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Age and Peripheral Blood Values Relationship Evaluation of Trichomonas Vaginalis, Candida, and Gardnerella Vaginalis Frequency in Cervicovaginal Pap Smear Screening in Aksaray Province

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ABSTRACT

This study aimed to explore the correlation between causative agents of vaginitis detected in Pap smear screenings and various hematological indices, alongside the severity of infections observed in Pap smears. We analyzed 348 Pap smear results, which were categorized into normal and abnormal findings and further subdivided into groups based on the presence of Vulvovaginal Candidiasis (VVC), Bacterial Vaginosis (BV), and Trichomoniasis (TV). The degree of inflammation (mild, moderate, severe) was assessed in relation to hematological indices (Platelet Index Value (PIV), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Lymphocyte to Monocyte Ratio (LMR)), guided by the 2014 Bethesda System for evaluation. Out of 1654 patients screened, 348 met the inclusion criteria (253 aged below 45 years; 95 aged 45 years and above). In the under-45 age group, 83.3% had normal findings, with prevalence rates for VVC, BV, and TV at 73.4%, 60.2%, and 80.0%, respectively. In the over-45 group, these figures were 16.7% (normal), 26.6% (VVC), 39.8% (BV), and 20% (TV). The prevalence of moderate vaginitis in Pap smears was 45.3% for VVC, 96.1% for mild BV, and 53.3% for moderate TV. In cases of Atypical Squamous Cells of Undetermined Significance (ASCUS), BV was predominant, while VVC and TV were absent in Low-Grade Squamous Intraepithelial Lesion (LSIL) and High-Grade Squamous Intraepithelial Lesion (HSIL) cases. BV was present in 7.8% of normal smears. Significant associations were observed between hematological parameters and the severity of inflammation in the normal smear category ($p<0.001$). In squamous cell anomaly cases, especially ASCUS, differences in SII, NLR, PLR, SIRI, and PIV were noted between severe and mild infections, as well as between moderate and severe infection groups. This research underscores the linkage between the severity of infection and cellular abnormalities identified in cervical cytology, causative agents of vaginitis, and hematological indices with inflammatory parameters, potentially informing clinical management strategies.

Keywords: Smear, Vaginitis agents, Hematological indices.

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Introduction

Vaginal infections are common health issues faced by women. Those with vaginitis experience local symptoms such as discharge, itching, and burning, leading to predominantly localized treatment. However, vaginitis often recurs, necessitating a better understanding of its systemic effects.

The Pap smear test is a screening method primarily employed to detect cervical cancer, precursor lesions, and certain viral, bacterial, and fungal infections causing vaginitis [1]. Infections causing inflammation in the cervix include primarily Trichomonas vaginalis, Candida albicans, and Gardnerella vaginalis. Additionally, bacterial infections such as Gardnerella mobiluncus, Haemophilus ducreyi, Neisseria gonorrhoeae, Chlamydia trachomatis, Escherichia coli, streptococci, staphylococci, peptostreptococci, and viral infections like HSV can contribute to cervical inflammation [2]. Vulvovaginal candidiasis (VVC) infections are caused by fungi, such as Candida albicans, leading to local symptoms like itching, burning, and vaginal discharge. Neutrophils surrounding squamous epithelial cells and the classic "spindle-shaped" or "dart" appearance may be observed in Pap smears. Trichomonas vaginalis (TV) causes an infection characterized by symptoms such as vaginal itching, malodorous discharge, and painful urination. In Pap smears, it appears as a flagellated microorganism with a pale, vesicular, and eccentrically located nucleus intertwined with inflammatory cells. Bacterial vaginosis (BV) results from an imbalance in vaginal flora, typically causing malodorous vaginal discharge. In Pap smears, the presence of small coccobacilli described as "clue cells" and the covering of squamous cells with a bacterial layer define this condition.

A plethora of studies have explored the role of various systemic inflammatory indices in exacerbating the severity of diseases [3-5]. In the context of this study, our aim was to investigate the systemic effects of vaginitis utilizing systemic inflammatory indices. This research underscores the potential pivotal role of systemic inflammatory indices in evaluating and monitoring the

severity of the disease in clinical applications. In this retrospectively planned study, inflammation indicators observed in Pap smear tests for VVC, BV, and TV cases are categorized. Hematological indices obtained from peripheral blood values are then used to test the hypothesis that vaginal infections may lead to systemic inflammation in addition to local symptoms. A secondary aim is to evaluate the association between the causative agents of vaginitis and cytological abnormalities observed in Pap smear tests. This understanding has the potential to enhance treatment strategies and improve women's health.

