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Оценка возможности применения модифицированной кумулятивной шкалы рейтинга заболеваний для прогнозирования инфекционных осложнений после кесарева сечения

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Обоснование. В акушерстве отсутствуют системы или шкалы для оценки соматической отягощенности, прогнозирования и выбора эмпирической антибактериальной терапии у родильниц с послеродовыми (послеоперационными) гнойно-воспалительными осложнениями.

Цель работы — оценить достоверность модифицированной для акушерских пациентов кумулятивной шкалы рейтинга заболеваний под названием CIRS-Obs, в которую авторы включили высокоинформативные предикторы развития инфекционных осложнений после кесарева сечения, вызванных антибиотикорезистентными возбудителями.

Материалы и методы. В период с сентября 2008 по сентябрь 2020 г. проведено ретроспективное исследование 406 историй болезни родильниц с диагнозом «эндометрит после кесарева сечения», госпитализированных в гинекологическое отделение Городской Мариинской больницы. При многофакторном регрессионном анализе выявлены и включены в CIRS-Obs показатели с высокой прогностической значимостью в отношении неблагоприятного течения эндометрита и выделения полирезистентных возбудителей у пациенток с отягощенным соматическим статусом.

Результаты. К наиболее значимым предикторам, ассоциированным с высоким риском выделения резистентных и полирезистентных возбудителей у пациенток с эндометритом, относят индекс по системе CIRS ≥ 4 баллам, экстренное кесарево сечение в сочетании с длительной родовой деятельностью и безводным промежутком, прием антибиотиков в III триместре беременности, а также госпитализации при беременности, инвазивные процедуры или операции.

Выводы. Шкала, разработанная авторами для оценки риска выделения резистентных и полирезистентных возбудителей у родильниц с эндометритом после кесарева сечения в зависимости от соматического статуса пациентки, приема антибиотиков и условий выполнения операции, позволяет повысить достоверность прогноза для принятия рациональных терапевтических решений.

Ключевые слова: эндометрит после кесарева сечения; полирезистентные возбудители; оценка рисков; коморбидность; кумулятивная шкала рейтинга заболеваний; акушерство.

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Estimating possibility of applying the modified cumulative illness rating scale (CIRS-Obs) for predicting postpartum infections and antimicrobial resistance

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BACKGROUND: In obstetrics, there are no systems or scales for assessing somatic burden, predicting and choosing empirical antibiotic therapy in postpartum (postoperative) pyoinflammatory complications.

AIM: The given research aims to assess the reliability and validity of the Cumulative Illness Rating Scale for Obstetrics (CIRS-Obs), which has been firstly modified for obstetric patients. The study is based on the inclusion of additional variables that may be used as highly informative predictors of the development of infectious complications resistant to antibiotics following caesarean section to assess the prognosis.

MATERIALS AND METHODS: A retrospective study of 406 clinical records of obstetric patients suffering endometritis following caesarean section and admitted to the Gynecology department of the Mariinskaya Municipal Hospital has been carried out during the period from September 2008 to September 2020. Multivariate regression analysis allowed to establish a number of indicators characterized by a high predictive value in relation to the unfavorable course of postpartum infections and the isolation of multidrug-resistant pathogens in patients with aggravated somatic status. The most significant factors have been included in the variant of the cumulative comorbidity index (CIRS-Obs), which was firstly modified by the authors for obstetric patients.

RESULTS: The most significant predictors associated with a high risk of isolating resistant and multidrug-resistant pathogens in the examined patients suffering endometritis include CIRS score ≥ 4 points, an emergency caesarean section in combination with a prolonged labor and a period without amniotic fluid, antibiotic therapy in the third trimester of pregnancy, as well as previous hospitalizations during pregnancy/invasive procedures or operations.

CONCLUSIONS: The CIRS-Obs scale modified for obstetric patients by including highly informative predictors and developed to assess the risk of isolating resistant and multi-resistant pathogens in obstetric patients suffering endometritis following cesarean section in terms of a patient's somatic status, antibiotic therapy, the category of urgency and conditions of the operation allows to increase the reliability of the prognosis to make efficient therapeutic decisions.

