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Original Article

Infection characteristics and risk factors in ovarian cancer patients with concomitant vaginitis

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Abstract: Objective: To investigate the infection characteristics in ovarian cancer (OC) patients with concomitant vaginitis and identify the risk factors for the patients. Methods: A retrospective analysis was conducted on the clinical data from 100 OC patients treated at the Yiwu Central Hospital from July 2019 to July 2024. Patients were assigned to the infection group (n=34) or non-infection group (n=66) based on the presence of vaginitis. Outcome measures included the infection rate and vaginal microbial characteristics of vaginitis, serum HE4 level, and concentrations of interleukin (IL)-4, IL-6, and IL-10 in vaginal secretions. Multivariate logistic regression analysis was performed to determine the influencing factors for vaginal infection in OC patients. Receiver operator characteristic (ROC) curve analysis was conducted to assess the predictive performance of independent risk factors for the occurrence of vaginal infections in OC patients. Results: Among the 100 OC patients, 34 cases (34%) had concomitant vaginitis. Among the 34 patients, the composition ratio of infection types from most to least common was as follows: 10 patients with vulvovaginal candidiasis (29.41%), 8 patients with bacterial vaginosis (23.53%), 7 patients with microbial imbalance (20.59%), 5 patients with mixed infections (14.71%), 3 patients with aerobic vaginitis (8.82%), and 1 patient with trichomonal vaginitis (2.94%). The two groups did not differ notably in HE4 levels (P=0.2366). However, IL-4, IL-6, and IL-10 levels were notably higher in the infection group compared to the non-infection one (P<0.0001). Multivariate logistic regression analysis identified education level, sexual frequency, self-vaginal douching, and history of vaginitis as independent factors influencing vaginal infection in OC patients, and the joint prediction of the vaginal infections with independent factors had an area under curve of 0.858, presenting better performance than a single factor. Conclusion: Vulvovaginal candidiasis is the predominant type of vaginitis in OC patients, followed by BV. Education level, sexual frequency, self-vaginal douching, and a history of vaginitis are independent factors influencing vaginal infection in OC patients.

Keywords: Ovarian cancer, vaginitis, vaginal microbiota, human epididymis protein, risk factors

Introduction

Ovarian cancer (OC) and vaginitis are two common gynecological diseases significantly affect women's health and quality of life [1]. OC, characterized by atypical early symptoms and insidious onset, is often diagnosed at advanced stages, resulting in a high malignancy and poor prognosis in late-stage cases [2]. On the other hand, vaginitis, a prevalent vaginal infectious disease, manifests symptoms such as itching, burning sensation, and abnormal discharge, causing discomfort and distress to affected patients [3].

In recent years, there has been growing interest in the application of microbiology to study tumors and infectious diseases. Vaginal microbiota, encompassing the community of bacteria, fungi, and other microorganisms in the vagina, plays a crucial role in maintaining vaginal health and function [4]. Studies suggest that alterations in gut and vaginal microbial composition are probably associated with various gynecological cancers, including cervical cancer [5], uterine cancer [6], and OC [7]. OC patients may be more susceptible to vaginal infections due to factors like weakened immunity, changes in endocrine function, and hormonal fluctuations, negatively impacting their prognosis and quality of life [8]. Moreover, vaginitis can have a detrimental impact on a patient's well-being, with long-term vaginitis potentially elevating the risk of precancerous

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lesions in gynecological tumors [9]. Therefore, investigating the vaginal microbial characteristics of OC patients with concomitant vaginitis is of significant importance for a deeper understanding of these two diseases.

HE4 is an important tumor marker extensively adopted in early screening and diagnosis of OC [10]. Its expression in inflammation and infection has also garnered attention. However, its expression status in OC patients with concomitant vaginitis has not been thoroughly studied. Therefore, investigating HE4 in OC patients with concomitant vaginitis may provide new insights and evidence for clinical diagnosis and treatment.

In this context, this study aimed to explore the vaginal microbial characteristics in OC patients with concomitant vaginitis and analyze their correlation with HE4 levels, offering guidance and inspiration for future clinical practice and scientific research. Through systematic research, we hope to reveal the patterns and features of vaginal microbial changes in OC patients with concomitant vaginitis, explore the clinical significance of HE4 in this group, and provide more detailed information for personalized diagnosis, treatment, and prognosis assessment.