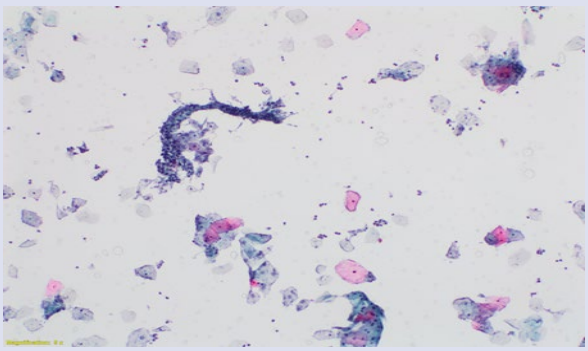
Materials and Methods

The study included 348 patients out of 1654 who applied to the Department of Obstetrics and Gynecology at Aksaray University Training and Research Hospital between January 2021 and December 2021 and had smear samples taken. The study encompasses women aged 18 and older, explicitly excluding those who have ingested antibiotics for any purpose in the preceding month, are currently pregnant, or are afflicted with chronic systemic ailments such as diabetes or hypertension. Eligibility extends to participants evidencing infections in vaginal smears, including Vulvovaginal Candidiasis (VVC), Bacterial Vaginosis (BV), and Trichomoniasis (TV), as well as to those exhibiting no infection. In instances of concurrent infections by the pathogens, the predominant infection will be prioritized. Conversely, exclusion criteria are applied to candidates not fulfilling the prerequisites, those combating other active infections, or presenting with indeterminate or analytically unsuitable smear results.

Smear samples were spread using the ThinPrep method in the pathology laboratory, stained with Papanicolaou (Pap), and evaluated by a pathology specialist according to the 2014 Bethesda system [6]. Smear results for those categorized as negative for intraepithelial lesions and malignancy were evaluated under cellular changes reactive to infection, encompassing organisms causing infection (Trichomonas vaginalis, Candida species, and shift towards bacterial vaginosis in the flora). Patients were grouped into three categories based on pathological evaluation of infections: VVC, BV, and TV.

In the smear sample where clue cells are observed, BV is identified (Figure 1).

In the smear sample of Candida infection, pseudo-hyphae, hyphae, and spores are observed (Figure 2).



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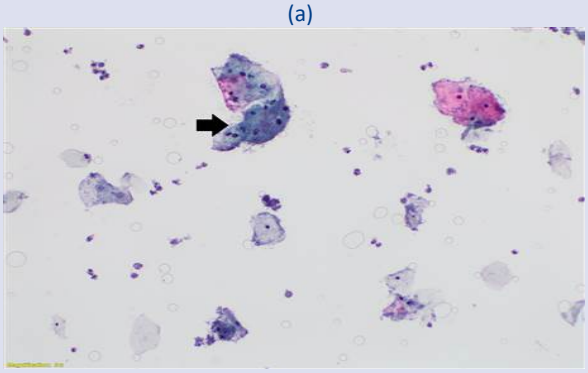

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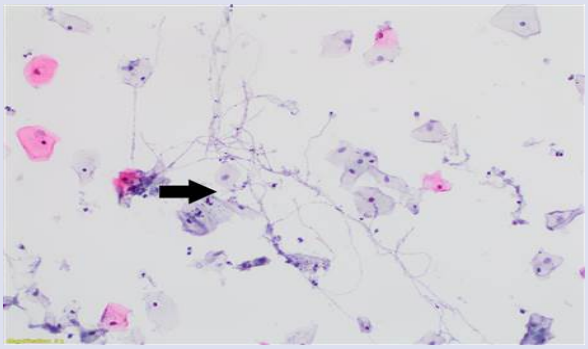
Figure 1 a- b. The bacterial layer covering the squamous epithelial cell (clue cell) is observed with a black arrow on the ThinPrep Pap-stained smear preparation (x10, x20) using the Olympus Bx43 microscope.



