

RUDN Journal of MEDICINE. ISSN 2313-0245 (Print). ISSN 2313-0261 (Online)

DOI 10.22363/2313-0245-2025-29-3-353-364 EDN PTDPEU

ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ ORIGINAL RESEARCH

Development of a prognostic scale for assessing the risk of cervicitis based on extracellular microscopy data in Pap tests

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Abstract. Relevance. Cervicitis remains a major health problem worldwide with a global prevalence ranging from 20% to 40% among women attending reproductive health clinics. In Russia, this disease affects approximately 15% to 30% of women of reproductive age. It's a significant problem requiring a revision of existing medical screening protocols for this population. The high prevalence of cervicitis indicates the need for a more systematic approach to diagnosis and treatment to reduce incidence and prevent possible complications. *Materials and Methods*. We analyzed data from 2991 studies from the archive of the Laboratory Diagnostics Center of the Medical Complex of the Far Eastern Federal University in Vladivostok for the period 2014–2023. Data analysis included statistical processing, searching for correlation dependencies between numerical and categorical indicators, and building a logistic regression model. The data were checked and validated on a test sample to ensure the representativeness of the results and their application in clinical practice. *Results and Discussion*. During the study, a mathematical predictive model of logistic regression was developed in the form of a scale for preliminary assessment of the presence of inflammatory processes in the cervix based on parameters including the presence of mucus and key cells, as well as the calculated indicator of the total microbiota. The resulting model demonstrated moderate accuracy in recognizing cervicitis (AUC = 72%), allowing it to be effectively used in practice for the early diagnosis of cervicitis. Conclusion. Mathematical analysis of extracellular elements data can be used as a diagnostic tool to assess the presence of changes associated with an increased risk of cervical inflammation. The use of this scale in clinical practice can significantly improve the quality of diagnosis and treatment of cervicitis, helping to reduce morbidity and improve women's reproductive health.

Keywords: Pap test, cervicitis, extracellular elements, mathematical model, prognostic scale

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Funding. The work was supported by the Far Eastern Federal University project No. 23-044-2.06-0008 "Scientific, educational and testing ground: artificial intelligence and digital medical services (FEFU AI testing ground: MedTech)" within the framework of the "Digital Development Center" of the strategic academic leadership program "Priority 2030".

Author contributions. B.O. Shcheglov, S.N. Shcheglova, I.V. Reva — statistical analysis, G.V. Reva, T.G. Lobova, I.V. Mikhailova, I.P. Koval, D.P. Puga — concept and design of the study, M.B. Khamoshina, V.V. Usov, K.V. Stegniy, Y.I. Gainullina — editing the manuscript. All authors made significant contributions to the conception, conduct of the study and preparation of the article, and read and approved the final version before publication.

Conflict of interest statement. The authors declare no conflict of interest.

Ethics approval. The study was approved by the local bioethics commission of the Far Eastern Federal University (Protocol N_0 . 6, 19.04.2023).

Acknowledgements — not applicable.

Consent for publication — not applicable.

Received 24.09.2024 Accepted 24.10.2024.

For citation: Shcheglov BO, Lobova TG, Mikhailova IV, Reva IV, Puga DP, Koval IP, Shcheglova SN, Khamoshina MB, Usov VV, Stegniy KV, Gainullina YI, Reva GV. Development of a prognostic scale for assessing the risk of cervicitis based on extracellular microscopy data in Pap tests. *RUDN Journal of Medicine*. 2025;29(3):353—364. doi: 10.22363/2313-0245-2025-29-3-353-364. EDN PTDPEU

Introduction

Cervicitis, or inflammation of the cervix, is a condition particularly common among sexually active women [1–3]. Studies estimate that the prevalence of cervicitis in women worldwide ranges from 20% to 40%, with higher rates in developing countries due to limited screening and treatment options [1, 3]. In Russia, cervicitis is also a major public health problem: recent epidemiological data indicate that it affects approximately 15% to 30% of women of reproductive age [1–4]. The variability in prevalence both globally and within Russia highlights the need for improved screening protocols and available treatment options.