Materials and methods

Case selection

After obtaining approval from the Medical Ethics Committee of Yiwu Central Hospital, clinical records of 125 OC patients treated at the Yiwu Central Hospital from July 2019 to July 2024 were retrospectively analyzed. Totally, 100 patients were selected based on the following inclusion and exclusion criteria.

Inclusion criteria: Patients who met the diagnostic criteria for OC according to the *Diagnosis and Treatment Guidelines for Malignant Ovarian Tumors* and were confirmed by pathological diagnosis [11]; patients who underwent preoperative secretion collection; patients who had not undergone vaginal rinsing within the past 7 days and had no sexual activity for more than 7 days; patients with complete clinical and statistical data.

Exclusion criteria: Patients with mental disorders; patients with other malignant tumors; patients with severe lesions in other organs; pregnant patients; users of hormones or immunosuppressants.

According to the diagnostic criteria for vaginitis outlined in the Expert Consensus on Vaginitis issued by the Chinese Medical Association Obstetrics and Gynecology Society in 2016 [12], patients were assigned to an infection group (n=66) or a non-infection group (n=34) based on the presence of vaginitis.

Diagnostic criteria for vaginitis

Based on the Expert Consensus on Vaginitis issued by the Chinese Medical Association Obstetrics and Gynecology Society in 2016 [12], the diagnostic criteria for vaginitis are as follows: (1) Normal vaginal microbiota: Any of the following abnormalities indicate microbial imbalance: moderate density of flora (Grade II-III), diversity (Grade II-III), predominance of lactobacilli, pH of 3.8-4.5, negative for leukocyte esterase; (2) Trichomonal vaginitis (TV): Presence of trichomonas; (3) Bacterial vaginosis (BV): Nugent score ≥7 points; (4) Vulvovaginal candidiasis (VVC): Presence of pseudohyphae or blastospores; (5) Mixed infection: Infection with two or more types of vaginitis; (6) Aerobic vaginitis (AV): Donders score ≥3 points. In cases of discordance between Gram staining morphology and results of the five-item combined test for vaginitis, morphology testing takes precedence.

Outcome measures

Primary outcome measures: (1) Infection characteristics and composition ratio in OC patients with vaginitis: secretions from the lower 1/3 of the vaginal wall was collected using a sterile swab. Two swabs were sent for examination: one was used for preparing a smear, which was air-dried, fixed, and Gram-stained for microscopic examination of bacterial flora, *Trichomonas*, pathogenic bacteria, and other indicators; the other one underwent a five-item combined test for vaginitis. (2) Comparison of serum human epididymis protein 4 (HE4) levels between the two groups: fasting venous blood (6 mL) was collected from each patient into anticoagulant tubes, left to stand at room temperature for 2 h, followed by centrifugation (4000 r/min, 4 minutes, centrifugal radius of

10 cm) using the BY-600A centrifuge from Beijing Baiyang Medical Instruments Co., Ltd. The upper serum layer was collected and stored at -20°C for later testing. Serum HE4 levels were measured using chemiluminescence immunoassay. (3) Multivariate logistic regression analysis: the influencing factors for OC comorbid with vaginitis were identified.

Secondary outcome measures: (1) The clinical baseline data were compared between the two groups. (2) Inflammatory factors in vaginal secretions were compared between the two groups. Chemiluminescence immunoassay was utilized to determine interleukin (IL)-4, IL-6, and IL-10 through an i2000SR fully automated chemiluminescence immunoassay analyzer from Abbott Laboratories, with reagent kits from Shanghai Shuangying Biotechnology Co., Ltd. (3) Receiver operator characteristic curve (ROC) curve analysis was used to assess the predictive performance of independent risk factors for the occurrence of vaginal infections in OC patients.