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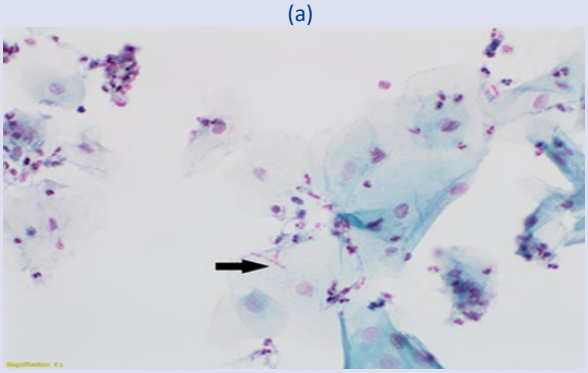


(b)

Figure 2 a- b. The smear sample stained with ThinPrep Pap exhibits a classic 'spindle-shaped' appearance with squamous epithelial cells intertwined with described Candida hyphae and spores. These are indicated by a black arrow on the Olympus Bx43 microscope at magnifications x20 and x40.

The sample shows Trichomonas vaginalis with ovoid or round-shaped nuclei and a sporadically elongated appearance of flagella (Figure 3).

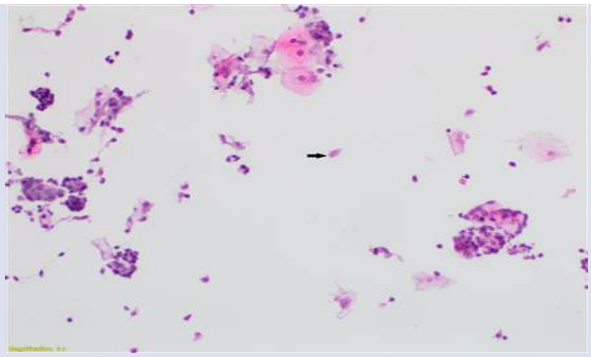
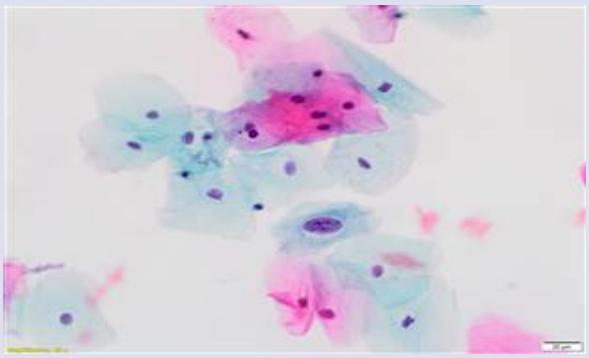


Figure 3: In the ThinPrep Pap-stained smear preparation, an infectious agent with an elongated nucleus consistent with Trichomonas vaginalis is observed (black arrow) among squamous epithelial cells.



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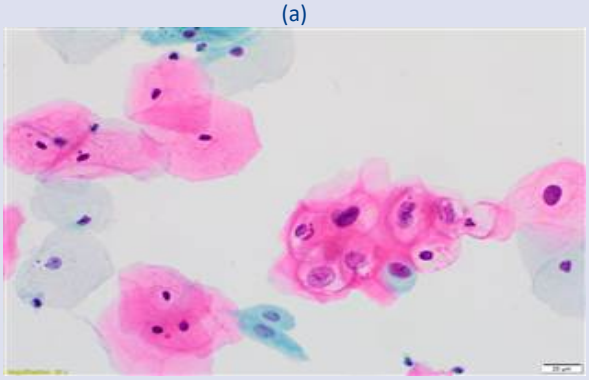

