



Performance of the Sysmex UF-1000i System in Screening for Significant Bacteriuria in Patients with Bladder Cancer Who Received Bacillus Calmette-Guérin Treatment

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Purpose: Diagnosing urinary tract infections by urine culture is time-consuming during a Bacillus Calmette-Guérin treatment. Because the urine culture results take time to collect, patients are treated presumptively, or Bacillus Calmette-Guérin is discontinued before the results. This study evaluated the ability of the Sysmex UF-1000i system to examine the urine bacterial count and determine if it could be used to predict a positive culture.

Materials and Methods: 180 patients who underwent transurethral resection for bladder tumors and received intravesical Bacillus Calmette-Guérin treatment between January 2017 and July 2018 were evaluated prospectively. For patients who received an intravesical Bacillus Calmette-Guérin treatment, urine flow cytometry, and urine cultures were assessed weekly during the treatment period.

Results: During Bacillus Calmette-Guérin instillation, 44, 146, and 27 patients had bacteriuria, pyuria, and positive urine nitrite, respectively. Multivariate analysis indicated that the predictors associated with bacteriuria included the urine flow cytometry results of >100 bacteria/ μ l (odds ratio, 22.73; $p < 0.001$) and positive urine nitrite (odds ratio, 5.67; $p = 0.012$) at the time of sampling for positive urine culture. The area under the receiver operative characteristic curve for diagnosing bacteriuria by urine flow cytometry was 0.825. A urine flow cytometry cutoff value of >100 bacteria/ μ l resulted in a sensitivity and specificity of 75% and 90.91%, respectively. Using the cutoff of $>1,000$ bacteria/ μ l, the sensitivity and specificity were 50% and 94.85%, respectively.

Conclusions: Rapid urinary tract infection diagnosis using Sysmex UF-1000i can be used to determine whether to treat an infection and to avoid unnecessary Bacillus Calmette-Guérin discontinuation and urine culture tests.

Keywords: Bacteriuria; Bacillus Calmette-Guérin; Bladder tumor; Flow cytometry; Urinary tract infections

Received: 10 July, 2020

Revised: 13 August, 2020

Accepted: 17 August, 2020

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INTRODUCTION

Urinary bladder cancer is one of the most common

urological malignancies [1]. Transurethral resection of bladder tumor (TURBT) constitutes the first-line treatment and the diagnostic modality for bladder cancer [2].

Intravesical chemotherapy or immunotherapy is used routinely worldwide as an adjunct treatment after TURBT to prevent or delay the recurrence of bladder cancer [3]. On the other hand, irritative symptoms are commonly found in patients who undergo TURBT with or without subsequent intravesical therapy [4]. These symptoms resemble those of an overactive bladder, such as urgency, frequency, and urge incontinence or cystitis [5].

A urinary tract infection (UTI) is an essential determinant in the discontinuation of a *Bacillus Calmette-Guérin* (BCG) treatment. A urine culture is necessary to confirm a UTI diagnosis and identify the causative agent. Because the urine culture results take one-two days, patients are treated presumptively, or BCG may be discontinued before the culture results are obtained.

Azuma et al. [6] reported that 24% of patients with non-muscle invasive bladder cancer (NMIBC) have pyuria. On the other hand, for bladder cancer patients receiving BCG treatment, pyuria might also occur as an inflammatory bladder response to BCG. Many patients experience dysuria and lower urinary tract symptoms (LUTS), such as cystitis. Therefore, clinicians often cannot differentiate between pyuria caused by UTI and that caused by an inflammatory response to BCG treatment. In addition, clinicians may treat patients presumptively with antibiotics or discontinue BCG treatment based on pyuria.

Flow cytometry analysis is capable of identifying bacteria, and the Sysmex UF-1000i (Sysmex, Kobe, Japan) flow cytometer has been developed to standardize urine analyses [7]. This system can analyze urine particles rapidly, such as white blood cells (WBC), red blood cells (RBC), bacteria, epithelial cells, and casts effectively and reliably. The unnecessary use of antibiotics can be avoided because these results can be obtained faster than the results of urine cultures. Previous studies [8-14] have shown reliable and valid results using the Sysmex UF-1000i system, which is comparable to the urine culture and microscopic counting results [15].