Statistical methods

Statistical analyses were performed using SPSS 20.0 (IBM Corp, Armonk, NY, USA), and graphs were generated using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Counting data were presented as [n (%)] and compared using the chi-square test between groups. Measurement data were normally distributed and expressed as (x±s), and their intergroup comparison was conducted using the t-test. Statistically significant variables from the univariate analysis were included in the multivariate analysis that was conducted with a logistic regression model. ROC curve analysis was conducted to assess the predictive performance of independent risk factors for occurrence of vaginal infections in OC patients. P<0.05 denoted a significant difference.

Results

Comparison of clinical baseline data between the two groups

An analysis comparing the clinical baseline data between the two groups revealed no significant differences in terms of age, body mass index (BMI), underlying diseases, history of smoking, alcohol consumption, and place of residence (all P>0.05, **Table 1**).

Infection characteristics and composition ratio in OC patients

Among the 100 OC patients, 34 cases (34%) were found to have concurrent vaginitis infections. Among the 34 patients with concomitant vaginitis, the composition ratio of infection types, ranked from most to least common, was as follows: 10 patients with VVC (29.41%), 8 patients with BV (23.53%), 7 patients with microbial imbalance (20.59%), 5 patients with mixed infections (14.71%), 3 patients with AV (8.82%), and 1 patient with TV (2.94%), as shown in **Figure 1**.

Comparison of HE4 levels between the two groups

The HE4 level was 259.98±40.01 pmol/L in the infection group and 250.37±37.33 pmol/L in the non-infection group. The two groups did not differ significantly in HE4 levels (P=0.2366, **Figure 2**).

Comparison of inflammatory factor levels in vaginal secretions between two groups

The IL-4 level in the infection group was 46.89±5.50 pg/mL, while in the non-infection group, it was 32.08±4.14 pg/mL. The IL-6 level in the infection group was 67.73±5.30 pg/mL, compared to 46.66±5.16 pg/mL in the non-infection group. Additionally, the IL-10 level in the infection group was 28.24±6.31 pg/mL, whereas in the non-infection group, it was 13.30±3.18 pg/mL. The infection group presented significantly higher vaginal secretion IL-4, IL-6, and IL-10 levels than the non-infection group (all P<0.0001, **Figure 3**).

Univariate analysis of vaginitis infections in OC patients

An analysis comparing age, BMI, education level, underlying diseases, history of smoking, alcohol consumption, sexual frequency, chemotherapy, self-vaginal douching, history of vaginitis, and place of residence between the two groups revealed that education level, sexual frequency, chemotherapy, self-vaginal douching, and history of vaginitis were factors influ-

Table 1. Clinical baseline data of the two groups

	Infection group (n=34)	Non-infection group (n=66)	χ^2	P
Age			0.1667	0.6831
≥50 years	20	36		
<50 years	14	30		
BMI			0.7300	0.3929
≥23 kg/m^2	18	29		
<23 kg/m^2	16	37		
Education level			9.6071	0.0019
Junior college or above	10	41		
Junior high school or below	24	25		
Comorbid diabetes mellitus			0.9293	0.3350
Yes	9	12		
No	25	54		
Comorbid hypertension			1.0811	0.2986
Yes	11	15		
No	23	51		
History of smoking			1.5571	0.2122
Yes	8	9		
No	26	57		
History of drinking			0.5691	0.4506
Yes	6	8		
No	28	58		
Place of residence			0.2997	0.5841
Rural areas	21	37		
Urban areas	13	29		

Note: BMI: Body mass index.

encing vaginal infections in OC patients (all P<0.05, **Table 2**).

Multivariate analysis of vaginitis infections in OC patients

The significant indicators from the above univariate analysis were assigned (**Table 3**). Subsequently, a multivariate logistic regression analysis was conducted with OC comorbid with vaginitis as the dependent variable and the above significant indicators as independent variables. The analysis identified education level, sexual frequency, self-vaginal douching, and history of vaginitis as independent factors influencing vaginal infections in OC patients (**Table 4**).

The combined predictive performance of independent risk factors for the vaginal infections in OC patients

ROC curves were plotted for education level, sexual frequency, self-vaginal douching, history of vaginitis and their combination in predicting the vaginal infections in OC patients (**Figure 4**). According to the results (**Table 5**), the prediction of vaginal infections in OC patients using combined detection of education level, sexual frequency, self-vaginal douching, and history of vaginitis demonstrated an area under curve (AUC) of 0.858, with sensitivity of 87.88%, specificity of 79.41% and accuracy of 85.00%. This combined model demonstrated better performance compared to individual risk factors.