Keywords: endometritis following caesarean section; drug-resistant and multi-resistant pathogens; risk assessment; comorbidity; cumulative illness rating scale; obstetrics.

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BACKGROUND

The comorbidity of primary extragenital diseases and postpartum infection is recognized by many experts [1–3]; however, a limited number of studies have been published on this issue. Of which, one revealed that chronic somatic pathology can be considered a predictor of a negative prognosis for the development of postpartum infectious complications due to the high risk of carrying antibiotic-resistant microflora [4]. To optimize the use of antimicrobials in obstetrics, as well as for effective treatment and prevention of postpartum infection, etiotropic therapy should be planned based on the predictors of infection in patients with multidrug-resistant strains.

Until now, systems or scales in obstetrics that assess somatic load and predict, and choose empirical treatment in puerperas with postpartum (postoperative) purulent-inflammatory complications (PPIC) are unavailable. Puerperal infection is associated with multiple etiologies, thus the national obstetrician-gynecological associations of most countries have adopted a routine de-escalation strategy for choosing an empiric antimicrobial treatment regimen. Following this strategy, the therapy was started with an antibiotic (a combination of antibiotics) that covered the range of suspected infectious agents as widely as possible, which led to a globally increased level of antibiotic resistance in hospitalized patients [5].

The list of recommended antibiotics by the federal clinical protocol for septic complications in obstetrics [6] and the clinical guidelines for postpartum endometritis of the Russian Society of Obstetricians and Gynecologists [7] are not detailed. An algorithm for choosing an antibiotic with an aggravated somatic background and resistance of infectious agents to broad-spectrum antibacterial drugs has not been proposed either. To date, these are the only specific approved documents in Russia that determine the PPIC treatment approach. As evidenced by our clinical experience and scientific literature, the approach of routine empirical de-escalation therapy is not justified [5, 8].

Individual risk prediction of PPIC is an urgent problem in obstetrics. Its promising solution is the stratification of pregnant women and puerperas depending on the level of risk of PPIC based on the analysis of highly informative predictors.

Recent studies have increasingly considered comorbidity as the cause of the development of antibiotic-resistant bacterial infections [9]. A high degree of comorbidity aggravates PPIC and increases the risk of clinical failure when prescribing empiric antimicrobial chemotherapy [4]. Thus, extragenital diseases are considered as promising predictors of an unfavorable prognosis for the course of endometritis after cesarean section.

Patient conditions are often expressed as indexes to be included in various predictive models for making rational therapeutic decisions. Adapted variants of the comorbidity index, such as the Charlson comorbidity index (CCI), Kaplan–Feinstein (KF), and the BT Bateman maternal comorbidity indexes, are most often used as a tool for monitoring, predicting, and assessing the impact of comorbidity. However, according to our earlier studies, the risk factors included in these scales are unspecific to the obstetric profile. The Cumulative Illness Rating Scale (CIRS), which is more effective and representative in determining the nosological forms of concomitant diseases in obstetric patients, has not been validated for puerperas with PPIC, which necessitates its reliability assessment. CIRS helps to determine the severity and the number of common concomitant somatic diseases in a patient, regardless of his age, and make a prognosis for a variety of nosologies [10]. A tool is required for the rational stratification of puerperas with PPIC into therapeutic groups with the inclusion of predictors of the carriage of multidrug-resistant pathogens for antibiotic therapy personification.

This study aimed to evaluate the reliability of the CIRS for Obstetrics (CIRS-Obs) modified for obstetric patients for the first time, in which highly informative predictors of the development of infectious complications after cesarean section were included, which were resistant to antibiotics.

MATERIALS AND METHODS

This retrospective study included 406 case histories of puerperas with endometritis after the cesarean section that are hospitalized in the gynecological department of the City Mariinsky Hospital from September 2008 to September 2020.