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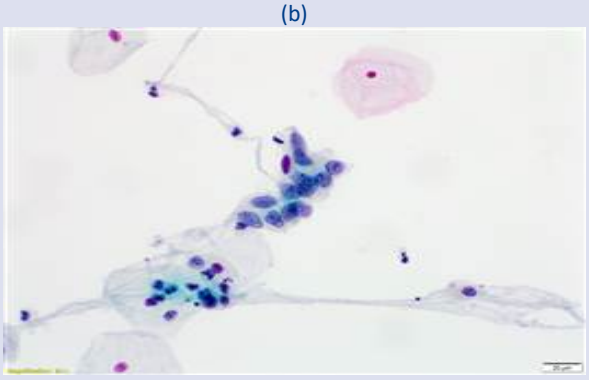
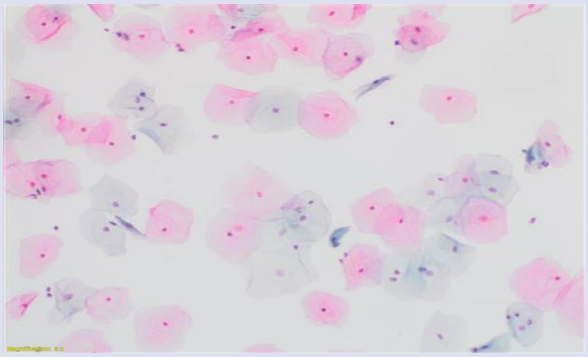


(c)

Figure 4. a. ASCUS example showing abnormalities in squamous epithelial cells, including approximately 3 times the size of the intermediate cell nucleus. b. LGSIL example with nuclear membrane irregularities and perinuclear halo in the ThinPrep Pap-stained smear preparation. c. HGSIL example in the ThinPrep Pap-stained smear preparation, displaying nuclear hyperchromasia.



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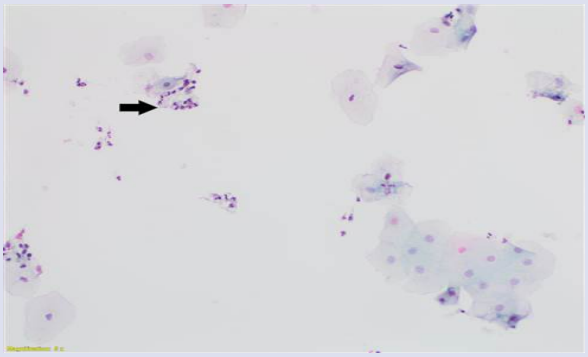

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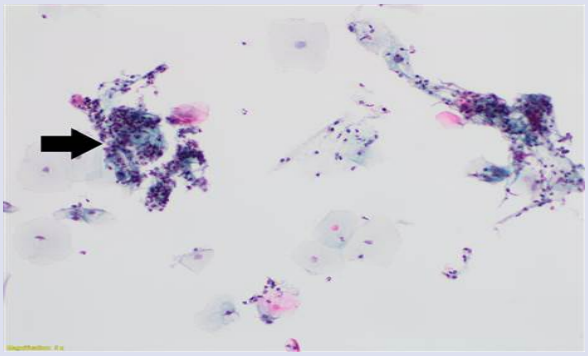

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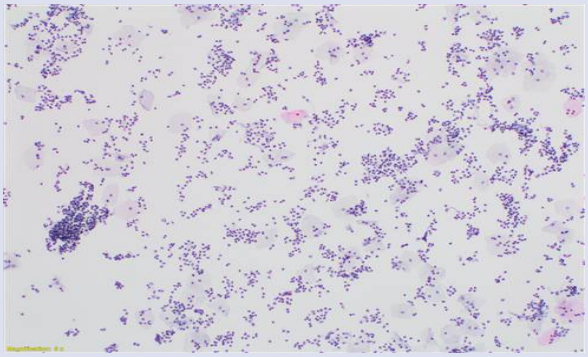

(d)

Figure 5. ThinPrep Pap-stained smear preparation depicting squamous epithelial cells and inflammatory cells overlying or interspersed with epithelial cells: a. Normal sample, b. Mild inflammation, c. Moderate inflammation, d. Severe inflammation.

In the study, the severity of inflammatory cells observed in smear samples was categorized as follows: mild; characterized by a sparse distribution of squamous cells covering a small area in the sample field, moderate; involving a greater coverage of squamous cells compared

to mild, and severe; where squamous epithelium nearly completely covered the field and was extensively present. Within the category of negative for intraepithelial lesions and malignancy, individuals with no observed infectious agents, no cellular abnormalities, and no inflammatory cells in the smear spread were classified as 'Normal' and included as the control group in the study (Figure 5).