A variety of factors may contribute to the development of cervicitis in women [2–4]. These factors include estrogen deficiency, cervical trauma that occurs during childbirth, abortion, or diagnostic curettage. Also, the use of intrauterine contraceptives (IUD) disrupts the integrity of the cervix and its protective mechanisms, facilitating the penetration of infection into the genital tract and causing inflammation, including exo- and

endocervicitis. Additional provoking factors may include benign tumors of the cervix, decreased immunity, prolapse of the cervix and vaginal walls, as well as practices such as sexual intercourse during menstruation, acid douching, and improper use of spermicides. Cervical pathology may also be caused by vaginal dysbiosis, since a deviation in the pH of the environment from the norm changes the composition of the vaginal microflora, creating conditions for infection [2, 4]. Women who have previously had cervicitis, suffer from concomitant inflammatory diseases of the genitourinary system, have had sexually transmitted infections (STIs), have had early sexual intercourse, have more than one partner, or have promiscuous sex without contraception are at increased risk of developing this pathology.

Cervicitis diagnostics include a few methods, each of which has its own advantages and disadvantages [3, 4]. Inflammation of the cervix is most often caused by infectious agents such as Chlamydia trachomatis and Neisseria gonorrhoeae, or non-infectious physicochemical factors listed above. Diagnostic tests usually

include a gynecological examination using speculums, colposcopy, ultrasound examination of the pelvic organs, nucleic acid amplification tests with polymerase chain reaction (PCR), culturing methods, microscopic examination, and serological tests. A pelvic examination with a speculum provides a basic visual assessment of the cervix, allowing for the detection of obvious signs of inflammation, discharge, or lesions. This method is a fundamental part of the pelvic examination and is usually the first step in the evaluation of a patient with symptoms of cervicitis [5–6]. However, its accuracy is limited because it relies solely on visual inspection, meaning that it cannot detect specific pathogens or cellular changes that may indicate infection.

Colposcopy offers a more detailed examination of the cervix using a specialized microscope — a colposcope. This method improves visual examination by magnifying the tissues of the cervix, allowing for the detection of abnormalities that are not visible during a standard gynecological examination [7, 8]. Colposcopy can detect precancerous changes, lesions caused by the human papillomavirus (HPV), and other structural changes, thereby increasing the accuracy of diagnosing conditions that may accompany cervicitis. However, since this method is invasive, it is contraindicated in acute inflammatory conditions (including acute vaginitis and cervicitis) [7, 8]. This method can also cause complications in the form of heavy bloody discharge, exacerbation of local inflammatory processes, discomfort in the genital area and lower abdomen, and an increase in temperature when taking biopsy material from altered areas. Pelvic ultrasound uses ultrasound waves to create images of the internal structures of the pelvis based on the physical principles of echolocation. This noninvasive imaging technique can identify associated macromorphologic complications of cervicitis such as abscesses, pelvic inflammatory disease, or other pelvic pathologies [9–11]. Ultrasound facilitates a comprehensive assessment, revealing abnormalities that cannot be detected by physical examination or laboratory testing alone. PCR is the gold standard for diagnosing infectious causes of cervicitis due to its high sensitivity and specificity. This test can detect the genetic material of pathogens with a sensitivity exceeding 90% and a specificity often exceeding 95%, making them highly accurate for identifying Chlamydia trachomatis and Neisseria gonorrhoeae and viruses such as human papillomavirus (HPV) strains and herpes virus. The ability to detect low levels of bacterial and viral DNA in clinical specimens such as endocervical swabs or urine provides a significant advantage over traditional methods [12–14, 17, 20, 21]. However, the major drawback of PCR is its high cost and the need for specialized equipment, which limits its availability in resource-limited settings.