The study included patients who are diagnosed with postpartum endometritis following the criteria of the Russian Society of Obstetricians and Gynecologists as follows [7]:

- hyperthermia of $\geq 38^{\circ}\text{C}$ starting from day 2 postoperative (the puerperal period of up to 30 days);
- purulent discharge from the genital tract with sanious odor;
- pelvic pain and/or uterine tenderness on examination;
- uterine subinvolution;
- microbiological confirmation (determination of an etiologically significant infectious agent in the uterine cavity using cultural or non-cultural methods).

The exclusion criteria were the condition after vaginal delivery and the insufficient possibility of additional examination of the primary medical documentation (copies and extracts), labor and delivery record, and prenatal record.

Clinical assessment of the state of puerperas at admission was performed by case follow-up according to the industry-standard protocol [11] and the determination of subjective and objective symptoms, as well as data from external and internal obstetric studies. The general clinical methods (analyses of the peripheral blood and urine composition, coagulogram, and biochemical analysis of blood plasma) were used. The level of biomarkers in the blood serum (C-reactive protein and procalcitonin) was determined. All patients underwent echographic examination of the pelvic organs over time. A hysteroscopy was performed as necessary.

Some cases used additional research methods (magnetic resonance, X-ray, etc.) in the presence of indications. In all patients, the results of microbiological examination of the metroaspirate were analyzed to identify the presence of antibiotic-resistant microorganisms.

Information about the comorbid status of patients was obtained by retrospective analysis of the primary medical records, discharge summaries, results of clinical and laboratory examinations, and consultations of specialized professionals. Based on the obtained data, reliable patient-dependent risk factors for the carriage of multidrug-resistant microorganisms were identified using multivariate regression analysis, their negative predictive value for the postpartum (postoperative) period was determined, and they were considered as additional variables for CIRS-Obs.

The impact of concomitant diseases that complicate the postpartum (postoperative) period was assessed using CIRS, which reflected a greater number of nosological forms that affect the course and outcome of postpartum infection than the CCI, KF, and BT Bateman indices (11.4 ± 0.6 ; 2.7 ± 0.4 , 8.2 ± 0.3 , and 6.8 ± 0.8 , respectively).

Multivariate regression analysis was used to identify the predictors of an unfavorable course of PPIC and the isolation of multidrug-resistant pathogens in patients with aggravated somatic status. The most significant prognostic are included in CIRS-Obs.

A comparative analysis of the significance between the CIRS and CIRS-Obs scales in predicting the development of PPIC and the isolation of multi-resistant infectious agents from the metroaspirate was performed to select the optimal tool for controlling the comorbidity in patients with endometritis after cesarean section. Based on the final average score, the patients were distributed into groups of negative (high risk multi-resistant pathogens isolation) and favorable (low and standard risks) prognoses.

The statistical data analysis was performed using the Microsoft Excel and Statistica 10.0 software package. Qualitative characteristics were calculated as a percentage and quantitative indicators were presented as median, as well as upper and lower quartiles.

A correlation analysis with the calculation of the Spearman correlation coefficient was used to search for the relationship between the course of endometritis and the presence of its antibiotic-resistant pathogens.

A multivariate regression analysis was performed to identify the predictors of the development of postoperative endometritis in puerperas with comorbidity caused by antibiotic-resistant pathogens. The significance of predictive capabilities of the CIRS-Obs scale was determined using the receiver operating characteristic (ROC) curves.

When assessing the statistical significance of differences, a threshold value of $p = 0.05$ was used.

RESULTS AND DISCUSSION

Table 1 presents the data from the case histories of patients that are significant for assessing the comorbidity.

The mean age of patients was 32.4 ± 0.6 years. The predominance of puerperas of late reproductive age (68.7%) determined the high frequency of detecting the primary and secondary extragenital pathologies (53% and 43.1%, respectively).

In the structure of extragenital diseases in patients, the blood pathology (anemia of various origins and hereditary thrombophilia) ranks first (69.9%), as well as diseases of the endocrine (58.4%), urinary (56.5%), cardiovascular (36.6%), respiratory (30.1%), musculoskeletal (20.8%), and digestive (19%) systems (Fig. 1).