Thus far, there are no reports on the incidence of pyuria or bacteriuria after TURBT and BCG treatment. Therefore, this study examined the incidence of pyuria or bacteriuria after TURBT and BCG treatment and evaluated the accuracy of the Sysmex UF-1000i system in counting bacteria and WBCs in the urine. The main goal was to determine if it could predict a positive urine culture, allowing the avoidance

of unnecessary BCG discontinuation and urine cultures.

MATERIALS AND METHODS

1. Ethics Statement

The Institutional Review Board of the Chonnam National University Hwasun Hospital approved this study (IRB no. CNUHH-2018-007). Ongoing studies on patients with bladder cancer receiving intravesical BCG were approved by the institutional review board, which allowed the collection of retrospective and prospective data on patients treated with BCG. All study procedures were performed according to the Declaration of Helsinki guidelines.

2. Patients and Samples

One hundred eighty patients who underwent TURBT and received intravesical BCG treatment between January 2017 and July 2018 were evaluated prospectively. Urinalyses and urine cultures were performed at the baseline and one-two weeks after TURBT. In patients who underwent an intravesical BCG treatment, urinalyses and urine cultures were performed weekly during the BCG treatment period. Patients diagnosed with muscle invasive urothelial carcinoma after TURBT and those showing pathological stage T3 or T4 bladder cancer were excluded.

Intravesical BCG therapy was determined after surgery, and a symptomatic questionnaire, urine analysis, and urine culture were performed. The treatment is stopped for one week if a patient complains of symptoms of fever or severe irritation. The discontinuation of this study was 30%. Bacteriuria was predicted based on the subjective symptoms, patient body temperature, pyuria, and urine nitrite. Physicians should use discretion in the management of symptoms during BCG therapy and the prophylactic use of antibiotics.

The accuracy of the Sysmex UF-1000i in counting bacteria in the urine was evaluated to determine if it could be used to predict a positive culture. Samples were excluded if urine analysis and urine culture were not performed within 24 hours of each other. The midstream urine specimens were collected in sterile containers for urine analyses and cultures. The urine specimens were placed in 10-ml urine sediment centrifuge tubes and sent for chemical analysis and a laser flow cytometry (Sysmex UF-1000i) examination in the laboratory. The Sysmex UF-1000i analysis was performed

within 30 minutes of collection.

3. Sysmex UF-1000i

In the authors' hospital, the standard urinalysis is performed by the Sysmex UF-1000i and one chemistry analyzer. The results of sediment analysis are presented as the number per μl and number per high power field (HPF).

The Sysmex UF-1000i is a fully automated fluorescence flow cytometer that uses a 635-nm semiconductor diode laser to separate the bacteria and sediment into two analytical channels without the need to centrifuge the urine specimens. In the bacterial channel, the urine specimen is mixed at 42°C. A special diluent, which increases the bacterial cell wall permeability, allows the polymethine fluorescent dye to stain the bacterial DNA. Each bacterial particle, exposed to a 635-nm laser beam, emits various degrees of forward-scattered light and side-scattered fluorescent light and are then counted to generate the BACT/ml. The sediment channel analyzes the WBCs, RBCs, yeast-like cells, epithelial cells, crystals, casts, spermatozoa, and mucus. The particles/ml can then be converted to the traditional number/HPF by multiplying specific factors. Pyuria was defined as WBC >10/HPF.

4. Statistical Analysis

The predictive validities of nitrite, pyuria (>10/HPF), and BACT/ml for determining significant bacteriuria were analyzed by logistic regression. Receiver operating characteristic (ROC) curve analysis was used to determine the best cutoff point to represent significant bacteriuria. A p-value <0.05 was considered significant.

RESULTS

1. Baseline Characteristics of the Patients and Screening for Significant Bacteriuria

Table 1 lists the baseline characteristics of patients who underwent TURBT. Bacteriuria is defined as the presence of bacteria in a urine culture during BCG treatment. Only bacteriuria after the BCG therapy was included in the bacteriuria group.

