

Neutrophil-lymphocyte ratio as a biomarker for urinary tract infection in female patients at Thumbay University Hospital, Ajman

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ABSTRACT

Short urethras make urinary tract infections (UTIs) common in women. Therefore, bacteria can enter the bladder more easily. This research aimed to determine if the neutrophil-to-lymphocyte ratio (NLR) can be used as a biomarker in UTI patients and compare C-reactive protein (CRP) and NLR to identify which is more effective in diagnosing UTI patients. This study examined urine culture, NLR, and CRP values in blood from 101 Thumbay University Hospital patients with UTI. Control group NLR and CRP values of 100 participants were also examined. NLR mean for UTI patients was 6.9881. The NLR mean for UTI-free participants was 3.0839. Comparison of NLR values between UTI patients and non-UTI patients showed significant results ($P < 0.001$). Thus, patients with UTI had significantly higher NLR results than those without UTI, indicating a strong correlation between UTI and higher NLR values. Our results showed that UTI patients had higher NLR and CRP values than healthy controls. In patients with UTI, clinical assessment of symptoms and complaints should be done first, followed by NLR and CRP as inflammatory markers.

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Introduction

The renal pelvis, ureters, bladder, and urethra are among the organs that make up the urinary tract system. All these organs work together to excrete urine out of the body. The kidney is responsible for forming urine, which is a clear, colorless fluid that normally has an amber color, that is produced when the kidney starts to filter the waste product of the blood and transfers it all the way to the bladder where the bladder will secrete it outside the body. Otherwise, if the urine does not excrete from the body, it will lead to the accumulation of toxins and harmful bacteria that will lead to urinary tract infections (UTI). That mainly occurs when the kidney is not functioning properly, that's why every person needs at least one functional healthy kidney.

All age groups and both genders are susceptible to UTI, although pregnant women are more likely to develop one. That is due to different physiological features and changes such urethra's short length and close placement to the anus risks of contamination from fecal flora, and increased bacteria growth as a result of glycosuria during pregnancy.¹ This condition is caused by bacteria traveling to the urinary tract causing an infection to its parts like the bladder, urethra, and kidneys. General symptoms of UTI can be when a burning sensation happens while urinating, cloudy bad-smelling urine, urinary incontinence, and oliguria. There are specific symptoms that can indicate which part of the urinary tract is infected, for pyelonephritis, it is back pain, fever, and nausea. Cystitis can be noted when feeling discomfort in the pelvic area, hematuria, and pain when urinating. As for the urethritis, increased discharge, and painful burning sensation

when micturating.² *Escherichia coli* is the most common causative agent of UTI, other than the other Gram-negative bacteria like *Klebsiella pneumoniae*, and *Proteus mirabilis*. Some Gram-positive bacteria like coagulase-positive and negative *Staphylococci* and *alpha hemolytic Streptococci* have also been recorded. Pregnant women with UTI should recover as early as possible because getting pyelonephritis can cause some serious complications that can affect both the mother and the fetus. These complications can be septic shock, anemia, bacteremia, renal dysfunction, preterm birth, and group B streptococcal infection along with neurological problems in the newborn. The detection of UTI can be performed through urinalysis to obtain a urine sample from the patient and through culturing along with microscopic examination.³

There are a few biomarkers to suspect the presence of UTI like C-reactive protein (CRP), interleukin (IL)-8, and neutrophil-to-lymphocyte ratio (NLR). Some studies are still ongoing on how the NLR levels can be affected.⁴ Neutrophils are the most spread white blood cells in our body and their role is to eliminate bacteria, thus, high levels can manifest the presence of acute infection. Whereas lymphocytes, the other type of leukocytes can induce adaptive immune reactions to annihilate pathogens.⁵ NLR illustrates the relation between the neutrophil count in acute and chronic inflammation along with adaptive cellular immune response which is lymphocyte count. It has also been shown that the levels of NLR differ in the perspective of various bacterial organisms.^{6,7} The aim of this group research was to appraise the NLR as a biomarker for UTI in female patients at Thumbay University Hospital, Ajman.

Materials and Methods

This descriptive cross-sectional study included 201 women between the ages of 18 and 45, 101 participants with UTI infection, and 100 healthy participants with no UTI infection.

Ethylendiamine tetraacetic acid (EDTA)-anticoagulated whole blood, serum, and midstream urine samples were obtained from all participants; then, complete blood count (CBC), C-reactive protein and urine for culture and sensitivity were performed in departments of microbiology, hematology, and clinical chemistry at Thumbay Labs in Gulf Medical University.

