A SYSTEMATIC REVIEW: THE ASSOCIATION BETWEEN URINE LEUKOCYTES AND THE TYPES OF URINARY TRACT INFECTION

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ABSTRACT

Objective: This study aimed to determine the functional role of the urine leukocyte count on type of UTI. *Material & Methods:* This is a systematic review study with searches for articles from 2010-2020 through the PubMed, ProQuest, and EBSCO databases. The exclusion criteria in this study are patients using catheters (CAUTI), UTI patients in the Intensive Care Unit (ICU), and pediatric or infant patients. There were 1158 studies found and 3 studies synthesized. *Results:* There are 1130 patients studied. Age range from 18 to 89.1 years. Three studies showed that there was an association between the number of urinary leukocytes and the type of UTI (Tommaso Cai et al., p < 0.0001; and Alexander R. Levine et al., p < 0.001) and one study had no relationship. *Conclusion:* There is a relationship between the number of urinary leukocytes with the type of UTI. An increase in the number of urinary leukocytes above the normal limit is the sign of body's immune response to eliminate uropathogens. The innate immune characteristic factors and the body's immune response have an important role in causing symptoms in UTI patients.

Keywords: Urine leukocytes, leukocyturia, pyuria, asymptomatic urinary tract infection, symptomatic urinary tract infection.

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk mengetahui peranan fungsi dari jumlah leukosit urin terhadap jenis ISK. *Bahan & Cara:* Penelitian ini merupakan penelitian systematic review dengan pencarian artikel dari tahun 2010 sampai 2020 melalui database PubMed, ProQuest, dan EBSCO. Adapun kriteria ekslusi pada penelitian ini adalah pasien penggunaan kateter (CAUTI), pasien ISK di Intensive Care Unit (ICU), dan pasien anak atau bayi. Terdapat 1158 studi yang ditemukan dan 3 studi yang disintesis. *Hasil:* Terdapat 1130 pasien yang diteliti. Rentang usia dari 18 hingga 89.1 tahun. Tiga studi menyatakan terdapat hubungan antara jumlah leukosit urin dengan jenis ISK (Tommaso Cai et al., p < 0.0001; dan Alexander R. Levine et al., p < 0.001) dan satu studi tidak terdapat hubungan. *Simpulan:* Terdapat hubungan antara jumlah leukosit urin terhadap jenis ISK. Peningkatan jumlah leukosit urin di atas batas normal merupakan respon imun tubuh mengeliminasi uropatogen. Faktor karakteristik imun bawaan dan respon imun tubuh memiliki peranan penting dalam memunculkan suatu gejala pada pasien ISK.

Kata Kunci: Leukosit urin, leukosituria, piuria, infeksi saluran kemih asimptomatik, infeksi saluran kemih simptomatik.

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INTRODUCTION

Urinary tract infection (UTI) is an infection that occurs in the urinary system (kidneys, ureters, bladder, and urethra).[1-3] The World Health Organization (WHO) states that the cause of the first 10 deaths in Indonesia is kidney disease (3%).[4] There are 150 million people worldwide who experience UTI due to bacteria each year.[5] The 2015 statistics by the Singapore Ministry of Health show that as many as 4.144 UTI patients were treated in private and government hospitals with a length of stay of 2-4.8 days. As many as 4% of these female patients have had a UTI since young adulthood and the incidence of UTI has increased by 7% at age 50.[6]

Data in the United States in 2007 showed that there were 10.5 million (0.9%) outpatients who have UTI. Nearly one-fifth of UTI patients are emergency patients.[5] UTI is also the most common disease seen in women in the United States.[7] One in 4

women is likely to have recurrent infections and at least 40 to 60 percent of women have had a UTI in their lifetime.[8] Adult women are also 30 times more likely to develop UTIs while adult men under 50 have a lower incidence of UTI.[3]

UTI can be asymptomatic and symptomatic. Asymptomatic UTIs are called Asymptomatic Bacteriuria (ASB), whereas symptomatic UTIs include cystitis and pyelonephritis.[9] The prevalence of ASB in healthy premenopausal women ranges from 1% to 5% and healthy postmenopausal women range from 2.8% to 8.6%.[10] ASB is rare in young men and is found only 1% to 2% in young women but the prevalence will increase to 6% to 16% in women and 5% to 21% in men aged 65 to 90 years.[11]

