the low-risk group underwent evaluation of risk factors and counseling. In the moderate-risk group, patients underwent evaluation of risk factors, counseling, and modification of lifestyle, with follow-up evaluations and active prophylaxis in motivated patients. In the high-risk group, all patients underwent evaluation of risk factors, counseling, and active prophylaxis. Moreover, during counseling, all patients were asked to avoid self-treatment or self-administered prophylaxis. As active prophylaxis, we considered the following strategies: any kind of nutraceuticals, phytotherapeutics, immunization with OM-89 (Uro-Vaxom), local estrogens, and antibiotic prophylaxis. The type of active prophylaxis was recommended based on international guidelines and the choice of the investigator [9]. The use of antibiotics was considered only in women for whom all other antibiotic-sparing prophylaxes had failed.

2.6. Microbiological sampling and culture technique

In case of symptoms related to UTI, all clean-catch midstream urine samples were collected at room temperature, and immediately transferred to the laboratory under refrigerated conditions and analyzed. All microbiological and laboratory analyses were performed as described previously [6,8]. Microbiological culture was performed according to the procedure described by Hooton et al [11] and Mazzoli et al [12].

2.7. Questionnaires on QoL and anxiety

The impact of rUTI on patients' QoL was evaluated by using an Italian version of the Quality of Well-Being, a validated, multiattribute health scale [13]. Higher scores on the QoL scale reflect higher QoL. Moreover, the impact of rUTI on patients' QoL in terms of stress and anxiety was evaluated by the Spielberger State-Trait Anxiety Inventory-Form Y (STAI-Y) [14]. The STAI-Y is a self-report questionnaire designed to measure anxiety. Higher scores suggest higher levels of anxiety [15].

2.8. Statistical analyses

This study was planned as a prospective longitudinal cohort study. At baseline, the independent sample two-tailed *t* test was used to compare the groups. For categorical parameters, the chi-square test was applied.

Changes in questionnaire scores from baseline to the end of the follow-up period were analyzed using ranked one-way analysis of variance with a term for the treatment group. Data were reported as means ± standard deviation. For all statistical comparisons, $p < 0.05$ was considered significant. All reported p values are two sided. All statistical analyses were performed using SPSS 22.0 for Apple-Macintosh (SPSS, Inc., Chicago, IL, USA).

2.9. Ethical considerations

All women were informed about the nature of the study. They were informed that the study would not change the standard management of their clinical condition. However, all women signed a dedicated written informed consent form before enrollment and have been informed that all anamnestic, clinical, and laboratory data containing sensitive information about patients were deidentified in order to ensure analysis of anonymous data only. The deidentification process was performed by nonmedical staff by means of dedicated software. The study was conducted in line with the Good Clinical Practice guidelines and the ethical principles laid down in the latest version of the Declaration of Helsinki.

3. Results

In total, 373 women were considered for this study. Twenty patients were lost to follow-up, and finally 353 women were included in the analysis. All patients' characteristics at baseline are displayed in Table 1.

3.1. Assessment of baseline characteristics and allocation to study groups

Successful counseling could be done and risk factors could be removed in 196 out of 353 patients (55.5%), who were allocated to the study group. In all, 157 patients in whom risk factor removal was not possible were included in the control group. At the enrollment time, the mean rates of symptomatic recurrence per year were 2.8 ± 0.9 and 2.7 ± 0.8 ($p = 0.27$) for the study and the control group, respectively. The mean questionnaire results at baseline were as follows: QoL: 0.65 ± 0.08 and 0.64 ± 0.09 ($p = 0.27$); STAI-Y: 47.5 ± 10.1 and 48.9 ± 12.1 ($p = 0.23$), respectively. The use of antibiotic (UDD) was 15 454 and 13 180, respectively. On the basis of the LUTIRE nomogram, 47 patients in the study group were considered at moderate risk, while 149 were considered to be at a high risk of recurrence. No patients were found to have a low risk of recurrence. On the contrary, in the control group 39 patients were considered at moderate risk and 118 at high risk. Table 2 shows all relevant patient characteristics on the basis of the LUTIRE nomogram stratification for all patients included in the study group.

3.2. Follow-up evaluations: clinical outcomes

At the end of the follow-up period (5 yr), a statistically significant reduction of symptomatic recurrence rate was

Table 1 – Patient characteristics at the enrollment on the basis of LUTIRE nomogram results

