INFECTIOUS DISEASES

Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, lymphocyte to monocyte ratio and Systemic Inflammatory Index in sexually transmitted diseases

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Abstract

Introduction. Hematologic biomarkers of inflammation may serve as valuable adjuncts in clinical practice, aiding in several aspects such as differential diagnosis, prognostic assessment for patient stratification and monitoring the efficacy of antimicrobial therapy. The aim of this study was to evaluate the efficacy of Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Lymphocyte to Monocyte Ratio (LMR), and Systemic Inflammatory Index (SII) in predicting bacterial sexually transmitted infections (STI).

Methods. This prospective study was conducted in the north-west region of Romania and included patients from several medical special units such as dermatology, obstetrics-gynecology, urology, and general practice. The study group comprised patients with a high suspicion of STI, while the control group consisted of healthy subjects. Quantitative data are presented as medians (interquartile ranges).

Results. The median values of SII, NLR, and SIRI were higher in the group of subjects with sexually transmitted diseases compared to the control group [604.06 (432.36 - 880.02) vs. 556.89 (388.63 - 874.19); 2.61 (1.57 - 3.3) vs. 2.29 (1.66 - 3.26); and 0.95 (0.53 - 1.52) vs. 0.89 (0.67 - 1.34)]. Regarding PLR, the median values were lower in the group of subjects with sexually transmitted diseases compared to the control group [138.1 (99.19 - 169.6) vs. 140.65 (117 - 190.32)]. As for LMR, the median values were equal between the two groups [4.64 (3.74 - 6.11) vs. 4.64 (3.75 - 5.45)]. Nevertheless, the differences did not reach the significance level.

Conclusion. Our study suggests that inflammatory biomarkers might aid in detecting bacterial STIs, but their significance was not statistically confirmed. Further research on alternative laboratory tests is needed for improved STI diagnosis and management.

Keywords: sexually transmitted diseases, NLR, PLR, LMR, SII, SIRI, inflammatory biomarkers, venereology

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Background and aims

Sexually transmitted infections (STIs) rank among the prevalent infectious diseases globally, with approximately 1 million newly reported cases daily. They significantly affect sexual, reproductive, and mental well-being [1]. STIs stem from various sources, including: bacteria (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Treponema pallidum*, *Haemophilus ducreyi*, *Calymmatobacterium granulomatis*), viruses (*Herpes simplex*, *Hepatitis viruses A, B*, and *C*, *Human Papillomavirus*), protozoa (*Trichomonas vaginalis*, *Entamoeba histolytica*), fungi (*Candida albicans*), metazoa (*Phthirus pubis*, *Sarcoptes scabiei*) [2]. In this investigation, we focused on treating bacterial STIs while examining their association with inflammatory biomarkers. A research of the medical literature shows the absence of any studies focusing on the link between Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Lymphocyte to Monocyte Ratio (LMR), Systemic Inflammatory Index (SII), and Systemic inflammation response index (SIRI) and bacterial STIs. This approach was chosen due to the existing research on viral STIs in prior studies [3-5] and absence of research on bacterial STIs.

The initiation of inflammation is prompted by cellular damage, which may result from diverse factors including trauma, burns, ischemia, surgical procedures, snakebites, exposure to corrosive substances, and extreme temperatures, along with the presence of infectious agents [6-7]. Neutrophils, a subset of granulocytes, constitute over half of all circulating white blood cells and are fully developed cells. Rapidly mobile, they are typically the earliest responders, arriving within approximately 90 minutesin cases of acute inflammation or infection. Neutrophils engulf microorganisms and cellular debris before undergoing cell death. Lymphocytes, categorized as agranulocytes, play a pivotal role in mounting immune responses against specific pathogens. Following neutrophils, they represent the second most abundant type of white blood cell in circulation. Monocytes, the largest among white blood cells, are immature cells that are present in the bloodstream or in transit to tissue sites. Upon exiting the bloodstream and migrating into tissues, these young monocytes undergo maturation into macrophages. Platelets play a critical role in the process of hemostasis, working in conjunction with coagulation factors to control bleeding in small and medium-sized blood vessels [8].