Cystitis has a probability of more than 50% occur in women with UTI symptoms and the probability is more than 90% in women with symptoms of dysuria and frequent urination without vaginal discharge or vaginal irritation.[12] Cystitis can be recurrent, affecting 25% of healthy women within 6 months after the first UTI.[13] The highest incidence of pyelonephritis occurs in young women aged 29 years, followed by infants and the elderly. The accounting for acute pyelonephritis is estimated at 250.000 office visits, 200.000 hospital visits (emergency or outpatient) each year in the United States, and an estimated 11 out of 10.000 cases of hospitalization in Canadian women each year.[14]

UTIs are predisposed to recurrence and are therefore at risk of pyelonephritis and Recurrent UTIs. The prevalence of recurrent pyelonephritis in children is 21% per 5 years, in women is 9% per year, and in men is 6% per year. The prevalence of recurrent UTI in children is 19-22% per 5 years, in women is 30-50% per year, and in men is 12% per year.[15]

The urinary tract must be sterile in normal condition. UTI can occur when bacteria infect the urinary tract ascending or through the hematogenous route.[6,9] Almost all upper UTIs are caused by infection via the ascending pathway from the bladder to the kidneys. The shorter distance between the urethra and the bladder in women, which causes bacteria to colonize and infect the female bladder more easily.[12] Escherichia coli is a bacterium that is the main cause of UTI, ASB, cystitis, pyelonephritis, and UTI due to catheter use (Infection Urinary Tract Associated Catheter / CAUTI).[6,9,15]

There are 3 examinations of investigations performed to diagnose UTIs, namely dipstick test, urinalysis, and bacterial culture.[9] Bacterial culture is the Gold Standard in diagnosing UTIs by finding the type of bacteria in urine culture, but urine culture is more expensive and time-consuming.[9,16,17]. Microscopic urinalysis by finding leukocytes is necessary to help diagnose a UTI. Urinalysis has the advantage of being able to use any specimen, including the collection of urine from the perineum, making it easier for clinicians to collect urine samples.[18]

Urinalysis can determine the number of leukocytes in the urine, which is a sign of inflammation in the urinary tract.[19] Leukocyturia or leukocytes in the urine is not always accompanied by bacteriuria.[20] Leukocyturia can occur if more than 5 leukocytes per field of view are found in the urine.[20-21] The findings of white blood cells in patients with UTI and ASB are ≥ 10 leukocytes/mm^3 in the urine.[22] The results of urinalysis can be bacteriuria, nitrite, haematuria, and proteinuria.[19-20]

Naid et al. (2015) told that adult patients (≥ 15 years) with UTI had an average leukocyte value = 37.75/µl at a volume of 12 ml, 22.67/µl at a volume of 10 ml, and 12.20/µl in volume 8 ml.[23] Karisma (2017) showed that 68% of 78 pregnant women had abnormal leukocyte levels with urine leukocyte values ≥ 5/HPF.[24] Putra (2015) stated that as many as 45.2% of 42 patients with diabetes mellitus have leukocyturia.[25]

Hasanah (2015) concluded that 62.1% of 87 patients suspected of UTI had leukocyturia with a urine leukocyte value of 6-20 per field of view.[26] Alpay et al (2018) stated that 140 patients aged 65-98 years with UTI has a urine leukocyte value of 11.9 (10^3µL).[27] Meylin (2017) stated that 76.9% of 52 UTI patients in Dr. M. Djamil Padang Central General Hospital has a urine leukocyte value >5 cells/HPF.[28]

OBJECTIVE

The purpose of this study is to know the functional role of the urine leukocyte count on the type of UTI.

MATERIALS & METHODS

This study is a systematic review to know the association between urinary leukocytes and the type of UTI. A systematic review is a study using systematic method to collect secondary data, critically assess research studies, and synthesize findings qualitatively or quantitatively.

The searching of this systematic literature was from November 2019 until December 2020 using three databases, namely PubMed, ProQuest, EBSCO from searches 2010 to 2020. The Inclusion criteria of this study include:

1. All studies that have an association between urinary leukocytes count and the type of UTI
2. Patients are male and female.
3. UTI patients with ASB and SUTI
4. Obtained from the specified database
5. There is full text that can be accessed
6. Obtained by using predetermined keywords
7. Literature release time for the period 2010 to 2020
8. The language used is Indonesian or English
9. The research design taken was a cohort study, case-control, and cross-sectional.

The exclusion criteria of this study are:

1. UTI patients with catheter use (CAUTI), UTI patients in the Intensive Care Unit (ICU), and pediatric or infant patients
2. Publication only with an abstract or title
3. Study in languages other than Indonesian and English
4. Review or case report.
5. Studies that do not provide enough data for processing.