The clinical follow-up analysis revealed that endometritis after cesarean section, as a rule, has a subclinical form (54.2%) with a late manifestation of symptoms, while mild and moderate disease severity is more often noted (67.2% and 21.4%, respectively). Of puerperas, 3.5% had uterine suture failure and secondary obstetric peritonitis, and 2% had sepsis.

Correlation analysis of the clinical course of endometritis and the treatment outcomes of the examined puerperas revealed that the isolation of multi-resistant pathogens of endometritis was statistically significantly associated with the main signs of its unfavorable course and poor prognosis, namely infection generalization and panhysterectomy (Table 2).

Antibiotic resistance of endometritis pathogens is associated with worse treatment outcomes, as evidenced by a statistically significant correlation of these pathogens with an increased duration of antibiotic therapy, duration of hospital stay, the frequency of transfers to an observational hospital, and the need to change the antimicrobial drug.

Each pregnant woman who enters for delivery should be stratified by the risk of carrying multidrug-resistant pathogens to personalize the treatment of endometritis after

Table 1. The main clinical and epidemiological characteristics of parturient females with endometritis after cesarean section in the comorbidity assessment**Таблица 1.** Основные клинико-эпидемиологические характеристики родильниц с эндометритом после кесарева сечения, включенных в оценку коморбидности

Data of patients' medical records	Number of patients	The proportion of patients, %
Age:		
• reproductive (17–34 years old)	127	31.3
• late reproductive (35–49 years old)	279	68.7
Clinical classification of endometritis:		
• classic form	43	10.6
• subclinical form	220	54.2
• abortive form	143	35.2
Endometritis severity:		
• mild	272	67
• moderate	87	21.4
• severe	47	11.6
Complicated forms of endometritis:		
• surgical site infection	77	18.9
• secondary obstetric peritonitis	14	3.5
• sepsis	8	2
Extragenital diseases:		
• primary	215	53
• secondary	175	43.1
Surgeries or invasive manipulations	112	27.6
Isolation from lochia of antibiotic-resistant and multi-resistant microorganisms	114	28.1

**Fig. 1.** Structure and frequency of involved systems in postpartum women with endometritis after caesarean section according to the cumulative disease rating scale**Рис. 1.** Вовлечение различных систем органов в патологический процесс в соответствии с кумулятивной шкалой рейтинга заболеваний

cesarean section, with an appropriate choice of antibiotic. This approach will help the timely identification of the category of puerperas with a high risk of carrying antibiotic-resistant strains and prescribe timely adequate etiotropic treatment with reserve drugs to them.

Correlation analysis showed a moderate statistically significant correlation between the CIRS index value and the isolation frequency of multidrug-resistant strains ($r = 0.562$; $p < 0.001$). At the next stage of the analysis, statistically significant differences in the CIRS scale levels were revealed

Table 2. Data on the relationships between the characteristics of the clinical course of endometritis after cesarean section with the probability of isolating multidrug-resistant pathogens**Таблица 2.** Результаты поиска взаимосвязи между характеристиками клинического течения эндометрита после кесарева сечения и вероятностью выделения его полирезистентных возбудителей

Characteristics of the clinical course of endometritis after cesarean section	Probability of isolation of multidrug-resistant pathogens	
	Spearman correlation coefficient	p-value
Total duration of etiotropic treatment	0.382	0.011
Change in antimicrobial chemotherapy drug	0.422	0.009
Transfer to an observation hospital (insufficient effect from conservative treatment)	0.517	0.003
Generalization of infection	0.625	<0.001
Oothecohysterectomy	0.489	0.016
Long-term hospitalization	0.446	0.06

with a discriminating value of the cumulative index (4 points) and were calculated to stratify puerperas with postoperative endometritis into groups of favorable and poor prognosis (Fig. 2).

The median CIRS index value in all patients was 3.3 points (range 1–8 points). Of them, 20.4% have no comorbidity (0–1 points), and resistant pathogens were not detected, which confirms the great importance of a compromised somatic background for the development of antibiotic-resistant postpartum infection.