The study was conducted to assess the potential variability in systemic impact based on the severity of infection within groups using hematological parameters derived from peripheral blood values. The following parameters were considered: neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI) calculated as neutrophil count × monocyte count / lymphocyte count, immune inflammation value (PIV) calculated as neutrophil count × platelet count × monocyte count / lymphocyte count, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic inflammatory index (SII) calculated as neutrophil count × platelet count / lymphocyte count.

Data Analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY) was used for data analysis. In addition to normality tests such as Kolmogorov-Smirnov and Shapiro-Wilk, the appropriateness of variable distributions to normality was examined through relevant distribution graphs. Chi-square and Fisher's exact test was employed for testing the distribution of categorical variables among groups, while Mann-Whitney U test was applied for investigating differences in continuous variables between groups. Kruskal-Wallis Variance Analysis technique was utilized for comparing more than two independent groups. Results were expressed as median (25th-75th percentiles) for continuous variables, and descriptive statistics in terms of frequency distributions and percentages for categorical variables. A statistical significance threshold of $p<0.05$ was considered.

Results

In our study, a total of 348 patients were included, comprising individuals diagnosed with VVC, BV, and TV based on the results of vaginal smear screenings, as well as a control group consisting of individuals with no detected infectious agents and no inflammatory cells. Patients were divided into two groups: those aged 45 and below, and those aged 45 and above. The study comprised 253 patients aged 45 and below and 95 patients aged 45 and above. Among patients aged 45 and below, 85 (83.3%) were reported in the normal category, 94 (73.4%) with VVC, 62 (60.2%) with BV, and 12 (80.0%) with TV (Table 1). In the group without squamous cell anomalies, 113 patients (88.3%) had VVC, 11 patients (73.3%) had TV, and 102 patients (100%) had no infectious agents (Table 1).

In the evaluation of the intensity of inflammatory cells observed in Thin-prep smear specimens; among cases with mild inflammation, 46 (35.9%) had VVC, 99 (96.1%) had BV, and 1 (6.7%) had TV. Among cases with moderate inflammation, 58 (45.3%) had VVC, 4 (3.9%) had BV, and 8 (53.3%) had TV. Cases with severe inflammation included 24 with VVC and 6 with TV (Table 1). These results demonstrate the impact of vaginal smear results and the detected types of infection on systemic inflammation and hematological indices.

Table 1. Age-Based Evaluation of Pap Smear Results and Infection Severity

n (%)	VVC	BV	TV	Normal
Age ≤ 45				
≤45	94 (73.4%)	62 (60.2%)	12 (80%)	85 (83.3%)
>45	34 (26.6%)	41 (39.8%)	3 (20%)	17 (16.7%)
Smear Results				
Normal	113 (88.3%)	0 (0.0%)	11 (73.3%)	102 (100%)
ASCUS	15 (11.7%)	67 (65.0%)	4 (26.7%)	0 (0%)
LSIL	0 (0%)	28 (27.2%)	0 (0%)	0 (0%)
HSIL	0 (0%)	8 (7.8%)	0 (0%)	0 (0%)
Inflammation Severity				
None	0 (0%)	0 (0%)	0 (0%)	102 (100%)
Mild	46 (35.9%)	99 (96.1%)	1 (6.7%)	0 (0%)
Moderate	58 (45.3%)	4 (3.9%)	8 (53.3%)	0 (0%)
Severe	24 (18.8%)	0 (0%)	6 (40%)	0 (0%)

Values are presented as count (percentage). VVC: Vulvovaginal Candidiasis, BV: Bacterial Vaginosis, TV: Trichomoniasis.

When patients were re-evaluated based on age groups for smear results, the presence of infection, the type, and severity of infection, it can be inferred that VVC is most common in the reproductive age, while in older ages, this tendency shifts towards BV (Table 1). Patients diagnosed with ASCUS showed a higher prevalence of BV in their smears. In cases diagnosed with LSIL and HSIL, VVC and TV were not observed, and BV was only seen in 7.8% of cases. According to the findings, the percentage of infection decreases as the degree of cytological abnormality in the smear increases (Table 1). According to the table, in the presence of TV infection, it can be stated that the infection tends to be severe.