Biomarkers of infection (NLR, PLR, LMR, SII, SIRI) serve as valuable adjuncts in clinical practice, aiding in several aspects such as differential diagnosis (e.g., distinguishing between bacterial and viral infections), prognostic assessment for patient stratification, and monitoring the efficacy of antimicrobial therapy. Traditional biomarkers like total white cell count and C-reactive protein (CRP) are commonly employed for these purposes. In recent years, procalcitonin has garnered significant attention as a potential biomarker for discriminating between bacterial and viral infections and evaluating the response to antimicrobial treatment. However, its utilization is hindered by cost and limited availability. In contrast, full blood count remains a cost-effective, rapid, and widely accessible laboratory test. Automated counters facilitate the enumeration of various circulating leukocytes, including neutrophils, lymphocytes, and monocytes, although these parameters are often interpreted individually [9].

NLR has been studied as a biomarker of diagnosis or prognosis in different bacterial, viral or other etiology studies [10-16]. NLR holds significance in cancer management, aiding in patient stratification based on various factors such as tumor size, stage, metastatic potential, and lymphatic invasion [17]. PLR was found useful in predicting the blood transfusion requirement [18]. LMR was statistically significant correlated with respiratory viruses [19,20]. Additionally, there were other pathologies where these biomarkers demonstrated no usefulness.

The objective of this study was to evaluate the efficacy of NLR, PLR, LMR, SII and SIRI in predicting undiagnosed bacterial STI infections. Specifically, the aim was to investigate whether bacterial STIs induce significant inflammation to affect these inflammatory biomarkers.

Methods

Study design and setting

This study with a prospective design was conducted in the north-west region of Romania, comprising patients from several medical special units such as dermatology, obstetrics-gynecology, urology, and general practice, from the counties of Cluj, Bistrița-Năsăud, and Sălaj. Notably, participants resided beyond these counties. Consecutive sampling was employed within dermatology, obstetrics-gynecology, and urology services, while convenience sampling was utilized for other patient sources. Data collection spanned from November 2021 to February 2024. The study group comprised patients with a high suspicion of STI, while the control group consisted of healthy subjects.

Informed consent was obtained from all participants prior to data and biological sample collection, explicitly outlining the utilization of questionnaires and samples of urine, urethral, or vaginal secretions. Ethical approval was secured from the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy in Cluj-Napoca, as well as from the respective ethics committees of the public and private institutions involved in the study (Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca - approval number AVZ10 from 8 November 2021, Bistrita Sanitary Theoretical High-School (Postsecondary School) - approval number 2531 from 15 November 2021, Neuropsychiatric Recovery and Rehabilitation Center for Youth Beclean - approval number 4939 from 22 November 2021, "Prof. Dr. Ioan

Pușcaș" City Hospital Șimleu Silvaniei - approval number 3521 from 21 December 2021, Emergency Hospital Cluj-Napoca - approval number 4980 from 10 February 2022). Personal data handling complied with EU Regulation no. 679/2016 and GDPR law, encompassing general patient data and demographic information.

Participants

The inclusion criteria for study subjects (those with suspected or confirmed STIs) encompassed adults aged 18 and above who presented at a medical facility with symptoms indicative of a bacterial STI, such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, or similar pathogens. Additionally, sexual partners of individuals infected with a sexually transmitted pathogen, who underwent a complete blood count in the current disease context and provided informed consent for participation, were included. Diagnosis was conducted by a physician based on patient history and objective examination. Criteria for bacterial STIs included dysuria, lower abdominal pain, dyspareunia, genital discharge, metrorrhagia, genital itching, and observable lesions (macules, papules, vesicles, pustules) on an erythematous background. Assessment of sexual partners of infected individuals was performed using a questionnaire. Exclusion criteria for the STI group comprised absence of characteristic STI symptoms, lack of an infected partner, refusal to undergo blood tests, unavailability of blood test results, and refusal to participate in the study. Inclusion criteria for the control group were: adults aged 18 and above, without symptoms suggestive of bacterial STIs (examined by a dermatologist), who sought care at a dermatology facility and were diagnosed with benign localized skin conditions without systemic effects (such as cutaneous dermal or junctional nevi, atypical nevi, lipomas, dermal or trichilemmal cysts, localized small hematoma, localized morphea). Control participants were from the same geographical area, age group, and environmental background as the study group and underwent blood tests at the time of examination. Exclusion criteria for the control group included systemic pathologies (cardiovascular, diabetes, other inflammatory skin diseases, respiratory, gastric, renal, infections in any body site, etc.) and lack of a complete blood count.