Culture methods, although historically central to the diagnosis of bacterial infections, have fallen into disuse due to their lower sensitivity compared with PCR. Culture sensitivities for N. gonorrhoeae and C. trachomatis range from 50% to 85%, depending on the pathogen and specimen quality [3, 4, 14, 15]. Cultures are useful for antibiotic susceptibility testing, which helps to select appropriate treatment. However, they are time-consuming, typically requiring several days to obtain results, and require strict specimen handling and transportation conditions. Serologic tests, although less commonly used in the routine diagnosis of cervicitis, may be useful in certain circumstances, such as in the diagnosis of herpes simplex virus (HSV) infections, which may present with cervicitis [1, 3, 4, 14]. These tests measure the presence of antibodies and may indicate past or current infections. The main disadvantage of serologic testing is the potential for cross-reactivity and the inability to differentiate acute from chronic infections.

Microscopic cytomorphological screening examination of Pap tests, including Gram, Romanovsky-Giemsa and Papanicolaou staining, provides rapid information on the presence of infection and the state of the cells [3, 4, 17–19]. However, these methods, despite their effectiveness in obtaining rapid results, have limitations in sensitivity and specificity compared with molecular methods, making them an additional tool in modern diagnostics.

Gram staining is used to detect typical bacteria such as Neisseria gonorrhoeae with a sensitivity of 50% to 70%, by detecting characteristic Gram-negative diplococci [16, 18, 19]. However, this method is less

effective in detecting Chlamydia trachomatis, which stains poorly with Gram.

Wet microscopy of unfixed tissue is useful for identifying Trichomonas vaginalis and assessing for the presence of clue cells indicative of bacterial vaginosis. This method allows direct observation of the characteristic flagella of Trichomonas vaginalis, which makes it informative for the diagnosis of trichomoniasis [16, 18, 19]. The presence of clue cells, which are epithelial cells coated with bacteria, indicates bacterial vaginosis. However, wet microscopy is less informative for other causes of cervicitis.

Papanicolaou staining (Pap test) is used to assess not only the morphology of epithelial cells, but also to detect infections [17–19]. The method allows identification of Chlamydia trachomatis by the presence of cytoplasmic inclusions in epithelial cells. For more accurate detection, additional use of immunocytochemical methods is often required. In addition, the Pap test helps to detect viral infections, such as human papillomavirus (HPV) infection, by detecting koilocytes, epithelial cells with characteristic changes in the nucleus and cytoplasm, as well as precancerous and cancerous changes in the cervical epithelium. Smear analysis for purity (or bacterioscopic analysis) with Romanovsky-Giemsa staining expands diagnostic capabilities, allowing observation of a wide range of microorganisms such as Candida, Gonococci, Gardnerella, and assesses the general condition of the vaginal, urethral and cervical flora [16–19]. This method allows identification of Trichomonas vaginalis, Gardnerella vaginalis and other bacteria associated with bacterial vaginosis, as well as detection of Candida spp. by the presence of pseudomycelium and fungal spores. Romanovsky-Giemsa staining is also useful for assessing vaginal microflora and diagnosing inflammatory processes. This method also allows detection of signs of cytolysis, which indicates cell breakdown and may be a sign of infection or other pathological processes. Although this analysis provides valuable information about secondary infections and the state of the vaginal environment, it cannot provide a complete diagnosis of cervicitis and is often used in combination with other diagnostic methods.

There is evidence that the presence and gradation of extracellular elements of bacterial and fungal flora, mucus, is most often associated with urogenital inflammatory changes [17, 20–22].