No. of total analyzed and enrolled patients	353				
	Control		Study group		*p* value
	Moderate risk	High risk	Moderate risk	High risk	
No.	36	121	47	149	
Mean age (±SD)	48.6 (±5.9)	48.4 (±5.7)	48.6 (±5.8)	48.9 (±5.7)	0.51
Sexual intercourse per week *(±SD)*	1.7 (±0.3)	1.7 (±0.4)	1.9 (±0.2)	1.8 (±0.2)	0.12
Hormonal status					0.26
Premenopausal	25 (69.5)	89 (73.5)	33 (70.2)	110 (73.8)	
Postmenopausal	11 (30.5)	32 (26.5)	14 (29.8)	39 (26.8)	
Daily water intake (ml/d)					0.31
<1500	21 (58.3)	73 (60.3)	28 (59.6)	89 (59.7)	
≥1500	15 (41.7)	48 (39.7)	19 (40.4)	60 (40.3)	
Bowel function					0.22
Normal	22 (60.1)	73 (60.3)	29 (61.7)	95 (63.7)	
Abnormal	14 (39.9)	48 (39.7)	18 (38.3)	54 (36.3)	
Chronic constipation	11/14 (78.5)	38/48 (79.2)	14/18 (77.7)	49/54 (90.7)	
Chronic diarrhea	3/14 (21.5)	10/48 (20.8)	4/18 (22.3)	5/54 (9.3)	
Number of UTIs per year					0.27
Mean (range)	2.7 ± 0.8	2.7 ± 0.7	2.8 ± 0.9	2.8 ± 0.9	
Mean time between two episodes (mo)	4.6 ± 4.5	4.7 ± 4.7	4.8 ± 4.6	4.7 ± 4.5	0.32
Start of recurrent UTI history (mo)	20 ± 4.1	20 ± 4.4	19 ± 4.2	20 ± 4.2	0.24
QoL score at baseline (mean)	0.63 ± 0.09	0.65 ± 0.07	0.65 ± 0.03	0.63 ± 0.02	0.27
STAI-Y score at baseline (mean)	47.9 ± 13.2	48.9 ± 12.1	47.7 ± 14.4	47.5 ± 14.3	0.23
UDD (mean ±SD)	12 980 ± 211	13 180 ± 231	15 109 ± 345	15 409 ± 355	0.94
Bacterial strains					0.61
E. coli	19 (52.8)	60 (49.6)	24 (51.1)	75 (50.3)	
Enterococcus faecalis	10 (27.8)	37 (30.6)	13 (27.7)	41 (27.5)	
Enterococcus faecium	3 (8.4)	13 (10.8)	5 (10.7)	17 (11.4)	
Klebsiella spp.	2 (5.6)	7 (5.8)	2 (4.2)	9 (6.1)	
Streptococcus agalactiae	1 (2.7)	2 (1.6)	2 (4.2)	3 (2.1)	
Serratia spp.	1 (2.7)	2 (1.6)	1 (2.1)	4 (2.6)	

QoL = quality of life; SD = standard deviation; STAI-Y = Spielberger State-Trait Anxiety Inventory-Form Y; UDD = used daily dose; UTI = urinary tract infection.
The table shows all patient clinical and microbiological characteristics at enrolment time on the basis of LUTIRE nomogram results.
Data in parentheses are percentage unless otherwise specified.

Table 2 – Outcome measures at the follow-up evaluation

	Control	Study group	*p* value
No.	157	196	
Symptomatic recurrences (mean)	2.6 ± 0.5	0.9 ± 0.2	<0.001
QoL score (mean)	0.63 ± 0.02	0.88 ± 0.06	<0.001
STAI-Y score (mean)	47.5 ± 14.3	32.7 ± 9.3	<0.001
Antibiotic use (UDD)	9821	4410	<0.001
Isolated bacterial strains in recurrent patients (%)			
E. coli	79.8	61.2	<0.001
E. faecalis	6.9	31.5	<0.001
Others	13.3	7.3	<0.001

QoL = quality of life; STAI-Y = Spielberger State-Trait Anxiety Inventory-Form Y; UDD = used daily dose.
The table shows all outcome measures at the follow-up evaluation.

reported between the two groups: 0.9 ± 0.2 for the study group versus 2.6 ± 0.5 ($p < 0.001$) for the control group. QoL was also significantly improved for the study group compared with that in the control group: QoL questionnaires (mean): 0.88 ± 0.06 and 0.63 ± 0.02 ($p < 0.001$), and STAI-Y: 32.7 ± 9.3 and 47.5 ± 14.3 ($p < 0.001$), respectively. Table 2 shows all follow-up results according to groups. Moreover, patients who presented with symptomatic recurrence episodes in the control group showed a higher prevalence of *Escherichia coli* than patients in the study group ($p < 0.001$). No difference was reported in the high-risk group in terms of recurrence risk according to the different therapeutic regimens.

3.3. Follow-up evaluations: antibiotic use

The use of antibiotic (UDD) was also significantly reduced in the study group, compared with the control group: 4410 and 9821, respectively ($p < 0.001$; Table 2).

4. Discussion

Here, we demonstrated that with prompt risk identification, stratification, and counseling we could change the natural history of rUTI, reduce the number of symptomatic episodes and the total antibiotic usage, and improve patients' QoL.