An association was found to be significant between hematological parameters and smear inflammation severity in the category considered normal in smear preparations ($p<0.001$) (Table 2). In the category of squamous cell anomalies, in ASCUS cases, significant differences were observed in SII, NLR, PLR, SIRI, and PIV between severe and mild infection groups, and between moderate and severe

groups (p<0.005), with no difference in other hematological parameters. When cases with ASCUS results were grouped according to infection, SII, NLR, and PLR were the most significant parameters (p<0.05, p<0.001). However, no significant differences were found in mild and moderate infection groups (p>0.05). There was no significant difference in LMR values between the moderate infection group and both the mild and severe infection groups (p>0.05). In the category of squamous cell anomalies, there was no significant difference in hematological parameters between the LGSIL and HGSIL groups. In the LSIL and HSIL groups, infection was only observed in mild or moderate severity, and when compared to those with infection, no significance was found in any inflammatory index (p>0.05). On the other hand, in the group without cytological abnormalities in smear findings, it was observed that the control group significantly differed from both the moderate and severe infection groups in all inflammatory markers (p<0.05) (Table 2).

In the peripheral blood values of patients diagnosed with VVC, hematological parameters obtained include SII, NLR, SIRI, PIV, PLR and LMR. Significant differences were observed in the medians of these parameters among mild, moderate, and severe groups (p<0.05, p<0.001). According to the results, a positive correlation was observed between the severity of VVC and all systemic inflammation indices in the study.

In the VVC group, significant disparities were observed across all parameters; notably, SII, NLR, SIRI, PIV, and PLR were found to be significantly elevated (p<0.001) (Table 3). Conversely, the LMR exhibited a decrease, indicating an intensified inflammatory and immune response within this group.

For the BV group, no statistically significant differences were discerned among the evaluated parameters (p>0.05), suggesting a negligible impact of BV on these measures.

In the TV group, no significant variations were detected across SII, NLR, SIRI, PIV, PLR, and LMR parameters (p>0.05), indicating that TV infection does not markedly alter these inflammatory and immunological parameters (Table 3).

These findings elucidate the heterogeneous impact of these three infections on inflammatory and immune responses. VVC appears to significantly affect the examined parameters, whereas BV and TV do not induce substantial changes. These distinctions contribute to a deeper understanding of disease mechanisms and the development of potential therapeutic approaches (Table 3).

Table 2. Assessment of Cellular Changes and Inflammation Severity in Smear Samples

		No inflammation Mean (Min- Max)	Mild Mean (Min- Max)	Moderate Mean (Min- Max)	Severe Mean (Min- Max)	p
Normal	SII	493.82(182.53-1019.64)	402.67(193.72-880.72)	564.57 (373.75 - 1029.76	913.06(479.41-4055.33)	<0.001
	NLR	1.81(0.94 - 3.54)	1.49(0.61-2.69)	2.12(1.22-3.15)	3.15(1.57-14.48)	<0.001
	SIRI	10.55(4.14 - 18.82)	8.48(3.14-25.02)	11.74(3.77-26.44)	18.76(8.02-95.59)	<0.001
	PIV	3036.21 (803.13 - 5706.56)	2341.16 (976.99-5155.06)	3246.54 (1246.97-6524.93)	5058.18 (2444.98-26765.20)	<0.001
	PLR	9.04(3.28 - 14.55)	7.58(4.39-13.72)	9.08(6.19-17.40)	13.01(7.96-46.67)	<0.001
	LMR	5.06(3.66 - 13.45)	6.22(2.31-13.47)	5.09(2.58-15.90)	3.94(0.91-6.96)	<0.001
ASCUS	SII		491.52(283.18-1236.75)	525.07 (268.68 - 758.26)	1026.68(546.17-1455.16)	<0.001
	NLR		1.76(0.98-4.03)	1.76(0.98 - 4.03)	3.58(1.63-5.27)	<0.001
	SIRI		10.25(4.62-34.34)	10.25(4.62 - 34.34)	19.30(7.34-46.51)	0.004
	PIV		3000.34(1370.35-7314.48)	3000.34(1370.35-7314.48)	6004.1(2457.79-14697.12)	0.002
	PLR		8.72(5.22-17.22)	8.72(5.22 - 17.22)	14.28(9.54-19.51)	<0.001
	LMR		5.72(1.89-10.11)	5.72(1.89 - 10.11)	3.98(1.60-7.76)	0.033
LSIL	SII		694.02(277.22-1188.77)	374.10(374.10 - 374.10)		0.286
	NLR		2.35(1.52 - 4.15)	1.83(1.83-1.83)		0.286
	SIRI		13.86(6.94 - 22.55)	9.90(9.90-9.90)		0.500
	PIV		3645.47 (1272.56 - 8255.08)	2020.16 (2020.16-2020.16)		0.286
	PLR		10.62(4.96 - 17.37)	6.28(6.28-6.28)		0.357
	LMR		4.75(2.94 - 9.61)	6.02(6.02-6.02)		0.500
HSIL	SII		895.28(510.98- 196.88)	747.3 (337.01 - 1212.27)		0.571
	NLR		3.25(2.41 - 11.49)	2.92(1.32-3.37)		0.571
	SIRI		20.8(13.01 - 92.07)	15.19(7-19.52)		0.25
	PIV		5461.18 (3213.02- 17678.34)	4334.32 (1786.15-6303.81)		0.571
	PLR		12.11(7.27 - 23.13)	10.42(6.41-13.09)		0.571
	LMR		3.38 (0.88 - 4.98)	6.10(3.67-7.51)		0.143