The isolation of antibiotic-resistant microflora was recorded with an index of >4 points in all patients, 4 points in 70.7% of patients, 3 points in 35.1%, and 2 points in 4.1%. Patients with a cumulative index of 4 points and higher constituted a high risk group for a poor prognosis

of complications (95 puerperas, 23.4%), and those with an index of <4 points constituted a low-risk group (311 puerperas, 76.6%).

A comparative analysis showed a severe course of endometritis with generalized infection in group 1, which was statistically significantly more common than in group 2 (58.7% and 5.1%, respectively; $p < 0.05$), as well as the isolation of antibiotic-resistant pathogens (87.4% and 12.6%, respectively, $p < 0.05$). Thus, the formed risk groups differ from each other in terms of the main prognostic characteristics of the disease course.

Using multivariate regression analysis, we established several indicators with high prognostic significance with the development of postoperative endometritis caused by antibiotic-resistant pathogens in puerperas with comorbid pathology. These indicators are included in CIRS-Obs.

The most significant associated factors with the development of antibiotic-resistant PPIC were the following:

- CIRS score of ≥ 4 points (odds ratio [OR]: 2.67; 95% confidence interval [CI]: 2.19–3.86);
- emergency cesarean section combined with a long rupture to delivery interval (≥ 12 h) and prolonged preoperative labor (≥ 10 h) (OR: 3.16; 95% CI: 2.28–4.81);
- the use of antibiotic therapy in trimester III or after cesarean section (OR: 2.90; 95% CI: 2.25–5.08);
- hospitalization during pregnancy (including day patient facility), invasive procedures, or surgeries (OR: 3.26; 95% CI: 2.62–4.74).

According to the OR and predictive weight, a score was assigned to each predictor, thus 0 points indicated no risk of antibiotic-resistant infection, 1 point indicated standard risk, and 2 points indicated high risk. Table 3 presents the results of the final multivariate model with predictive parameters included in CIRS-Obs.

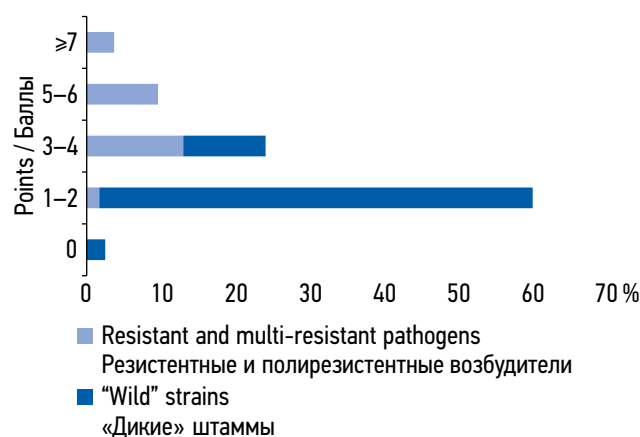
**Fig. 2.** Distribution of the patients by the levels of the cumulative illness rating scale (CIRS) according to the proportion of resistant and multidrug-resistant pathogens isolated from lochia

Рис. 2. Распределение пациенток по уровням кумулятивной шкалы рейтинга заболеваний (CIRS) в соответствии с долей изолированных из лохий резистентных и полирезистентных возбудителей

Table 3. Multivariate regression analysis of predictors for the development of pyoinflammatory complications after cesarean section, of which the causative agents are resistant to antibiotics**Таблица 3.** Многофакторный регрессионный анализ предикторов развития гнойно-воспалительных осложнений после кесарева сечения, возбудители которых устойчивы к антибиотикам