Variables and measurement

Patient data were gathered via questionnaires administered in the presence of the investigator, with multiple-choice options provided for all questions, except age, where participants were required to provide numerical responses. Gender options included female, male, and other; origin environment options included urban and rural settings. Participants could select from various symptoms such as pain during urination, lower abdominal pain, genital discharge, pain during sexual intercourse, bleeding between menstruations, and genital itching. Comorbidities were assessed with responses including pelvic inflammatory disease, cervicitis/salpingitis/endometritis, human papillomavirus infection, infertility, history of ectopic pregnancies, prostatitis/epididymitis, and arthritis. Blood counts with leukocyte formula were conducted in an accredited laboratory by a certified laboratory physician.

The calculation of NLR involved dividing the Absolute Neutrophil Count by the Absolute Lymphocyte Count [21]. PLR was defined as the ratio of the total number of platelets to the total number of lymphocytes. LMR was defined as the absolute number of lymphocytes divided by absolute number of monocytes. SII was calculated using the formula SII = (P × N)/L, where P, N, and L represent peripheral platelet, neutrophil, and lymphocyte counts, respectively [22,23]. SIRI was calculated using the formula SIRI = (N x M)/L, where N, M, and L represent peripheral neutrophil, monocyte, and lymphocyte counts, respectively [24].

Statistical analysis

The statistical analysis consisted of presenting categorical data in the form of counts and percentages. Quantitative variables that follow a normal distribution are represented using the mean and standard deviation. The presentation of skewed quantitative variables was done using medians and interquartile ranges. The qualitative attributes of the two groups were compared using either the chi-squared test or the Fisher exact test. The t-test for independent samples was used to compare normally distributed quantitative variables between two groups, whereas the one-way ANOVA test was employed for three groups. The Wilcoxon rank-sum test was employed to compare skewed continuous variables between two groups, whereas the Kruskall-Wallis test was utilized for three groups. Nonparametric tests were used to do post-hoc comparisons for the latter scenario. The receiver operator characteristic (ROC) curve was used to evaluate the performance of inflammatory markers in classifying the presence of sexually transmitted infections (STIs). A bootstrapped 95% confidence interval was calculated to assess the accuracy of the classification. The statistical analyses were performed using the R environment for statistical computing and graphics (version 4.3.1) created by the R Foundation for Statistical Computing in Vienna, Austria [25].

Results

The STI group consisted of 8 confirmed and 60 suspected participants, while the control group consisted of 69 participants (Table I). The mean age in the control group was higher than that in the STI group. There were more female participants in the STI group compared to the control group. There were no significant differences between groups concerning their place of residence.

Table I. Participants characteristics.

Characteristics	STI all (n=68)	STI confirmed (n=8)	STI suspected (n=60)	Control (n=69)	P-value
Age (years), mean (SD)	37.62 (10.13)	33.38 (13.77)	38.18 (9.56)	50.33 (13.51)	<0.001
Sex, n (%)	63 (92.65)	7 (87.5)	56 (93.33)	40 (57.97)	< 0.001
Place of residence, n (%)	33 (48.53)	3 (37.5)	30 (50)	39 (56.52)	0.548

STI, sexually transmitted infection; SD, standard deviation; the p-value is the result of a statistical test comparing the three groups.