Beckman Coulter DxM 1096 MicroScan was used for urine culture and sensitivity, DXC 700 AU analyzer (Beckman Coulter) was used for CRP and Beckman Coulter UniCel DxH- 800/900 was used for CBC.

About 5 microliters of the sample were taken and inoculated in the cystine lactose electrolyte deficient agar (CLED) and HiCrome UTI agar. Different uropathogen morphological features in the agar such as colony colors, size, form, elevation, and margins were used for the identification of the organism in the agar. After culture, confirmation of the pathogen was done by performing Gram-stain. The results consisted of the Gram-positive or Gram-negative bacteria biochemical tests such as triple sugar iron. A motility indole urease test catalase was also performed to confirm the bacteria: this process was done before the confirmation of the bacteria's genera and species; however, in this research, chromogenic agar was used to identify the bacteria.

The susceptibility test was done to determine which antibiotics the bacteria had acquired resistance to, CBC was performed to calculate the NLR by the Coulter principle and the CRP measurement was based on the immunoturbidimetric method.

Maintenance, calibration, and quality control of all the instruments were done properly as per the quality manual of Thumbay labs and the quality control results were between +2SD and -2SD around the mean, and Westgard's rules were implemented for monitoring and evaluation of the control performance.⁸

All isolates and specimens used in the study were de-identified to maintain patient confidentiality. The proposal of the study was submitted and approved by the Institutional Review Board as per Gulf Medical University research policies. During the study, only the principal investigator and supervisor had access to the data.

Statistical analysis was performed using the statistical software package (SPSS) version 17.0 (SPSS Inc, Chicago, IL).

Results

A urine culture on CLED and UTI chromogenic agar revealed that 101 out of 201 samples had UTIs and 100 had not.

Among the 101 participants with previous and present infection (UTI), it was discovered - due to an irregularity in the NLR findings - which might be low or high. For those who did not have UTI, the findings were mixed; sometimes it was considered normal, while other times it was considered high or low.

CRP was employed as a control to compare with NLR. It was discovered that when patients had UTI, their CRP levels increased. The outcomes for those who did not have UTI varied; however, they were mainly normal.

Discussion

UTI is a common infection that affects people of all ages. In certain situations, doctors must rely on test results, which may have a weak predictive value, leading to practitioners' oversights misleading diagnoses, and excessive antibiotic administration. Therefore, the need for trustworthy biomarkers in UTIs is crucial. Most articles are related to young children and many other biomarkers such as CRP, IL-8 and 6 or neutrophil gelatinase-associated lipocalin and so on, to diagnose UTI, and there are articles that mention the NLR as biomarkers for other diseases, not many related to UTI. There were no articles regarding the use of NLR as a biomarker for females who suffer from UTI. So, this study was focused on these groups of people and NLR as a biomarker. There is a study that states that NLR can play a special role as a predictive marker of bacterial infection compared to neutrophilia or lymphocytopenia alone.⁹ Their results mentioned that NLR had a significant correlation. In this research, a strong significant between having UTI and NLR results ($P < 0.001$) has been found, as shown in Table 1. This means that when the patients experience UTI, the NLR will increase rapidly. There were some cases where the NLR dropped, but most of them increased, the reference range for NLR was 0.78 to 3.53, and the calculated mean was 6.9881 (Table 1), in the other hand, after

calculating the NLR mean for the patients who didn't have UTI, the mean was 3.0839 (Table 1). It was needed to look for sensitivity and specificity for NLR'UTI, so after doing the calculations it was found that the sensitivity was 95% and the specificity was 99%, which indicates that NLR increases while going through UTI as shown in Table 2. CRP was taken as a control based on many articles that stated that CRP is a very common biomarker for infections. After doing correlations between CRP and NLR, it was found that the correlation is weak and significant at the 0.010 level (2-tailed) as shown in Figure 1. In one study, CRP was not sufficient as a predictive value, with a sensitivity of (83%).¹⁰ In another study, CRP had a sensitivity of 100%, but a specificity of (18.5%).^{9,10} Such results are not adequate to meet expectations. in other words, CRP may increase in UTI, but it cannot be described as a biomarker for only UTI, because it may increase in many other inflammations and infections.

Based on the results, it can be concluded that NLR is a good indicator of the presence of UTI (Table 1). It can be used to detect a UTI even before the presence of any symptoms. It can also help to identify those patients who have a higher risk

of developing a UTI. Moreover, NLR can be used as an alternative biomarker instead of CRP. This is important as it can help to get an accurate diagnosis of UTI and enable early treatment, thus preventing the complications associated with a UTI. Furthermore, NLR can be used as an additional tool to diagnose UTI in combination with other tests. This can help to reduce the unnecessary use of antibiotics and better management of the condition.