The Exposure of this study is the type of UTI; the exposed group consisting of individuals who have ASB or SUTI and validated with diagnostic procedures. Literature search using keywords can be seen in table 1.

The literature search results from 3 databases were examined to exclude duplicate studies. Titles and abstracts from the literature were collected and screened individually by the researcher to review the literature. The relevant full text literature will be seen whether it fits the inclusion and exclusion criteria, then the researcher decides to use or reject the literature.

The data will then be extracted from the literature selected according to the inclusion criteria set by the researcher. Demographic characteristics per literature are mean age, age range, and prevalence of UTI types. The size of the association using p-value will be extracted. Study quality and risk of bias in articles will be assessed using The Joanna Briggs Institute (JBI) Critical Appraisal for cross-sectional, case-control, and cohort study designs.

RESULTS

The 1158 articles were obtained through keyword searches from 3 databases. After the duplicates were removed, 582 studies were screened. A total of 577 studies were excluded so that the remaining 5 studies were assessed. Furthermore, 2 studies were excluded because the outcome data were insufficient. The studies that were finally synthesized were 3 studies. The study search method uses PRISMA flow diagrams and can be seen in Figure 1.

The results of studies in accordance with the criteria for this systematic review are as follows:

Table 1. Keywords

| Database	Keyword	Article
PubMed	(("pyuria or leukocyte in urine" or leukocyturia") AND ("asymptomatic UTI" or "asymptomatic urinary tract infection" or "asymptomatic bacteriuria")) AND ("symptomatic UTI" or "symptomatic urinary tract infection")	17
ProQuest	(("pyuria or leukocyte in urine" or leukocyturia") AND ("asymptomatic UTI" or "asymptomatic urinary tract infection" or "asymptomatic bacteriuria")) AND ("symptomatic UTI" or "symptomatic urinary tract infection")	500
EBSCO	(("pyuria or leukocyte in urine" or leukocyturia") AND ("asymptomatic UTI" or "asymptomatic urinary tract infection" or "asymptomatic bacteriuria")) AND ("symptomatic UTI" or "symptomatic urinary tract infection")	641
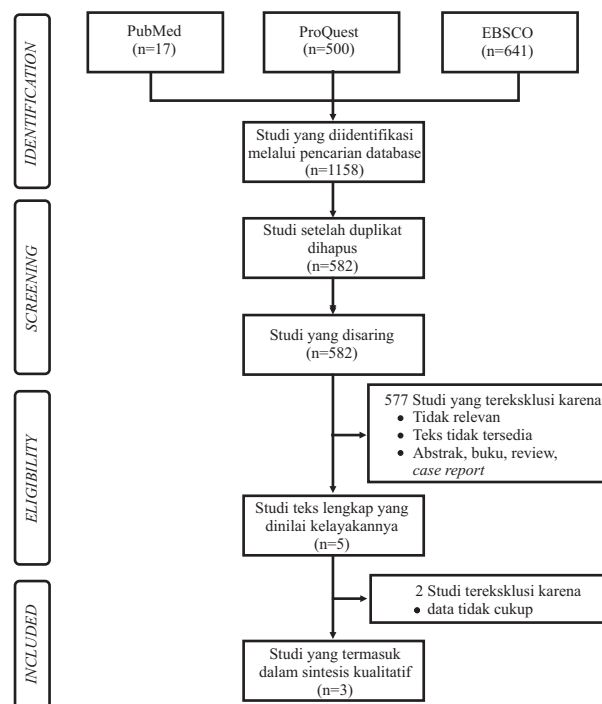
Figure 1. Search Method with PRISMA Flow Diagram.

The study by Tommaso Cai et al., Showed that out of 500 female patients (mean age = 38.3 - 38.5 years) with rUTI (recurrent UTI) and ABU in ABU episodes there were 301 patients (group A; patients with symptomatic recurrence) had mean leucocytes in urine of 19 ± 6 cells/HPF, while 249 patients (group B; patients without recurrence) had a mean leucocyte mean of 13 ± 1 cells/HPF (p = 0.09).