Table 2 lists the urine culture, microscopic analysis, and urine flow cytometry results. Of the 180 patients evaluated, 155 (86.1%) were male, and the median age was 70 (interquartile range 62-77) years. During BCG instillation, 44 (24.4%), 146 (81.1%), and 27 (15.0%) patients had

Table 1. Baseline characteristics of patients who underwent transurethral resection of bladder tumor

Variable	Total (n=180)	BCG treatment with bacteriuria ^{a)} (n=44)	BCG treatment without bacteriuria ^{a)} (n=136)	p-value
Median age (y)	70.0 (62.0-77.0)	76.0 (70.0-79.5)	69.0 (60.0-77.0)	0.002
Male	155 (86.1)	27 (61.4)	128 (94.1)	<0.001
Smoking				0.004
Non-smoker	93 (51.7)	31 (70.5)	62 (45.6)	
Current and ex-smoker	87 (48.3)	13 (29.5)	74 (54.4)	
BMI	24.6 (22.6-26.7)	23.9 (21.9-25.9)	24.7 (22.8-26.9)	0.355
Hypertension	87 (48.3)	23 (52.3)	64 (47.1)	0.521
History of nephroureterectomy	21 (11.7)	9 (20.5)	12 (8.8)	0.035
Tumor stage				0.365
Tis	10 (5.6)	3 (6.8)	7 (5.1)	
Ta	111 (61.7)	29 (65.9)	82 (60.3)	
T1	59 (32.8)	12 (27.3)	47 (34.6)	
Grade				0.896
PUNLMP	2 (1.1)	1 (2.3)	1 (0.7)	
Low	48 (26.7)	11 (25.0)	36 (26.5)	
High	131 (72.8)	32 (72.7)	99 (72.8)	
Immediate intravesical treatment	63 (35.0)	14 (31.8)	49 (36.0)	0.572
BCG treatment				
Induction only	148 (82.2)	35 (79.5)	113 (83.1)	0.579
Induction and maintenance	32 (17.8)	9 (20.5)	23 (16.9)	0.579
Antibiotics during BCG instillation				0.110
Prophylactic use	68 (37.8)	12 (27.3)	56 (41.2)	
Therapeutic use	7 (3.9)	6 (13.6)	1 (0.7)	
Discontinuation of BCG instillation	44 (24.4)	17 (38.6)	27 (19.9)	0.012

Values are presented as median (interquartile range) or number (%).

BCG: Bacillus Calmette-Guérin, BMI: body mass index, PUNLMP: papillary urothelial neoplasm of low malignant potential.

^{a)}The definition of bacteriuria is the presence of bacteria in the urine culture during BCG treatment.

Table 2. Urine culture, microscopic analysis, and urine flow cytometry results

Variable	Total (n=180)	BCG treatment with bacteriuria (n=44)	BCG treatment without bacteriuria (n=136)	p-value
Preoperative bacteriuria	10 (5.6)	5 (11.4)	5 (3.7)	0.051
Preoperative pyuria	59 (32.8)	14 (31.8)	45 (33.1)	0.582
Preoperative positive urine nitrite	7 (3.9)	1 (2.3)	6 (4.4)	0.055
Preoperative urine flow cytometry bacterial count (/μl)				0.451
0-100	137 (76.1)	27 (61.4)	110 (80.9)	
>100	31 (17.2)	13 (29.5)	18 (13.2)	
>1,000	11 (6.1)	3 (6.8)	8 (5.9)	
>10,000	1 (0.6)	1 (2.3)	0	
Immediate postoperative bacteriuria	12 (6.7)	6 (13.6)	6 (4.4)	0.030
Immediate postoperative pyuria	134 (74.4)	36 (81.8)	98 (72.1)	0.176
Immediate postoperative positive urine nitrite	15 (8.3)	7 (15.9)	8 (5.9)	0.035
Immediate postoperative urine flow cytometry bacterial count (/μl)				0.007
0-100	138 (76.7)	28 (63.6)	110 (80.9)	
>100	32 (17.8)	10 (22.7)	22 (16.2)	
>1,000	6 (3.3)	2 (4.5)	4 (2.9)	
>10,000	4 (2.3)	4 (9.1)	0	
Bacteriuria after BCG treatment	44 (24.4)	44 (100.0)	0	
Pyuria after BCG treatment	146 (81.1)	41 (93.2)	105 (77.2)	0.027
Positive urine nitrite after BCG treatment	27 (15.0)	20 (45.5)	7 (5.1)	<0.001
Urine flow cytometry bacterial count (/μl) after BCG treatment				<0.001
0-100	106 (58.9)	4 (9.1)	102 (75.0)	
>100	45 (25.0)	18 (40.9)	27 (19.9)	
>1,000	20 (11.1)	14 (31.8)	6 (4.4)	
>10,000	9 (5.0)	8 (18.2)	1 (0.7)	
Bacteriuria 1 year after BCG treatment	22 (12.2)	8 (38.1)	14 (10.3)	0.083
Pyuria 1 year after BCG treatment	21 (11.7)	8 (36.4)	13 (9.6)	0.141
Positive urine nitrite one year after BCG treatment	8 (4.4)	5 (22.7)	3 (2.2)	0.025
Urine flow cytometry bacterial count (/μl) 1 year after BCG treatment				0.001
0-100	66 (36.7)	13 (59.1)	53 (39.0)	
>100	11 (6.1)	3 (13.6)	8 (5.9)	
>1,000	4 (2.2)	3 (13.6)	1 (0.7)	
>10,000	4 (2.2)	3 (13.6)	1 (0.7)	