NLR can also be used to monitor the response to treatment. By measuring NLR, it can help to determine whether the treatment is responding. This can help to guide clinical decisions and reduce the risk of complications.

For this study it was concluded that most cases that got UTI were between the ages 26-35, then 36-45, and, lastly, 18 to 25, as shown in Figure 2; however, when it was calculated while having an abnormal result of NLR it was found that the ages between 18 to 25 got 54.8% of having abnormal NLR. The females between 26 to 35 got 54.1% and the last group of 36-45 got 41.0% based on the results shown in Figure 3. It may indicate that the young adult females (18-25) are still in the age of developing many leukocyte cells and have active hormone states. On the other hand, females

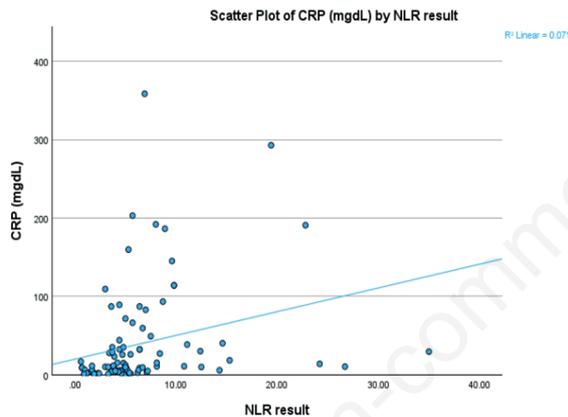


Figure 1. Weak correlation between C-reactive protein and neutrophil-to-lymphocyte ratio. CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio.

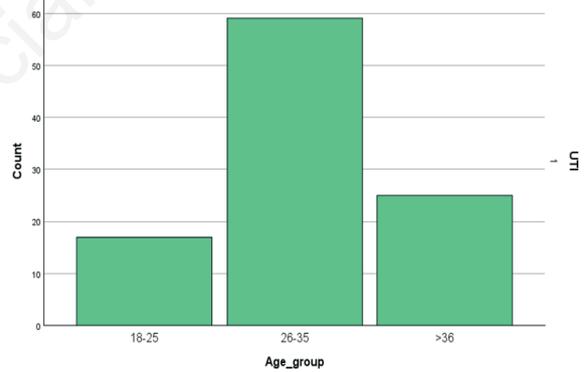


Figure 2. Frequency of urinary tract infections in different ages. UTI, urinary tract infection.

Table 1. Association between neutrophil-to-lymphocyte ratio and urinary tract infection.

	UTI infection	N	Mean of NLR	SD of NLR	Sig.
NRL results	Presence	101	6.9881	5.5	<0.001
	Absence	100	3.0839	2.1	

UTI, urinary tract infection; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation.

Table 2. Sensitivity and specificity of urine culture x neutrophil-to-lymphocyte ratio.

		NLR		Total	
		Above RR	Below RR		
Urine culture	Sig. growth	Count (%)	96 (95)	5 (5)	101 (50.2)
	No growth	Count (%)	1 (1)	99 (99)	100 (49.8)
Total	Count (%)	97 (48.3)	104 (51.7)	201 (100.0)	

NLR, neutrophil-to-lymphocyte ratio; RR, reference range. Above RR: NLR >3.5; below RR: NLR <3.5.

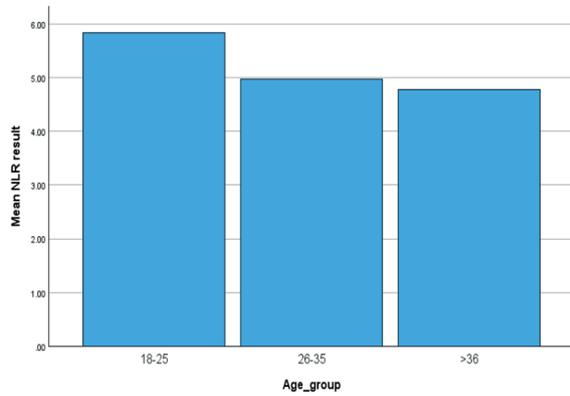


Figure 3. Association between the neutrophil-to-lymphocyte ratio and age.