The extracellular elements in question are assessed by laboratory diagnostic specialists during bacterioscopic analysis by indicating the range of values in the field of view (for example, from 5 to 15 units in the field of view) or by categorical gradations (absent, few, moderate, many, abundant, etc.) of various localizations: in the vagina (label V in bacterioscopic analysis), urethra (label U) and cervix (label C) in the research protocol. However, a literature review revealed that the topic of quantitative assessment of extracellular structures in the field of view during microscopic examination of gynaecological material has been poorly studied and requires further research. This would allow establishing objective boundary factors and developing scales that would allow medical professionals to associate quantitative parameters of extracellular elements with the presence of cervicitis [17, 20, 26–28]. This information could be used to create prognoses for the risk of developing inflammation in the cervix.

The aim of this study is to investigate the relationship between the quantitative assessment of extracellular structures in the field of view during microscopic examination of gynaecological material and the presence of cervicitis in patients.

Materials and methods

The study retrospectively analysed the archival data of the Laboratory and Diagnostic Centre of the Medical Complex of FEFU in Vladivostok. The study was conducted in compliance with the standards of the Helsinki Declaration (2000, 2013) and with the permission of the local Ethics Committee of FEFU. The data set included the results of 2991 Pap tests performed between 2014 and the first half of 2023 using the ALIS laboratory system, as well as the corresponding 1080 medical records of female patients aged 36.01 [22.79; 49.75] years [29]. Information on the primary diagnosis was obtained from the medical information system (MIS) 1C Hospital by matching

the full name and date of birth of the patients [6]. The main clinical diagnosis associated with changes in the cervix, according to ICD-10 categories (N72-N74), was revealed in 31.7% of patients aged 30.37 [21.12, 39.61] years, who underwent 1633 tests. In 1358 tests in patients aged 42.0 [28.92, 56.68] years, the main disease corresponded to the diagnoses of ICD-10 group Z. Mathematical and statistical analysis of the data included descriptive statistics, statistical tests (Mann-Whitney and assessment of correlation dependencies for quantitative data and Chi-square for categorical data). As a result, a predictive logistic regression model was developed to assess the relationship between the parameters of quantitative microscopy of extracellular elements observed in the field of vision with the presence of the main disease of the cervix. The modelling was carried out by dividing the data into training and test samples in a ratio of 80% to 20%, respectively, and evaluating the model hyperparameters using the K-Folding algorithm with the calculation of averaged model quality metrics over 30 cycles and the selection of maximum values.

Calculations and data visualization were carried out using the high-level Python programming language and the Loginom analytical system.

Results and discussion

During the study, the integral indicator was determined, equal to the total number of elements in the vagina, urethra and cervix (1):

$$\sum V = \sum V_v + \sum V_u + \sum V_c \tag{1}$$

where Σ^{v_o} is the sum of elements in the urethra (designated in bacterioscopic analysis as U), Σ^{v_c} is the sum of elements in the cervix (label C), Σ^{v_v} is the sum of elements in the vagina (label V).

Statistical analysis of the data set revealed several significant predictors associated with the presence of cervical inflammation. Continuous predictors were age at the time of examination and calculated total microbiota index in the visual field, identified using the Mann-Whitney test (p-value < 0.05) according to the data in Table 1.

Statistical indicators when assessing continuous data using the Mann-Whitney test

Table 1

Parameter	Number of tests in patients with cervicitis (n = 1633)	Number of tests in patients without cervicitis (n = 1358)	p-value
Age at the time of testing, years	30.37 [21.12, 39.61]	42.0 [28.92, 56.68]	<0.0001
Integral indicator V, number	4.0 [3.83, 4.17]	5.0 [4.82, 5.18]	<0.05

The categorical predictors, whose association with the presence of pathology was assessed using the Chisquare criterion, were the presence of key cells and the presence of mucus in the cervix according to the data in Table 2. In this case, the categorical values "absent", "little", "moderate", "many", "all" were pre-coded into the corresponding numerical values 0, 1, 2, 3 and 4 to enable statistical evaluation.

Additionally, an analysis of correlation interactions between the model predictors was performed, presented in Table 3.