Values are presented as number (%).

BCG: Bacillus Calmette-Guérin.

bacteriuria, pyuria, and positive urine nitrite, respectively. Multivariate analysis indicated that the predictors associated with bacteriuria included the urine flow cytometry results of >100 bacteria/μl (OR, 22.73; $p < 0.001$) and positive urine nitrite (OR, 5.67; $p = 0.012$) at that time of sampling for a positive urine culture.

2. ROC Curve Analysis

The ROC curves were used to define the optimal cutoff point of BACT/ml for predicting a positive culture (single bacterial growth $\geq 10^5$ CFU/ml). The area under the ROC curve for the diagnosis of bacteriuria by urine flow cytometry was 0.872 (Fig. 1). A flow cytometry cut off value of >100 bacteria/μl resulted in a sensitivity and specificity of 75% and 90.91%, respectively. Using the cutoff value of >1,000 bacteria/μl, the sensitivity and specificity were 50% and 94.85%, respectively (Table 3). Pyuria showed low specificity (28.08%), and positive urine nitrite showed low sensitivity

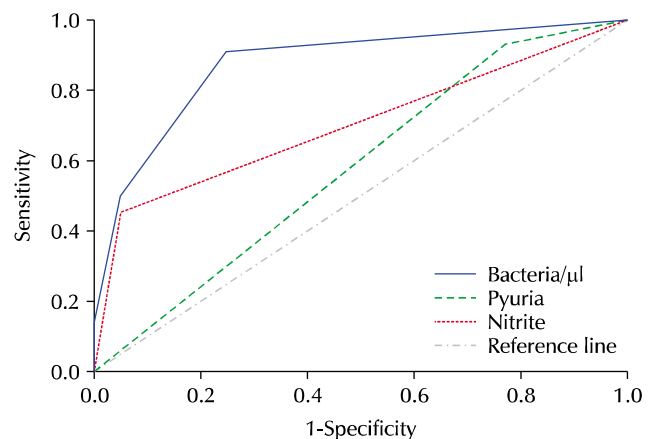


Fig. 1. Receiver operating characteristic (ROC) curves for bacteriuria detection using urine flow cytometry (when a bacterial count $< 10^5$ CFU/ml is used as the gold standard definition for negative cultures). The area under the ROC curve for the diagnosis of bacteriuria by urine flow cytometry was 0.872.

Table 3. Predictive value of urine microscopy and urine flow cytometry for bacteriuria diagnosis

	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
Pyuria-positive	28.08	91.18	22.79	93.18
Nitrite-positive	94.85	54.55	77.42	86.58
Urine flow cytometry bacterial count >100/μl	90.91	75.00	54.05	96.23
Urine flow cytometry bacterial count >1,000/μl	94.85	50.00	75.86	85.43

PPV: positive predictive value, NPV: negative predictive value.