SII: Systemic inflammatory index (neutrophil x platelet/ lymphocyte count) , NLR: Neutrophil-to-Lymphocyte Ratio, SIRI: Systemic inflammatory response index (neutrophil × monocyte/ lymphocyte count), PIV: Pan-immune inflammation value (neutrophil × platelet x monocyte/lymphocyte count), PLR: Platelet-to-Lymphocyte ratio, LMR: Lymphocyteto- Monocyte Ratio, ASCUS: Atypical Squamous Cells of Undetermined Significance, LSIL: Low-Grade Squamous Intraepithelial Lesion , and HSIL: High-Grade Squamous Intraepithelial Lesion.

Table 3. Investigation of the Relationship Between Infectious Agents and the Severity of Smear Inflammation

		Mean	Min.	Max.	Mean	Min.	Maks.	Mean	Min.	Maks.	p
VVC	SII	402.82	193.72	880.72	563.61	268.68	1019.52	1016.47	513.27	4055.33	**<0.001**
	NLR	1.50	0.61	2.72	2.13	1.20	3.10	3.44	1.63	14.48	**<0.001**
	SIRI	8.50	3.14	25.02	11.73	3.77	26.44	20.10	7.34	95.59	**<0.001**
	PIV	2378.58	976.99	5155.06	3232.70	1246.97	6524.93	6314.49	2457.79	26765.20	**<0.001**
	PLR	7.58	4.39	13.72	9.08	5.80	17.40	14.15	7.96	46.67	**<0.001**
	LMR	6.19	2.31	13.47	5.11	2.58	15.90	3.66	0.91	7.76	**<0.001**
BV	SII	560.52	277.22	1976.88	560.70	337.01	1212.27				0.899
	NLR	2.01	0.98	11.49	2.38	1.32	3.37				0.711
	SIRI	11.03	4.62	92.07	12.55	7.00	19.52				0.863
	PIV	3129.52	1272.56	17678.34	3177.24	1786.15	6303.81				0.736
	PLR	9.25	4.96	23.13	8.41	6.28	13.09				0.558
	LMR	5.40	0.88	10.11	6.06	3.67	7.51				0.558
TV	SII	579.55	579.55	579.55	556.67	429.68	1029.76	620.18	479.41	788.52	0.619
	NLR	2.28	2.28	2.28	1.81	1.58	3.15	2.24	1.57	3.57	0.507
	SIRI	12.09	12.09	12.09	12.11	7.97	16.14	14.55	8.02	16.45	0.57
	PIV	3071.61	3071.61	3071.61	3397.24	2588.34	4777.06	3690.22	2444.98	5182.96	0.869
	PLR	8.94	8.94	8.94	9.40	7.88	14.34	9.68	8.59	11.54	0.869
	LMR	5.36	5.36	5.36	4.86	3.73	7.36	4.80	3.96	6.96	0.869

VVC: Vulvovaginal Candidiasis. BV: Bacterial Vaginosis. TV: Trichomoniasis.