Statistical indicators when assessing categorical data

Table 2

Parameter	Chi² statistics	p-value by Chi² test	CI by Chi² test
Presence of key cells in the field of view, category	24.38	<0.0001	[18.8; 30.0]
Presence of mucus in the field of view, category	37.14	<0.0001	[31.2; 43.1]

Table 3

Correlation matrix between predictors

Parameters	Age at the time of the test, years	Presence of key cells in the cervix, number	Presence of mucus in the cervix, number	Integral indicator, number
Age at the time of the test, years	1.00	-0.05	0.09	-0.01
Presence of key cells in the cervix, number	-0.05	1.00	-0.06	0.23
Presence of mucus in the cervix, number	0.09	-0.06	1.00	0.43
Integral indicator, number	-0.01	0.23	0.43	1.00

Most predictors do not correlate with each other. There is a moderate direct relationship between the integral indicator and the presence of key cells and mucus in the cervix, based on equation (1). The obtained result of the analysis indicates a weak influence

of multicollinearity in constructing a logistic regression model. For each predictor, averaged logistic regression model coefficients were calculated over 30 cycles and are shown in Table 4.

Coefficients of the developed model

Table 4

Attribute	Coefficient	
Constant, β_0	-3.534	
Age of the patient at the time of the study, years	0.087	
Presence of key cells in the cervix, number	-0.785	
Presence of mucus in the cervix, number	0.158	
Integral indicator, number	0.018	

The developed logistic regression model achieved an average area under the curve (AUC) of 72%, indicating moderate prediction accuracy (Figure). The specificity and sensitivity values corresponded to the calculated optimal cutoff threshold within 67–75%. Based on the obtained coefficients, the developed scale takes the form of a logistic regression equation (2):

$$S = \beta_0 + Age \times \beta_1 + PKC \times \beta_2 + PM \times \beta_3 + PM \times \beta_4$$
 (2)

Where S is the calculated value of the logistic regression equation, Age is the patient's age at the time of the study, PKC is the number of key cells in the cervix, PM is the amount of mucus in the cervix, and TM is the total microbiota as an integral indicator.

Based on the calculated value of the logistic regression equation, the risk of having cervical cancer is assessed using the logit activation function (3):

$$p = \frac{1}{1 + e^{-S}} \tag{3}$$

Where p is the probability of the patient having cervical cancer, e is the Euler constant.

The probability p obtained during the calculation can be dichotomized as follows (4):

Modern methods of cervicitis diagnostics, including visual examination, instrumental, molecular, microscopic and serological tests have their advantages and limitations

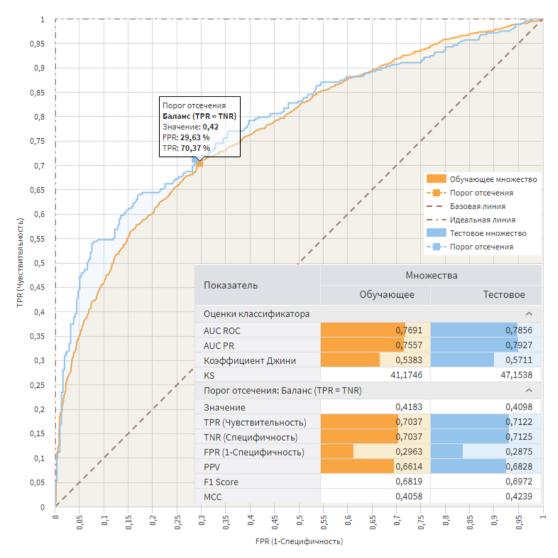


Fig. Quality metrics of the developed scale on training and test samples

in application. Visual examination using a gynaecological speculum provides only a basic assessment of changes in the mucosa condition without the ability to assess cellular changes [5–6]. Examination using a colposcope, despite the ability to assess altered tissues and take them for biopsy, has a significant limitation in the form of a contraindication to its implementation in acute inflammatory processes and the risk of developing post-diagnostic complications [7–8]. Ultrasound examinations, despite their non-invasiveness, allow you to see only macromorphological structures associated with inflammation and complications, without the ability to assess