Table 4. Bacteriuria analysis by each diagnostic method according to cultured bacteria

Microorganism	N	Urine nitrite test	Microscopic urine analysis	UF bacterial count				
		(+)	Pyuria (WBC >10)	0	1	2	3	4
<i>Escherichia coli</i>	13	9	13	1	5	4	2	1
<i>Enterococcus faecalis</i>	8		7		3	4	1	
<i>Staphylococcus epidermidis</i>	4	2	4		3	1		
<i>Coagulase negative Staphylococcus</i>	3	2	3	1	1	1		
<i>Streptococcus agalactiae</i> Gr. B	3		3		1	2		
<i>Klebsiella pneumoniae</i>	2	2	2		1			1
<i>Non-hemolytic Streptococcus</i>	2	1	2	1	1			
<i>Proteus mirabilis</i>	2	2	2				2	
<i>Streptococcus mitis/oralis</i>	2		1	1	1			
<i>Aeromonas hydrophila/caviae</i>	1							1
<i>Corynebacterium striatum</i>	1	1	1			1		
<i>Enterococcus faecium</i>	1		1		1			
<i>Morganella morganii</i>	1	1	1			1		
<i>Viridans Streptococcus</i>	1		1		1			
Total	44	20	41	4	18	14	5	3

WBC: white blood cell, UF: urine flow cytometer.

(54.55%).

3. Differences between the Bacterial Species

In the case of *Escherichia coli*, nitrite positive, pyuria, and urine flow cytometer (UF) bacterial counts >100 were 9/13 (69.2%), 13/13 (100%), and 12/13 (92.3%), respectively (Table 4). When the UF count was 0 to 1,000, it tended to be nitrite (-) (Fig. 2A). In the case of finding pyuria, the UF count was evenly distributed, reflecting the high sensitivity of microscopic pyuria (Fig. 2B).

DISCUSSION

Because UTIs are common in bladder cancer patients undergoing a BCG treatment, reliable automatic screening systems are needed to reduce unnecessary BCG discontinuation. This study evaluated the ability of the Sysmex UF-1000i system to predict a positive culture accurately so that unnecessary BCG discontinuation and urine cultures can be avoided.

The predictors associated with bacteriuria in patients undergoing a BCG treatment included urine flow cytometry results of >100 bacteria/μl (OR, 22.73; $p<0.001$) and positive urine nitrite (OR, 5.67; $p=0.012$) at the time of sampling for a positive urine culture. A urine flow cytometry cutoff value of >100 bacteria/μl resulted in a sensitivity and specificity of 75% and 90.91%, respectively. Using the cutoff >1,000 bacteria/μl, the sensitivity and specificity were 50% and 94.85%, respectively. On the other hand, the urine nitrite positivity had low sensitivity (54.55%) for bacteriuria after BCG treatment was initiated.

In this study, pyuria showed a low specificity for bacteriuria after the BCG treatment. Azuma et al. [6] reported that 24% of patients with non-muscle-invasive urothelial carcinoma demonstrated pyuria, as defined by WBCs ≥ 10 /HPF in their urine. Satake et al. [16] reported that 116 out of 237 (48.9%) of patients with NMIBC had preoperative pyuria. On the other hand, unlike the present study, they only assessed pyuria. The rate of bacteriuria was not determined. In this study, the rates of preoperative pyuria