Prognostic parameter	Number of patients (percentage, %)	Multivariate regression analysis			Score
		OR	95% CI	p-value	
CIRS scale index:					
• 0–1 point	83 (20.4)	1.68	1.36–1.98	0.029	0
• 2–3 points	228 (56.2)	2.12	1.76–2.89	0.015	1
• ≥4 points	95 (23.4)	2.67	2.19–3.86	<0.001	2
Cesarean section:					
• elective/emergency (intact amniotic sac, absence of birth contraction)	118 (29.1)	1.85	1.22–2.18	0.002	0
• emergency (labor activity <10 h/untimely amenorrhea)	71 (17.5)	2.75	1.77–3.67	0.011	1
• emergency (prolonged labor activity ≥10 h/rupture to delivery interval ≥12 h)	217 (53.4)	3.16	2.28–4.81	<0.001	2
Antibacterial therapy:					
• absent during pregnancy	166 (40.9)	2.06	1.58–2.79	0.037	0
• in trimesters I and II	153 (37.6)	2.45	2.03–3.36	<0.001	1
• in trimester III (after cesarean section)	87 (21.5)	2.90	2.25–5.08	0.019	2
Hospitalizations and invasive procedures					
• absent during pregnancy	127 (31.2)	1.97	1.26–2.80	0.007	0
• hospitalizations in trimesters I and II	175 (43.1)	2.82	2.16–3.77	0.021	1
• hospitalizations in trimester III	104 (25.7)	3.26	2.62–4.74	0.004	2

Note: OR — odds ratio; CI — confidence interval.

Further, all patients were stratified into groups according to CIRS-Obs, thus 0–1 points indicated no risk of an antibiotic-resistant infection (125; 30.7% of puerperas), 2–3 points with a standard risk (215; 53.0 % of puerperas), and 4 points or more with high risk (66; 16.3% of puerperas).

Group 1 mainly included patients without somatic pathology with an elective cesarian section in the complete absence of inpatient healthcare system contact, a history of antibiotic therapy, and preferential isolation of highly sensitive pathogens. In group 2, a cesarean section was performed for emergency indications; hospitalizations and antibiotics were recorded in the first half of pregnancy due to a compromised somatic background; and pathogens resistant to antibiotics were isolated in significant amounts from lochia. For puerperas of group 3, the use of standard schemes for the prevention and treatment of endometritis was associated with clinical failure (Fig. 3).

The probability of infection with antibiotic-resistant strains is based on our proposed stratification principle. It is this indicator that affects the efficiency of antimicrobial treatment of endometritis (Table 2). The division of patients into prognostic groups according to the value of the CIRS-Obs index exceeds the results of CIRS in terms of the severity of selection (Fig. 2, 3).

Using CIRS-Obs, a special group of puerperas was identified with the lowest risk of developing an antibiotic-resistant postpartum bacterial infection. A retrospective result analysis of an *in vitro* study revealed the lowest resistance of pathogens of postoperative endometritis

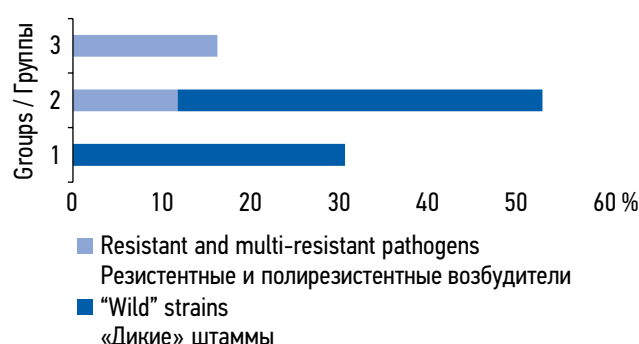
**Fig. 3.** The ratio of antibiotic-resistant phenotypes causative agents of endometritis and CIRS-Obs indices: 0–1 points — 1st group (no risk of developing an infection resistant to antibiotics); 2–3 points — group 2 (standard risk) and ≥4 points — group 3 (high risk)

Рис. 3. Соотношение фенотипов антибиотикорезистентных возбудителей эндометрита и индексов CIRS-Obs: 0–1 балл — 1-я группа (отсутствие риска развития инфекции, резистентной к антибиотикам); 2–3 балла — 2-я группа (стандартный риск) и ≥4 баллам — 3-я группа (высокий риск)