Discussion

Ovarian cancer (OC) lacks specific biomarkers for early detection, making it one of the deadliest cancers in women [13]. With the rising incidence of OC, it poses a significant threat to individual health and quality of life [13]. Patients with OC, given their compromised immunity, experience substantially lowered physical and mental well-being, as well as quality of life, especially when enduring prolonged vaginitis

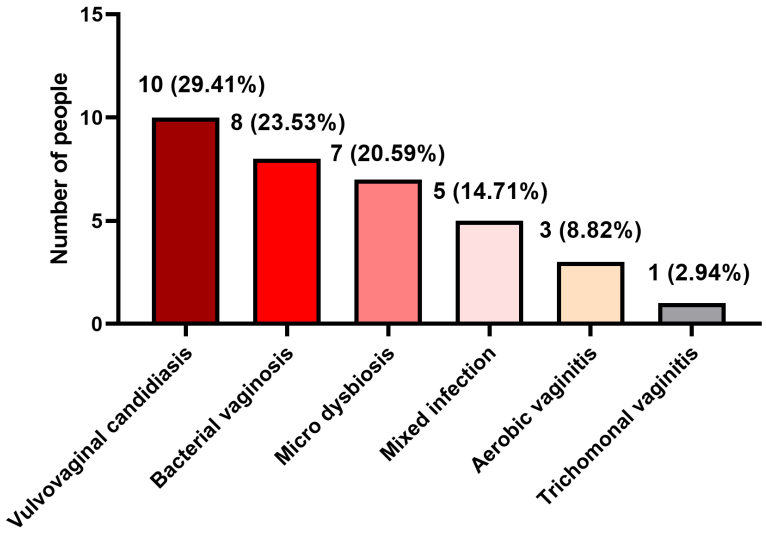

Figure 1. Infection characteristics and microbial composition in ovarian cancer patients with vaginitis.

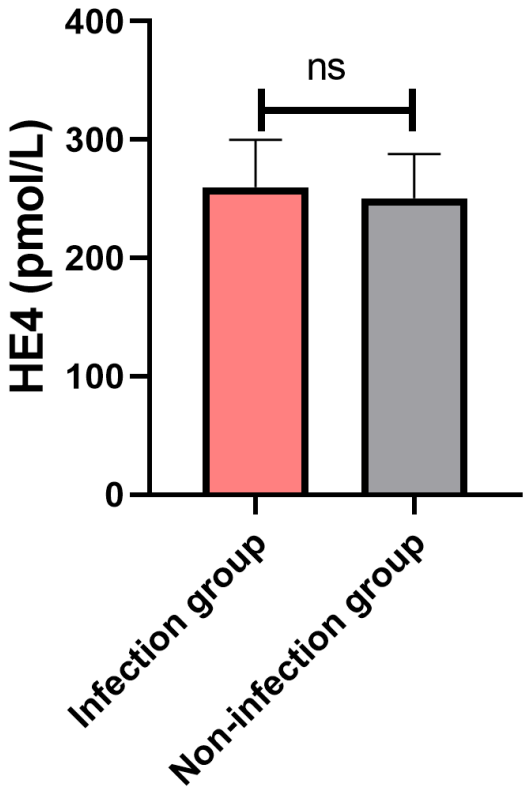

Figure 2. Comparison of HE4 levels between the two groups. Note: ns: Non-significant; HE4: human epididymis protein 4.

infections in addition to the burden of their illness [14]. Therefore, analyzing the characteristics of vaginal infections in OC patients holds significant importance.