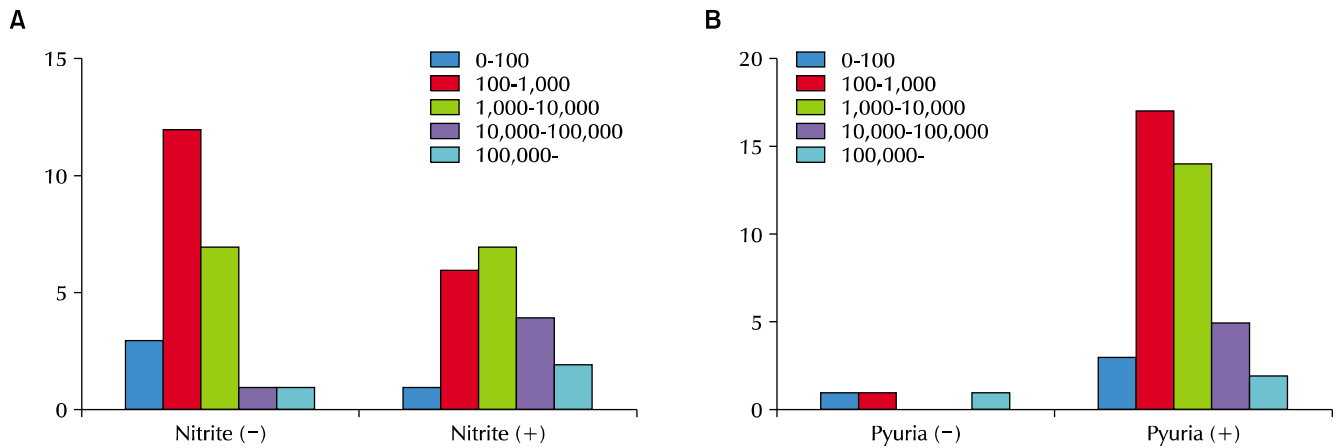


Fig. 2. (A) Urine flow cytometer (UF) bacterial counts by nitrite test. (B) UF bacterial counts by pyuria.

and bacteriuria were 32.8% and 5.6%, respectively. Pyuria in bladder cancer patients undergoing TURBT and receiving BCG treatment increased up to 74-81% due to postoperative inflammation or an inflammatory response to BCG treatment. Despite the high rate of pyuria after the TURBT and BCG treatment, the rate of postoperative bacteriuria was 6.8%. The rate of bacteriuria after the BCG treatment increased to 24.3%. Therefore, pyuria cannot predict bacteriuria because of its low specificity and low positive predictive value for bacteriuria.

The incidence of postoperative UTIs in TURBT ranged from 10% to 40% [17,18]. Therefore, prophylactic antibiotics are recommended. In this study, all patients received prophylactic antibiotics for TURBT, and the postoperative UTI rate did not increase. The bacteriuria rate increased after the BCG treatment because antibiotics are not administered routinely after intravesical BCG instillation. Before BCG treatment, the bacteriuria rate ranged from 18.1% to 25% [19,20]. In this study, 37.8% of patients received prophylactic antibiotics after BCG instillation based on clinical symptoms and pyuria to reduce BCG complications. On the other hand, the bacteriuria rate after BCG treatment increased to 24.3%.

Adjuvant intravesical immunotherapy with BCG is the standard treatment after surgery in patients with high-risk NMIBC [21], but BCG therapy is associated with a significant risk of local and systemic adverse events [22]. Because UTIs are regarded as a risk factor for BCG complications, symptomatic UTIs are an absolute contraindication to the therapy [21]. Some experts believe that bacterial cystitis causes trauma to the BCG barrier, allowing it to reach the

bloodstream [23]. On the other hand, an antimicrobial treatment delays adjuvant oncological treatment and potentially contributes to the increase in bacterial resistance to antibiotics, with no apparent clinical benefit.

The predisposing factors for intravesical BCG related complications are not well known. Some conditions may result in hematogenous dissemination of the bacilli (i.e., disruption of the urothelial barrier due to traumatic urinary catheterization, early instillation after TURBT, or concurrent UTI) [24].

Urologists are reluctant to administer BCG to patients with infections because of the possible risk of bacterial- or BCG-related sepsis or an abrogated response to BCG [25]. Poletajew et al. [26] reported in their systematic review that asymptomatic bacteriuria does not adversely affect the safety and efficacy of intravesical BCG immunotherapy. The authors suggested that there was no evidence to support the routine screening for and treatment of asymptomatic bacteriuria in bladder cancer patients scheduled for intravesical BCG instillations. Therefore, antibiotics are not administered routinely after intravesical BCG instillation [26]. Many patients receiving BCG treatment have LUTS, such as dysuria, frequency, urgency, and hematuria, which cannot be differentiated from UTI symptoms. Because urine culture results take one-two days, patients are treated presumptively based on pyuria, and LUTS or BCG treatment is discontinued before obtaining the urine culture results. Although symptomatic UTIs remains an absolute contraindication for BCG therapy, bacteriuria cannot be assessed on the day of the BCG treatment. Therefore, evidence of pyuria on urine analysis is normally used to determine the presence of a

UTI. On the other hand, in this study, pyuria was found to have low specificity for bacteriuria and was observed frequently after the BCG treatment. As a result, patients should not be treated presumptively based on pyuria or be discontinued from receiving BCG treatment based on this finding.