There was no significant relationship between the urine leukocyte count and the type of UTI. In the recurrent episodes of SUTI, there were: 301 patients (group A) had a mean leukocyte in urine of 54 ± 5 cells/HPF vs 19 ± 6 cells/HPF from baseline (p < 0.0001). Meanwhile, 249 patients (group B) had a mean leukocyte in urine of 12 ± 3 cells/HPF vs 13 ± 1 cells/HPF from baseline. There is a significant relationship between the number of urinary leukocytes and the incidence of SUTI. Leukocytes count in urine obtained a cut-off value of increased urinary leukocytes (per HPF) of 150% from baseline (95% CI 0.78-0.94; p = 0.01). An increase in urinary leukocytes per HPF ≥ 150% from baseline has a sensitivity of 90.1% and a specificity of 91.2% (positive predictive value = 70%, negative predictive value = 88.4%) for patients with SUTI.[30]

Jonas Marschall et al. found that out of 287 patients (mean age = 64 - 67 years) there were 62 men (21.6%) and 225 women (78.4%) with bacteriuria condition due to E. coli, 65 of 110 patients (63%) had ASB with urinary leukocytes >10 cells/HPF and 121 of 177 patients (74%) had SUTI with urinary leukocytes >10 cells/HPF (p = 0.1). There is no association between the urine leukocyte count and the type of UTI. In this study, it was also stated that there was no relationship between pyuria (>10 cells/HPF) and the incidence of SUTI (p = 0.3).[31]

In a study conducted by Alexander R. Levine et al., It was found that out of 293 patients with suspected UTI (mean age = 67 - 77.1 years) there were 146 men (49.83%) and 147 women (50.17%). Forty of 48 patients (87%) had a positive UTI with a urine leukocyte count ≥ 6 cells/HPF and 57 of 245 patients (24.5%) had a negative UTI (asymptomatic) with a urine leukocyte count ≥ 6 cells/HPF. This study explained that there was a significant relationship (p < 0.001) between the number of urinary leukocytes and the type of UTI.

The results of demographic data in the study showed that the mean age of patients with positive UTI was 77.1 ± 12.0 while the mean age in negative UTI (asymptomatic) patients was 67 ± 17.4 (p <0.001). There was a relationship between age and type of UTI. Alexander R. Levine et al. told that the count of leukocyte cells in urine ≥ 6 cells/HPF (OR 19.7; 95% CI 7.68-50.5, p <0.001) and age ≥ 65 years (OR 3.66; 95% CI 1.40-9.61, p = 0.008) was a significant predictor of UTI.[32]

Table 2. Summary of Study Results of Patients with UTIs.

No.	Article and Year	Study Design	Sample	Summary of Results
1.	(Tommaso Cai et al., 2018)	*Cross sectional* (retrospective)	550 female patients with rUTI and ABU in Italy	**Mean urine leukocyte count (ABU episode) :** - Group A (with symptomatic recurrence) = 19 ± 6 cells/HPF - Group B (without recurrence) = 13 ± 1 cells/HPF - (p = 0,09) - There is no significant association between the leukocyte count and the incidence of ABU **Mean urine leukocyte count (recurring episodes of SUTI) :** - Group A (with symptomatic recurrence) = 54 ± 5 cells/HPF vs 19 ± 6 cells/HPF from baseline (p < 0,0001) - Group B (without recurrence) = 12 ± 3 cells/HPF vs 13 ± 1 cells/HPF from baseline - There is a significant association between the number of leukocytes and the incidence of SUTI
2.	(Jonas Marschall et al., 2013)	*Cohort Study* (prospective)	287 Patients with *E.coli* bacteriuria at Barnes-Jewish Hospital (BJH), United States	**Urine leukocyte count :** - **ASB** (65 patients/ 63%) = >10 cells/HPF - **SUTI** (121 patients/ 74%) = >10 cells/HPF - (p = 0,1) - There is no relationship between the number of urinary leukocytes with the type of UTI There is no relationship between pyuria and SUTI (p = 0,3)
3.	(Alexander R. Levine et al., 2018)	*Cross sectional* (retrospective)	293 patients in the Emergency Room at Saint Francis Hospital and Medical Center, USA	**Urine leukocyte count :** - **Positive UTI** (40 patients/ 87%) = =6 cells/HPF - **Negative UTI (asymptomatic)** (57 patients/ 24,5%) = =6 cells/HPF - (p < 0,001) - There is a significant association between the urine leukocyte count and the type of UTI

DISCUSSION

Urinary Tract Infection (UTI) is a disease that often affects people around the world. UTI is a common disease that can be found in the age range of infants to the elderly. The disease is often asymptomatic and can complicate become a life-threatening condition. There have been many studies explaining diagnostic tools for UTI, but until now the Gold Standard in diagnosing UTI is by bacterial culture which is quite costly and time-consuming.[8,17] Urine leukocyte count in UTI patients is expected to predict UTI and its types so that the management of UTI patients can be more convenient.