Jacobson et al. [15] discovered a complex relationship between the reproductive tract microbiome, gut microbiome, and OC. Graham et al. [16] also found that both the gut and vaginal microbiomes influence women's health. In this study, 34% of the 100 OC patients were found to have concurrent vaginitis infections, with VVC and BV representing a significant proportion. Some studies have indicated that the detection rate of vaginitis in OC patients ranges between 10% to 50%, with BV and VVC being the most common types [17, 18], and our findings also fall within this range. VVC and BV are prevalent reproductive tract diseases that impact millions of women each year. Over three-quarters of women experience at least one VVC infection in their lifetime, with nearly half of them experiencing recurrent infections [19]. BV infections account for one-third of vaginal infections [20]. Physiological changes, compromised immunity, and elevated hormone levels are associated with the increased risk of VVC and BV infections [17]. Reproductive tract infections greatly impact human health, emotions, and economic burdens [18]. Therefore, clinical attention should be given to the reproductive health of OC patients, particularly in relation to VVC, BV, and vaginal infections caused by dysbiosis, emphasizing enhanced monitoring of such conditions.

HE4 is a biomarker associated with OC, with levels typically elevated in OC patients [21]. However, in this study, no significant differences were observed in HE4 levels between the infection and non-infection groups, indicating that vaginal infections may have a minor impact on HE4 levels or that other factors may be at play. Furthermore, in this study, the levels of IL-4, IL-6, and IL-10 in vaginal secretions were significantly higher in the infection group compared to the non-infection group, potentially indicative of an inflammatory response triggered by the infections. IL-4, IL-6, and IL-10 are crucial inflammatory mediators, and their elevation may be associated with immune system activation and the inflammatory process [22-

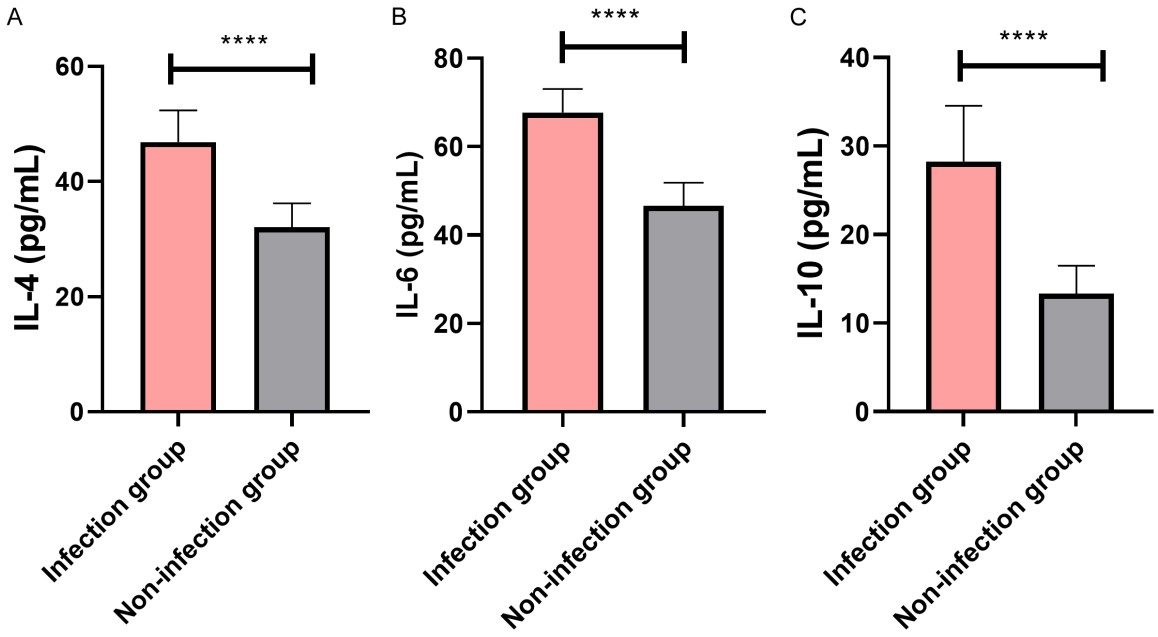

Figure 3. Comparison of inflammatory factor levels in vaginal secretion between the two groups. A: Comparison of IL-4 levels in vaginal secretions between the two groups; B: Comparison of IL-6 levels in vaginal secretions between the two groups; C: Comparison of IL-10 levels in vaginal secretions between the two groups. Note: ****P<0.0001 *vs*. infection group. IL-4: interleukin-4; IL-6: interleukin-6; IL-10: interleukin-10.