cellular processes occurring in tissues [9–11]. Nucleic acid amplification tests (PCR) have high sensitivity and specificity, making them the "gold standard" in the diagnosis of infectious causes of cervicitis [12–14, 17, 20, 21]. However, their high cost and the need for specialized equipment limit the availability of such tests in resource-limited healthcare settings. Cultivation methods, although less sensitive and more time-consuming, are useful for antibiotic susceptibility testing [16, 18, 19]. Microscopic methods such as bacterioscopic analysis and the cytomorphological Pap test provide information on the presence of infection and the state of cells, but are

inferior to molecular methods in sensitivity and specificity [17–19]. At the same time, it is known that cervicitis is associated in most cases with infectious and non-infectious agents [1–4]. When performing cytomorphological and bacterioscopic analysis, cytologists focus on studying the morphology of cells and assessing the amount of mucus and searching for bacterial agents similar to coccal, gonococcal and fungal flora, which are associated with a high risk of the presence of an inflammatory process [3, 4, 16–19]. However, other parameters of quantitative bacterioscopic analysis are included only in the protocol part without their interpretation and possible connection with the clinical picture with certain numerical values that would allow them to be associated with various diseases, in particular, with cervicitis. Due to the fact that the scientific literature provides little information on the influence of extracellular elements on the risk of developing gynecological diseases, an analysis was conducted and a mathematical model was developed to describe their connection with the risk of inflammation of the cervix [29].

The developed logistic regression model is a modernization of the existing method of microscopic screening study and uses quantitative data of extracellular elements obtained during microscopic bacterioscopic examination of gynecological material to predict inflammatory processes in the cervix. The main predictors of the model include the patient's age, the presence of clue cells and mucus in the cervix, as well as the integral indicator V, which is the total number of elements in the urethra, cervix and vagina. These predictors were selected based on their significant correlation with the presence of inflammation revealed during statistical analysis of the data. The patient's age affects the hormonal status and the state of local immune homeostasis (LIH). An increase in the amount of mucus in the cervix and the integral indicator V reflects the overall level of extracellular activity and is associated with an increased risk of an infectious process. At the same time, an increase in clue cells in the cervix is associated with a reduced risk of an inflammatory process. The advantage of this model is its ability to link data obtained during routine microscopic bacterioscopic examination with the presence of a clinical diagnosis of cervicitis. Presented in a simplified form as a logistic regression equation and a logit function, it will allow medical professionals to independently or automatically calculate and assess the risk of cervicitis in medical information systems. This will make it possible to conduct a preliminary assessment of the risk of cervicitis during screening studies, especially in resource-limited settings where access to expensive molecular methods may be difficult or in cases where inflammatory processes may not be associated with infectious agents. Assessing the odds of the risk of having an inflammatory process in the cervix with an assessment of such predictors as age, key cells, and the integral V index in routine diagnostic protocols can significantly improve the accuracy of diagnosis and contribute to a more targeted approach to treatment. The results of the study demonstrate the importance of extracellular elements in the diagnosis of cervicitis and offer a new tool for medical professionals. However, since the obtained results were obtained on the basis of a single medical institution, further studies are needed aimed at validation and adaptation of this model in other clinical settings and populations to improve screening protocols and diagnosis of cervicitis during screening microscopic examinations of gynecological smears.

Conclusion

The study presents the results and demonstrates the potential of quantitative microscopic analysis of extracellular elements in the field of view during smear microscopy as a method for additional detection of cervicitis. The identified patterns make it possible to improve the screening protocols for material from the cervical canal and increase the accuracy of detection of inflammatory processes in the cervix. However, further studies are needed to verify and clarify the parameters of prognostic models and integrate them into routine clinical diagnostic practice.