Table II. Evaluation of the differences between the group of subjects with sexually transmitted diseases (confirmed or suspected) and the control group regarding the inflammatory hematological ratios.

Inflammatory hematological ratios	STI (n=68)	Control(n=69)	P
Systemic inflammation index, median (IQR)	604.06 (432.36 - 880.02)	556.89 (388.63 - 874.19)	0.762
Systemic inflammation response index, median (IQR)	0.95 (0.53 - 1.52)	0.89 (0.67 - 1.34)	0.909
Lymphocyte/monocyte ratio, median (IQR)	4.64 (3.74 - 6.11)	4.64 (3.75 - 5.45)	0.586
Neutrophil/lymphocyte ratio, median (IQR)	2.61 (1.57 - 3.3)	2.29 (1.66 - 3.26)	0.577
Platelet/lymphocyte ratio, median (IQR)	138.1 (99.19 - 169.6)	140.65 (117 - 190.32)	0.33

IQR, interquartile range; STI, sexually transmitted infection.

Table III. Evaluation of the differences between the group of subjects with confirmed sexually transmitted diseases, those with suspected STIs, and the control group regarding the inflammatory hematological ratios.

Inflammatory hematological ratios	STI confirmed (n=8)	STI suspected (n=60)	Control (n=69)	P{(1,2)/(1,3)/(2,3)}
Systemic inflammation index, median (IQR)	807.63 (339.09 - 1369.62)	597.16 (442.49 - 864.92)	556.89 (388.63 - 874.19)	0.89 {0.933/0.954/0.977}
Systemic inflammation response index, median (IQR)	1.5 (0.82 - 2.38)	0.93 (0.52 - 1.5)	0.89 (0.67 - 1.34)	0.444 {0.587/0.584/0.978}
Lymphocyte/monocyte ratio, median (IQR)	4.57 (3.44 - 4.97)	4.68 (3.74 - 6.15)	4.64 (3.75 - 5.45)	0.664 {0.751/0.943/0.764}
Neutrophil/lymphocyte ratio, median (IQR)	2.79 (1.74 - 3.77)	2.52 (1.57 - 3.3)	2.29 (1.66 - 3.26)	0.823 {0.971/0.892/0.897}
Platelet/lymphocyte ratio, median (IQR)	133.86 (88.73 - 178.55)	138.1 (112.54 - 167.07)	140.65 (117 - 190.32)	0.632 {0.993/0.864/0.638}

IQR, interquartile range; STI, sexually transmitted infection; the last column shows the p-value for the comparison between all three groups, while in curly brackets are the post-hoc tests between the first and second groups, the first and third groups and the second and third groups.

We evaluated the differences between the group of subjects with confirmed or suspected STIs and the control group regarding the inflammatory hematological ratios SII, SIRI, LMR, NLR, PLR, but we did not find statistically significant differences (Table II). It can be observed that the median values of SII, NLR and SIRI are higher in the group of subjects with sexually transmitted diseases compared to the control group. Regarding PLR, the median values are lower in the group of subjects with sexually transmitted diseases compared to the control group. As for LMR, the median values are equal between the two groups.

To delve deeper into the analysis, we assessed the differences between the group of subjects with confirmed STI, those with suspected STI, and the control group regarding the inflammatory hematological ratios SII, SIRI, LMR, NLR, PLR. However, we did not find statistically significant differences here either (Table III). It can be observed that the median values of SII, NLR, and SIRI are higher in the group of subjects with confirmed STIs compared to the group with suspected STIs, as well as compared to the control group. Regarding PLR, the median values are lower in the group of subjects with confirmed STIs compared to the group with suspected STIs and the control group. As for LMR, the median values are similar among the three groups.

A receiver operating characteristic (ROC) analysis was conducted to assess the classification/diagnostic ability of inflammatory hematological ratios in diagnosing the presence of STI, whether confirmed or suspected. The area under the ROC curve values were appropriately 0.5, suggesting the absence or very poor diagnostic accuracy of these indicators (Table IV).