Discussion

Smear is an effective and cost-efficient method used in the screening of cervical cancer. In our country, according to the cervical cancer screening policy of the Ministry of Health, women between the ages of 30-65 undergo smear and HPV screening every five years. Since smear is a routine screening, additional information that can be obtained through it is valuable as it does not require additional procedures for the patient.

Vaginitis is a leading cause of women seeking gynecological clinics, and most women experience vaginitis at some point in their lives [7]. The most common causes of vaginitis are Vulvovaginal Candidiasis (VVC), Bacterial Vaginosis (BV), and Trichomonas vaginalis (TV) [8]. Vaginitis is known to result in societal productivity loss and economic burdens [9,10]. Additionally, studies have shown adverse pregnancy outcomes in women with BV and TV [11,12].

This study investigated the potential effects of VVC, BV, and TV detected in vaginal smear results on systemic inflammation and hematological indices. The significant increases observed in PIV, SII, SIRI, NLR, and PLR support the hypothesis that VVC may lead to systemic inflammation. However, in the treatment of VVC, choosing systemic over local therapy will be important to eliminate the disease and prevent recurrence. Furthermore, the occurrence of TV in the reproductive period, often leading to moderate or severe infection when present, is noteworthy. Despite this severe inflammation, TV did not significantly alter systemic inflammation indices, suggesting that local treatment may be sufficient in TV treatment.

A meta-analysis evaluating the risk of cervical neoplasia associated with TV has indicated a significant increase in cervical neoplasia [13]. In our study, however, TV was not detected except in those with cytological abnormalities, excluding those with ASCUS. In the evaluation of smear samples, TV organisms may be overlooked as squamous cell abnormalities become more prominent in LGSIL and HGSIL cases. Considering this, TV should always be kept in mind in evaluations. TV was not observed in our study in the LGSIL and HGSIL groups.

One of the most important aspects of this study is its presentation of the comparison of smear infection severity, types of vaginitis, and hematological parameters with cytological abnormalities, a topic rarely found in the literature. Another important finding of our study is that, contrary to Candida, which is most commonly associated with ASCUS in the literature, BV was the most commonly associated infection in cases of ASCUS [14]. Additionally, the presence of only BV in those with LSIL and HSIL smear results suggests the need to investigate the role of this factor in cytological abnormalities. In a study evaluating the relationship between cervical intraepithelial lesions and BV, BV was found to be associated with HPV positivity and HSIL [15]. In our study, similarly, BV was the most commonly detected infection in all cytological abnormalities.

A meta-analysis of ten studies compiled in 2023 suggested an increase in aerobic vaginitis, BV, and TV with HPV positivity, but no association was found with VVC concerning cytological abnormalities [16]. In our study, VVC was not observed in patients with LSIL and HSIL, and its prevalence in those with ASCUS was lower (11.7%) compared to TV (26.7%) and BV (65%).

The results of this study emphasize the clinical significance that VVC may contribute not only to local symptoms but also to systemic inflammation. These findings can assist in evaluating treatment strategies for vaginal Candida infections and monitoring systemic inflammation in patients with such infections. Specifically, further research is needed to explore the systemic effects of vaginal Candida infections and their impact on clinical outcomes. Additionally, as a second inference, the relationship between BV and cytological abnormalities, which is still unclear, requires prospective, large-scale studies to be elucidated.

Limitations of the Study

This study has some limitations. Firstly, as it is retrospective, its ability to establish cause-and-effect relationships is limited. Moreover, prospective studies and larger patient groups are needed to better understand the relationship between the severity of infections and systemic inflammation. Finally, the influence of other potential factors (such as age, obesity, immune status) that were not considered or adjusted for should be taken into account. Simultaneous HPV typing could not be performed with smears, and as a result, the distribution of infection types with HPV could not be evaluated. In conclusion, this study, demonstrating the potential effects of VVC, BV, and TV infections detected in vaginal smear results on systemic inflammation and hematological indices, encourages further research in this area. The systemic effects of these infections and their impact on clinical outcomes should be further examined. Additionally, it is important to develop new approaches to minimize the impact of these infections on treatment strategies.

Conflicts of interest

There are no conflicts of interest in this work.

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