4.1. Results in the context of previous studies

In a recent paper about the natural history of uncomplicated UTI without antibiotics, Hoffmann and coworkers [16] call for more research on the natural history of uncomplicated UTIs as a means to improve antimicrobial stewardship in urology. The authors highlight that clinicians and patients overestimate the benefits and underestimate the harms of antibiotic treatment in UTI, and focus on the need for nonantibiotic approaches in uncomplicated UTI. Here, we focused on the role of risk factors, specific counseling, and removal of risk factors in order to reduce the recurrence rates and the total use of antibiotics. Understanding the risk factors associated with rUTI can help physicians tailor prophylactic strategies to reduce the risk of recurrence effectively [17]. Storme and coworkers [17] highlighted that the following risk factors should be assessed in patients with rUTI: frequent sexual intercourse, vulvovaginal atrophy, changed local bacterial flora, history of UTI during premenopause or in childhood, family history of UTI, and nonsecretor blood type. Nonindicated treatment of asymptomatic bacteriuria and voiding disturbances in patients with prolapse are also important risk factors for rUTI. Furthermore, Storme and coworkers [17] stress the need for an aggressive prophylactic strategy in high-risk patient groups, while underlining the paucity of clinical trials assessing prophylaxis. Until now, no other studies have met this need. Here, we stratified all women with rUTI according to risk factors and intervened with counseling, removal of risk factors, and administration of antibiotic prophylaxis according to risk group. In the moderate-risk group, active prophylaxis was suggested for all motivated patients in addition to specific counseling about UTI risk factors and the need for modifying lifestyle, and in the high-risk group, all patients were given prophylaxis. We believe that this stratification into risk groups for symptomatic recurrence and the use of differentiated interventions are the key to a successful therapeutic approach to these patients. Moreover, structured counseling about UTI risk factors and patients' risk of recurrence is probability also important for adherence to the suggested therapeutic regimen. In 1992, Allan et al [18] highlighted that patients' nonadherence to treatment is associated with economic consequences such as loss of working days and earning, and not only recurrence of illness [19]. This finding demonstrates the importance of patients' adherence to treatment, while our findings underline the value of good communication between the healthcare provider and the patient, including structured, evidence-based counseling [18]. Successful management of rUTI is based on risk factor assessment, counseling, and risk factor removal [20]. In women with rUTI, one of the most important risk factors related to the recurrence is the role of bowel function and microbiota, as reported by several authors [21]. In this context, an antimicrobial-sparing approach using probiotics as a prophylactic strategy could have a potential impact. However, a recent meta-analysis found no convincing benefit of orally administered lactobacilli in the prophylaxis of rUTI, and these are not yet recommended in the guidelines [9,22]. However, further trials are needed before any definitive recommendation [9]. Finally, from a microbiological point of view, we found that patients who presented with symptomatic recurrence in the control group showed a higher prevalence of *E. coli* than patients in the study group ($p < 0.001$). We believe that this finding is due to higher antibiotic use in the control group, as demonstrated by several authors [8,10,20–23].

4.2. Strengths and limitations of this study

The large number of patients included and the long follow-up are strengths of this study, and the risk assessment using the validated LUTIRE score also strengthens our results. Moreover, recruitment of patients from everyday practice and the use of inclusion criteria from routine assessment increase the clinical applicability of study findings. Inclusion of women with different risk factors and different demographic, anamnestic, and clinical characteristics also increase the clinical applicability of the study results. A limitation to consider is the lack of a randomized design for the active approach in the high-risk group. This aspect was,

however, not among the study aims and did not influence the main results, but in future studies, this aspect should be addressed in embedded side studies. Effects of the respective blood groups were not considered in this study, as these do not represent parameters in the LUTIRE nomogram. Finally, the study is limited by its single-center design, although the center in which all women were evaluated is a national referral center for the treatment of UTI.

4.3. Implications for clinical practice

The natural history of rUTI in women is highly correlated with risk factors and their early removal [24]. Prompt identification of risk factors related to rUTI by using a validated and easy–to-use tool and stratification of patients into risk categories are recommended in everyday clinical practice for all women affected by rUTI. This approach reveals objective data for patient counseling and planning of active prophylaxis, and is expected to increase patients' adherence to the treatment regimen [25,26].

5. Conclusions

Our results highlight the important aspects in the management of rUTIs and emphasize the clinical utility of the LUTIRE nomogram. Early risk identification, patient stratification, and counseling can change the natural course of rUTIs by reducing the number of symptomatic episodes and antibiotic consumption, and by improving patients' QoL. Larger studies that also take into account economic aspects are to be welcomed.

Author contributions: Tommaso Cai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cai, Tateo.
Acquisition of data: Cai, Tamanini, Migno, Collini.
Analysis and interpretation of data: Rizzo.
Drafting of the manuscript: Cai, Pilatz.
Critical revision of the manuscript for important intellectual content: Brugnolli, Mereu.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.01.014.

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