24]. This finding underscores the impact of vaginal infections on inflammatory factors in OC patients, with the abnormal levels of these inflammatory factors potentially being linked to the development and progression of OC. Therefore, for OC patients, especially those with concurrent vaginal infections, monitoring the levels of inflammatory factors can aid in evaluating disease status and formulating more effective treatment strategies.

In this study, univariate analysis identified receiving chemotherapy, having an education level of high school or below, a frequency of sexual activity of twice a week or more, self-vaginal douching, and a history of vaginitis as risk factors for vaginal infections in OC patients. Moreover, multivariate logistic regression analysis identified the latter four factors as independent risk factors for vaginal infections in OC patients, indicating that multiple factors may contribute to the occurrence of vaginal infections in OC patients. Possible reasons for this analysis are as follows: Preoperative chemotherapy for OC patients not only eliminates tumor cells but also damages the body's immune defense system and causes tissue organ damage, leading to changes in microbial flora composition and increasing the likelihood of vaginal dysbiosis [25]. With increasing rounds of chemotherapy, the body's immune response and bone marrow hematopoietic capacity are suppressed, resulting in insufficient white blood cells and neutrophils, which also increases the risk of vaginal infections [26]. Patients undergoing chemotherapy should focus on boosting their immune system, monitoring changes in vaginal microbiota, and consider administering immune-boosting agents when appropriate. Patients with higher education levels typically have greater awareness of health education and preventive practices, pay more attention to personal health, and prioritize seeking medical treatment as needed [27]. Therefore, patients with lower education levels should focus on enhancing their awareness of physiological health and preventive knowledge. Frequent sexual activity hinders the restoration of the vaginal ecosystem, providing an ideal environment for pathogen growth. Moreover, frequent sexual activity increases the likelihood of transferring bacteria from the perianal and perineal areas to the vagina, leading to infections [28]. Regular self-vaginal douching can damage the vaginal mucosa, compromise its defense function, introduce exogenous bacte-

Table 2. Univariate analysis of factors for vaginitis infections in ovarian cancer patients

	Infection group (n=34)	Non-infection group (n=66)	χ^2	P
Age			0.1667	0.6831
≥50 years	20	36		
<50 years	14	30		
BMI			0.7300	0.3929
≥23 kg/m^2	18	29		
<23 kg/m^2	16	37		
Education level			9.6071	0.0019
Junior college or above	10	41		
Junior high school or below	24	25		
Comorbid diabetes mellitus			0.9293	0.3350
Yes	9	12		
No	25	54		
Comorbid hypertension			1.0811	0.2986
Yes	11	15		
No	23	51		
History of smoking			1.5571	0.2122
Yes	8	9		
No	26	57		
Alcohol consumption			0.5691	0.4506
Yes	6	8		
No	28	58		
Sexual frequency			10.1710	0.0014
≥2 times/week	21	19		
<2 times/week	13	47		
Chemotherapy			3.8721	0.0491
Yes	22	29		
No	12	37		
Self-vaginal douching			12.7710	0.0004
Yes	23	20		
No	11	46		
History of vaginitis			4.2941	0.0382
Yes	28	41		
No	6	25		
Place of incidence			0.2997	0.5841
Rural areas	21	37		
Urban areas	13	29		

Note: BMI: Body mass index.

Table 3. Assignment

	Assignment	
	0	1
Education level	Junior college or above	Junior high school or below
Sexual frequency	<2 times/week	≥2 times/week
Chemotherapy	No	Yes
Self-vaginal douching	No	Yes
History of vaginitis	No	Yes
Comorbid with vaginitis	No	Yes

Table 4. Multivariate logistic regression analysis of risk factors for vaginitis infection in ovarian cancer patients

Factors	B	S.E,	Wals	df	Sig.	Exp (B)	95% C.I. for EXP(B)	
							Lower limit	Upper limit
Education level	3.261	0.871	14.018	1	<0.0001	26.071	4.730	143.718
Sexual frequency	1.817	0.684	7.050	1	0.008	6.154	1.609	23.530
Chemotherapy	1.298	0.836	2.410	1	0.121	3.663	0.711	18.873
Self-vaginal douching	2.684	0.793	11.459	1	0.001	14.637	3.095	69.222
History of vaginitis	1.585	0.651	5.923	1	0.015	4.877	1.361	17.475