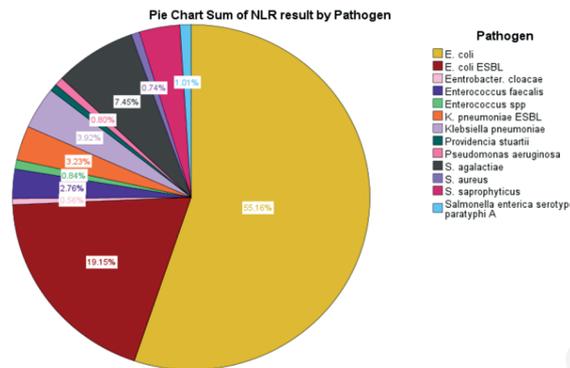


Figure 4. The frequency of the microorganisms found in urinary tract infection patients.

above 25 years old are now in a steady stage (further study may intend for this statement).

Furthermore, it was noticed in many studies that the most common pathogen while having UTI is *E. coli*.⁴ This study also agrees that the females who had UTI mostly got *E. coli* (Figure 4); it was also observed that *E. coli* extended-spectrum beta-lactamase (ESBL) was giving abnormal NLR results compared with the other pathogens (Figure 5). In this research, it was found that *E. coli* ESBL is sensitive to most drugs so there are a lot of effective discs that can be used in the patients (Figure 6). It was also concluded that most drugs are good for treating UTI, except for ampicillin and trimethoprim because as it was shown, most pathogens give ESBL or resistance reaction. It was also noticed that *E. faecalis* is the pathogen that gives more resistance in reacting to the drugs that were displayed, so it was concluded this pathogen may be the hardest to treat while going through UTI (Figure 6).

Conclusions

The results of the study showed that NLR was significantly higher in patients who had UTI compared to those who did not. This suggests that NLR could be an effective biomarker to help diagnose and treat UTI in female patients. Furthermore, this indicates that NLR could also be used to monitor the progression of UTI in female patients. Therefore, this study has demonstrated the potential of using NLR.

Recommendation for future research

A future recommendation would be a larger sample size and advanced techniques. Also, this study requires more time to obtain more accurate results. Further studies can be done to prove that the NLR can be used as a biomarker for the classification of severity of the UTI.

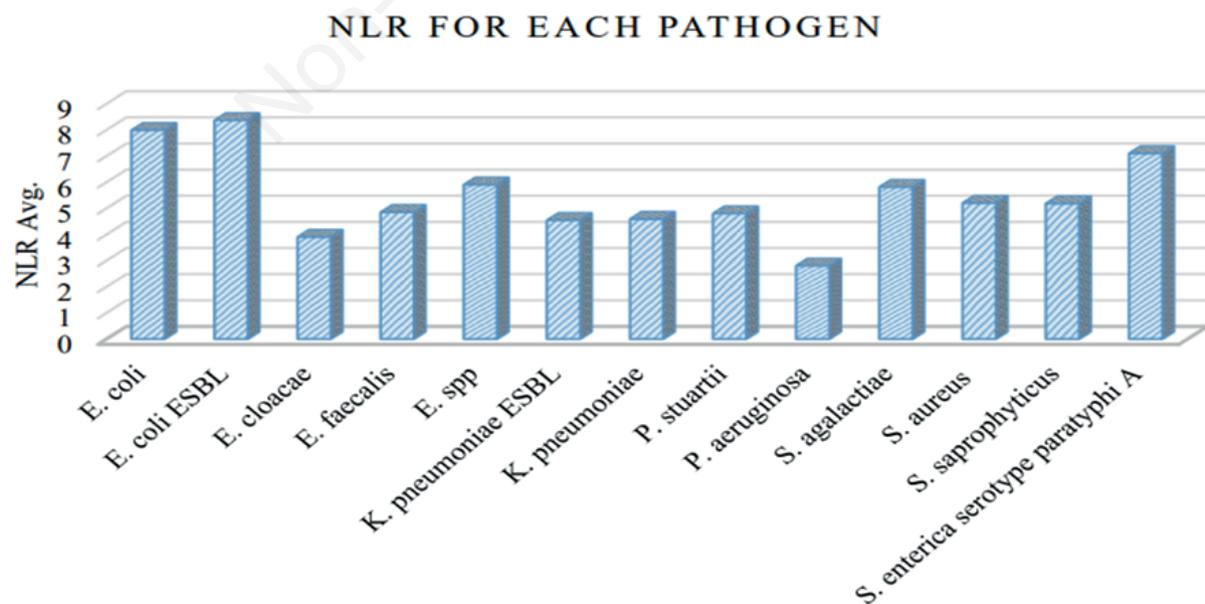


Figure 5. Neutrophil-to-lymphocyte ratio for each pathogen.