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Разработка прогностической шкалы оценки риска наличия цервицита на основе данных внеклеточной микроскопии в Пап-тестах

Аннотация. *Актуальность*. Цервицит, глобальная распространенность которого колеблется от 20% до 40% среди женщин, посещающих клиники репродуктивного здоровья, остается серьезной проблемой здравоохранения во всем мире. В России этим заболеванием страдают примерно от 15% до 30% женщин репродуктивного возраста. Это является значительной проблемой, требующей пересмотра существующих протоколов медицинского скрининга для данной

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категории населения. Высокая распространенность цервицита указывает на необходимость более системного подхода к диагностике и лечению для снижения заболеваемости и предотвращения возможных осложнений. Цель — разработать шкалу для оценки влияния количественных показателей внеклеточных элементов на риск наличия цервицита, основываясь на данных количественной оценки внеклеточных структур в полях зрения при микроскопическом исследовании гинекологического материала. Материалы и методы. Для разработки шкалы использовались данные 2991 исследований из архива Центра лабораторной диагностики Медицинского комплекса Дальневосточного федерального университета в г. Владивостоке за период 2014–2023 гг. Анализ данных включал статистическую обработку, поиск корреляционных зависимостей между числовыми и категориальными показателями и построение модели логистической регрессии. Данные были проверены и валидированы на тестовой выборке для обеспечения репрезентативности результатов и их применения в клинической практике. Результаты и обсуждение. В ходе исследования была разработана математическая прогностическая модель логистической регрессии в виде шкалы для предварительной оценки наличия воспалительных процессов в шейке матки на основе параметров, включающих наличие слизи и ключевых клеток, а также расчетного показателя суммарной микробиоты. Полученная модель продемонстрировала умеренную точность в распознавании цервицита (AUC = 72 %), позволяя эффективно использовать её в практике для ранней диагностики цервицита. Выводы. Математический анализ данных внеклеточных элементов может быть использован как диагностический инструмент для оценки наличия изменений, ассоциированных с повышенным риском воспалительного процесса в шейке матки. Применение данной шкалы в клинической практике может значительно улучшить качество диагностики и лечения цервицита, способствуя снижению заболеваемости и улучшению репродуктивного здоровья женщин.

Ключевые слова: тест Папаниколау, цервицит, внеклеточные элементы, математическая модель, прогностическая шкала

Информация о финансировании. Работа выполнена при поддержке проекта Дальневосточного федерального университета № 23-044-2.06-0008 «Научно-образовательный и испытательный полигон: искусственный интеллект и цифровые медицинские сервисы (ИИ-полигон ДВФУ: МедТех)» в рамках «Центра цифровых разработок» программы стратегического академического лидерства «Приоритет 2030».

Вклад авторов: Б.О. Щеглов, С.Н. Щеглова, И.В. Рева — статистический анализ, Г.В. Рева, Т.Г. Лобова, И.В. Михайлова, И.П. Коваль, Д.П. Пуга — концепция и дизайн кабинета, М.Б. Хамошина, В.В. Усов, К.В. Стегний, Ю.И. Гайнуллина — редактирование рукописи. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликтов интересов.

Этическое утверждение. Исследование одобрено локальной комиссией по биоэтике Дальневосточного федерального университета (протокол № 6 от 19.04.2023).

Благодарности — неприменимо.

Информационное согласие на публикацию — неприменимо.

Поступила 24.09.2024. Принята 24.10.2024.

Для цитирования: Shcheglov B.O., Lobova T.G., Mikhailova I.V., Reva I.V., Puga D.P., Koval I.P., Shcheglova S.N., Khamoshina M.B., Usov V.V., Stegniy K.V., Gainullina Y.I., Reva G.V. Development of a prognostic scale for assessing the risk of cervicitis based on extracellular microscopy data in Pap tests // Вестник Российского университета дружбы народов. Серия: Медицина. 2025. Т. 29. № 3. С. 353—364. doi: 10.22363/2313-0245-2025-29-3-353-364. EDN PTDPEU

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