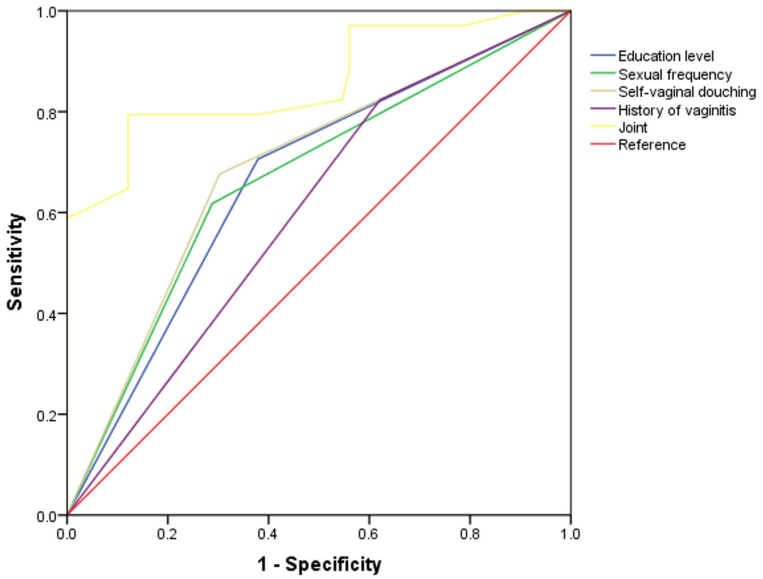

Figure 4. The predictive performance of independent risk factors for vaginal infections in ovarian cancer patients analyzed by ROC curve. Note: ROC: Receiver operator characteristic curve.

ria into the vagina through improper procedures, and alter the vaginal microbiota by suppressing lactobacilli [29]. Patients with a history of vaginitis have a higher risk of developing concurrent infections compared to those without such a history. This could be related to recurrent vaginitis due to improper treatment, changes in local pH levels, and alterations in the vaginal microbiota [29, 30].

Moreover, ROC curve analysis was conducted to evaluate the predictive ability of independent risk factors in combination for vaginal infections in OC patients, and showed an AUC of 0.858, with sensitivity of 87.88%, specificity of 79.41% and accuracy of 85.00%. The finding suggests the potential significance of education level, sexual frequency, self-vaginal douching, and history of vaginitis as predictive factors for vaginal infections in OC patients, highlighting the importance of a comprehensive risk factor assessment in clinical practice.

While this study provides valuable information on the vaginal microbiota characteristics of OC patients with concurrent vaginitis and their correlation with HE4, there are some limitations to consider. The study is limited by its small and restricted sample size, potentially lacking representativeness. The cross-sectional design makes it challenging to establish causal relationships, and potential confounding factors were not fully accounted for, limiting the interpretation of results. Therefore, while the study has uncovered meaningful findings, caution should be exercised in interpreting and generalizing the results. More large-scale, long-term follow-up studies are needed to validate and refine these conclusions.

In summary, OC patients with concurrent vaginitis primarily exhibit VVC, followed by BV. Education level, sexual frequency, self-vaginal douching, and history of vaginitis are independent factors influencing vaginal infection in OC patients. Clinically, targeted interventions should be developed based on infection characteristics and risk factors. Correcting adverse lifestyle habits and enhancing the dissemination of physiological health and disease prevention knowledge are crucial steps in addressing the risk factors involved.

Table 5. ROC curve parameters for independent risk factors in predicting vaginal infections in ovarian cancer patients

	Education level	Sexual frequency	Self-vaginal douching	History of vaginitis	Combination
AUC	0.664	0.665	0.687	0.601	0.858
Sensitivity	62.12%	71.21%	69.70%	37.88%	87.88%
Specificity	70.59%	61.77%	67.65%	82.35%	79.41%
Accuracy	65.00%	68.00%	69.00%	53.00%	85.00%

Notes: ROC: Receiver operator characteristic curve; AUC: area under the curve.

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Disclosure of conflict of interest

None.

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