There were 1158 articles found using the PubMed (n = 17), EBSCO (n = 641), and Proquest (n = 500) databases. A total of 3 articles can be used for systematic review since there were several duplicate articles and were also excluded because they did not match the inclusion and exclusion criteria. In these

three articles, it can be seen that the patient's age ranges from adult to elderly, from 18 years to 89.1 years. All studies included urinary leukocyte values from microscopic urinalysis. Two studies stated that there was an association between the number of urinary leukocytes and the type of UTI (Tommaso Cai et al., P < 0.0001; and Alexander R. Levine et al., P < 0.001) and 1 study stated that that there was no relationship (Jonas Marschall et al., p < 0.1).[30–32]

Research by Tommaso Cai et al. and Alexander R. Levine et al. showed that there is a significant association between the number of urinary leukocytes with the type of UTI.[30,32] The study by Tommaso Cai et al. found that an increase in the urine leukocyte count ≥ 150% from the initial examination before symptoms can be a predictive value (indicator) and initial screening to determine changes in the state of ASB to SUTI or symptomatic in female patients with recurrent UTI (sensitivity 90.1% and specificity 91.2 %).[30] This can be caused because when the patient does not experience a significant increase in the number of urinary leukocytes, it means that the infection does not occur in deep tissues so that the increase in the number of leukocytes is an indicator of the body's immune response against infection by carrying out an inflammatory reaction.[19,29,30]

These researchers also mentioned that interleukin-6 is a useful marker to differentiate ASB from SUTI. The combination examination of interleukin-6 with leukocyturia can give excellent results in sensitivity and specificity to determine the degree of SUTI.[30] These studies also reported that leukocyturia was an independent diagnostic factor for detecting changes in ASB to SUTI (p = 0.003). Researchers Nicolle et al. also showed that the non-pyuria condition is an indicator that UTI does not occur with a negative predictive value of 80-90%.[30] Study by Alexander R. Levine et al. stated that in UTI patients (with >1 episode of lower UTI) having a urine leukocyte count ≥ 6 cells/HPF can be a significant predictor in determining the type of UTI (p <0.001).[32]

Research by Jonas Marschall et al., states that there is no significant relationship between the number of urinary leukocytes and the type of UTI.[31] The result can be caused by host factors and not related to the pathogenic factors (virulence). Patient susceptibility, such as innate immune characteristic factors and individual immune response, may be associated with the onset of symptoms when the patient has a UTI.[31]

All studies (3 articles) used different cutoffs for urine leukocyte counts.[30–32] Three studies found that patients with symptomatic (SUTI) and asymptomatic (ASB) UTIs had a high urine leucocyte value or above the normal limit (≥ 5 cells/HPF). This could be related to the inflammatory reaction that occurs in the urinary tract of patients who are experiencing UTI. The greater number of urinary leukocytes, the more severe the ongoing inflammation is.[26]

The distinguishing indicator between a UTI with symptoms or without symptoms is the increase in the number of leukocytes in the urine. Patients with SUTI (symptomatic) had a high and significant increase in leukocyte cells, compared with patients with ASB which was not significant.[30] The results also showed that patients with symptomatic UTIs, most of them definitely had high leukocyte count, but in UTI patients without symptoms, most of the patients had normal leukocyte count.[31]

CONCLUSION

This systematic review study concludes that there is a relationship between the number of urinary leukocytes and the type of UTI. An increase in the number of urine leukocytes above the normal limit is a sign of the body's immune response in eliminating uropathogen. The innate immune characteristic factors and the body's immune response have an important role in causing symptoms in UTI patients.

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Research on the number of urinary leukocytes with the type of UTI is a new study, so it is very difficult to find journals on these two variables. Many studies focus more on the association between other examination tools, such as the dipstick test with the type of UTI. Researchers also limited studies in the last 10 years and studies that met the inclusion and exclusion criteria. Many articles are discussing the number of urinary leukocytes in UTI patients, but many were excluded because of examining infant patients or patients with CAUTI (Catheter Associated Urinary Tract Infection). The solution

that can be provided for future researchers is to use a wider database source so that they can access journals that are broader and more holistic.

Researchers also have resistance in extracting journals from the database, such as the download capacity has reached a maximum of 500 journals using the University account in the ProQuest database. The solution is to be able to use a wider database system so that they can get more opportunities for open access to journals.

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