In this study, positive urine nitrite (OR, 5.67; $p=0.012$) at the time of sampling for a positive urine culture was a risk factor for bacteriuria. On the other hand, urine nitrite positivity had low sensitivity for bacteriuria after the BCG treatment was initiated. A nitrite test is a standard component of a urinary test strip. A positive test result for nitrites in the urine is called nitrituria. This test is commonly used to diagnose UTIs. A positive nitrite test result suggests that the cause of the UTI is a gram-negative organism, the most common being *E. coli*. The reason for the presence of nitrites in a UTI is the bacterial conversion of endogenous nitrates to nitrites. This may be a sign of infection. Other parameters, such as the leukocyte esterase levels and urine WBC count, and symptoms, such as dysuria, urinary urgency, fevers, and chills, must be correlated to diagnose an infection.

False-negative nitrite test results in UTIs occur in cases involving a low CFU count or in recently voided or dilute urine [27]. In addition, a nitrite test does not detect organisms unable to reduce nitrate to nitrite, such as enterococci, staphylococci (*Staphylococcus saprophyticus*), acinetobacter, or adenovirus [27].

According to this study, a urine flow cytometry result of >100 bacteria/ μl (OR, 22.73; $p<0.001$) at the time of sampling for a positive urine culture was a predictor for bacteriuria; these results could be determined before the urine cultures. The area under the ROC curve for the diagnosis of bacteriuria by urine flow cytometry was 0.825. A flow cytometry cutoff value of >100 bacteria/ μl resulted in a sensitivity and specificity of 75% and 90.91%, respectively. Using the cutoff of $>1,000$ bacteria/ μl , the sensitivity and specificity were 50% and 94.85%, respectively. There are many opposing opinions regarding the optimal cutoff point that can be used with the Sysmex UF-1000i system. According to some studies, the cutoff point ranges from 25 to 230 bacteria/ μl [9,10,14,28-30]. In the present study, an optimal flow cytometry cutoff value of >100 bacteria/ μl was established.

This study showed that flow cytometry using the Sysmex UF-1000i system is a useful method to exclude a UTI and

may contribute to the reduction of unnecessary BCG discontinuation and urine cultures. The cutoff points used with the Sysmex UF-1000i in this study resulted in a decrease in the number of urine cultures drawn.

The limitation of this study is that there is no consensus on the optimal management of symptoms and the use of antibiotics in patients who received BCG therapy. The purpose of this study was to show the validation of Sysmex UF-1000i for bacteriuria in patients who received BCG therapy. Therefore, physicians should use discretion when managing the symptoms during BCG therapy and the use of antibiotics. Additional prospective studies will be needed to evaluate the management further according to the results of flow cytometry. A prospective study will be needed to follow the clinical outcomes of specific antibiotic use based on the timely result provided by Sysmex UF-1000i.

CONCLUSIONS

The rate of pyuria and bacteriuria increased after the BCG treatment. Because UTIs are considered a risk factor for BCG complications, symptomatic UTIs are an absolute contraindication to the therapy. On the other hand, many patients receiving BCG have LUTS, such as dysuria, frequency, and urgency caused by irritation associated with the BCG treatment, which cannot be differentiated from the UTI symptoms. In this situation, the rapid diagnosis of UTI using Sysmex UF-1000i (results of >100 bacteria/ μl) and positive urine nitrite may help determine whether to treat an infection and avoid unnecessary BCG discontinuation and urine cultures.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This study was supported by a grant (HCRI 19017) from the Chonnam National University Hwasun Hospital Institute for Biomedical Science.

AUTHOR CONTRIBUTIONS

T.H.K. participated in data collection and wrote the manuscript. H.J.C. participated in data collection. M.S.K., H.S.C., and E.C.H. participated in the study design and performed the statistical analysis. S.I.J. and D.D.K. participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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