Table IV. Classification/diagnostic capacity of inflammatory hematological ratios

Indicator	AUROC (95% CI)
Systemic inflammation index	0.515 (0.417 - 0.609)
Systemic inflammation response index	0.506 (0.41 - 0.603)
Lymphocyte/monocyte ratio	0.473 (0.377 - 0.569)
Neutrophil/lymphocyte ratio	0.528 (0.429 - 0.628)
Platelet/lymphocyte ratio	0.548 (0.452 - 0.642)

AUROC, area under receiver operator characteristic; CI, confidence interval.

Discussion

We investigated the utility of inflammatory biomarkers in detecting new bacterial STIs. It was noted that the median values of SII and NLR were higher in the group of subjects with STIs (both suspected, confirmed or combined) compared to the control group. Conversely, the median values of PLR were lower in the STI group compared to the control group. Nevertheless, the difference did not reach statistical significance.

The observed trend aligns with existing literature indicating that bacterial infections increase SII, SIRI and NLR levels [9]. In the medical literature, NLR was found useful in: critical illness and sepsis, bacteremia, bacterial respiratory tract infection, community acquired pneumonia, urinary tract infection, diabetic foot infection, pulmonary tuberculosis, pertussis [10-16].

On the other hand, LMR is typically negatively correlated with bacterial infection [26]. The medical literature lacks clarity regarding PLR values in bacterial infections and the utility of PLR in diseases caused by bacteria [27,28].

The typical range for NLR falls between 1 and 2. Values exceeding 3.0 or falling below 0.7 in adults are considered pathological. NLR levels within the gray zone, ranging from 2.3 to 3.0, may indicate an early warning of pathological conditions or processes such as atherosclerosis, infection, inflammation, and psychiatric disorders [17]. The median NLR values for both the STI-confirmed and STI-suspected groups fall between 2.3 and 3, while the median for the control group is below 2.3. This suggests that the indicator may increase susceptibility to STIs. Medical literature also discusses the fact that NLR is usually utilized for more severe pathologies, meaning that incipient STIs have a less important impact on systemic inflammation [17].

The NLR and PLR exhibited robust unadjusted associations with mortality and hepatic decompensation in HIV or hepatitis C infected patients, while showing a weaker correlation with other inflammatory biomarkers [4]. NLR independently contributes to prognostic assessment, impacting overall, cancer-free, and cancer-specific survival rates. Moreover, NLR proves valuable in monitoring the efficacy of oncological therapies, including treatments involving biological and immune checkpoint inhibitors [17].

Strengths and limitations

To our knowledge this is the first study to assess the relation of inflammatory biomarkers and bacterial STIs. The present literature focuses on viral STIs. This knowledge gap motivated our research. However, the absence of published studies could stem from the lack of statistical significance in the results, which may have deterred their publication.

As a limitation, to better assess whether these biomarkers are influenced by STIs, it would have been beneficial to include patients with STI complications (such as abscesses, bacteremia, pelvic inflammatory disease, etc.). However, our study focused solely on newly diagnosed STIs and suspected cases. The number of participants is relatively low, and this affects its statistical power. The causality cannot be sustained since this is an observational study. Residual confounding might have influenced our results, a drawback of observational studies.

Conclusions

In conclusion, our study sheds light on the potential relevance of inflammatory biomarkers in the detection and evaluation of bacterial STIs. While we observed trends suggesting associations between certain biomarkers, such as LMR, NLR, PLR, SII, SIRI and STIs, we have to acknowledge that these associations did not reach statistical significance. Thus, it remains uncertain whether these biomarkers could serve as reliable indicators for STIs or early or developing STIs appear to have a minimal effect on systemic inflammation, rendering these biomarkers ineffective.

Moving forward, it is imperative to explore the potential utility of other laboratory tests in assessing STIs. By advancing our understanding of the diagnostic landscape for STIs, we can develop more effective strategies for their identification and management, ultimately improving patient outcomes and public health.

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