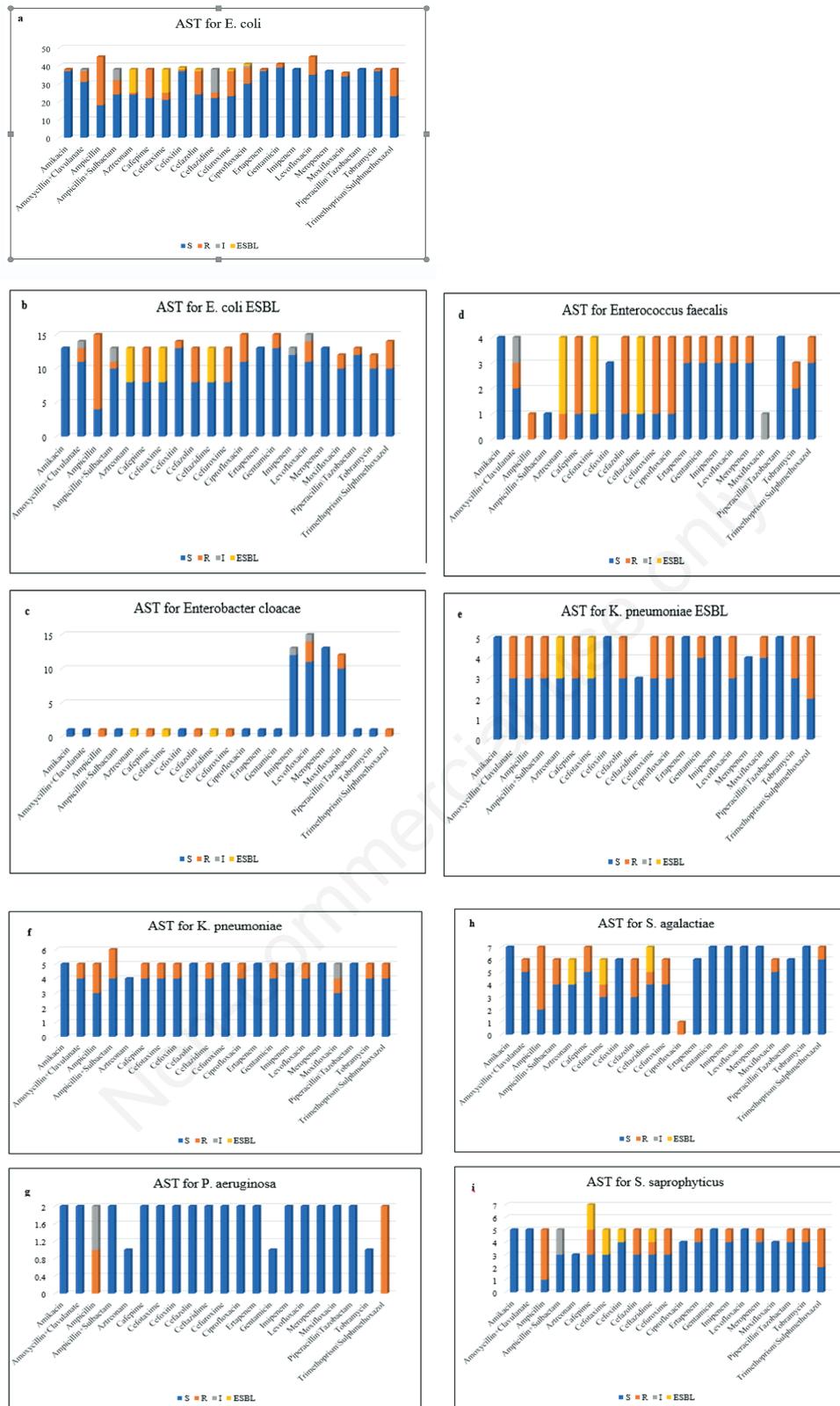


Figure 6. The antimicrobial-sensitive test for each pathogen: a) antimicrobial susceptibility testing for *E. coli*; b) antimicrobial susceptibility testing for *E. coli* extended-spectrum beta-lactamase; c) antimicrobial susceptibility testing for *Enterobacter cloacae*; d) antimicrobial susceptibility testing for *Enterococcus faecalis*; e) antimicrobial susceptibility testing for *K. pneumoniae* extended-spectrum beta-lactamase; f) antimicrobial susceptibility testing for *K. pneumoniae*; g) antimicrobial susceptibility testing for *P. aeruginosa*; h) antimicrobial susceptibility testing for *S. agalactiae*; i) antimicrobial susceptibility testing for *S. saprophyticus*. S, sensitive; R, resistance; I, intermediate; ESBL, extended-spectrum beta-lactamase.

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