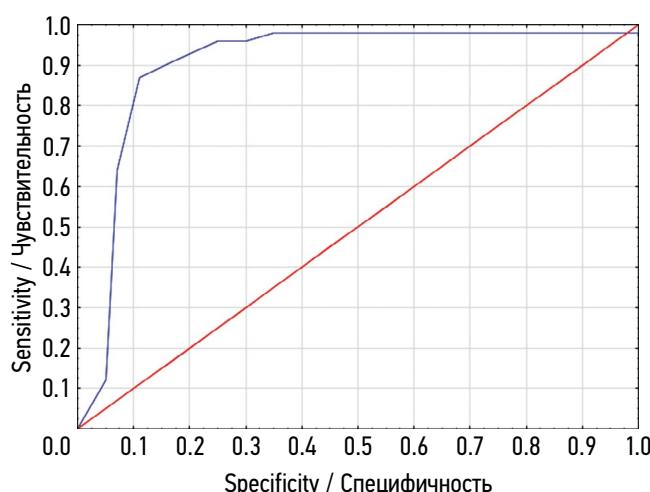


Fig. 4. ROC-curve of modification of the Cumulative Illness Rating Scale (CIRS-Obs)

Рис. 4. ROC-кривая модификации кумулятивной шкалы рейтинга заболеваний (CIRS-Obs)

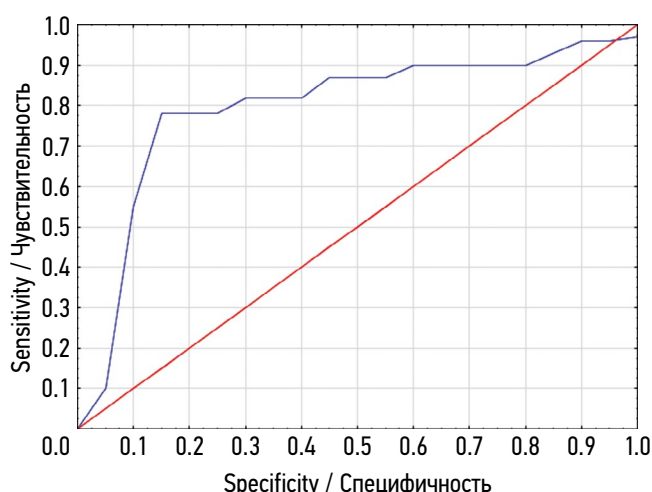


Fig. 5. ROC-curve of the Cumulative Illness Rating Scale (CIRS)

Рис. 5. ROC-кривая кумулятивной шкалы рейтинга заболеваний (CIRS)

to antimicrobial drugs in this group recommended by the federal clinical protocol for septic complications in obstetrics [6] and clinical guidelines for postpartum endometritis of the Russian Society of Obstetricians and Gynecologists [7] for the prevention and treatment of postpartum infection.

ROC curves were generated to confirm further the significance of the CIRS-Obs predictive characteristics. With their use, the dependence of the proportion of false-negative diagnostic results on true positives can be calculated in the prognosis of the event under study (in the case of our study, the isolation of resistant and multi-resistant pathogens).

The area under the ROC curve (an indicator of the probability of a correct conclusion) is 0.903 (95% CI: 0.862–0.949; $p = 0.006$), and the levels of sensitivity and specificity are close to 100%, which indicates a high diagnostic and prognostic significance of CIRS-Obs (Fig. 4). The ROC curve does not cross the diagonal of a completely uninformative test.

For a comparative analysis of the prognostic value bridges between the CIRS-Obs scales and its prototype CIRS we built ROC-curve of CIRS (Fig. 5).

The study results confirm that the new predictive model significantly outperforms the CIRS scale in terms of diagnostic accuracy. The area under the CIRS ROC curve was 0.794 (95% CI: 0.682–0.832; $p < 0.001$).

The CIRS-Obs scale that we proposed in terms of the level of prognostic significance for assessing the risk of infection with antibiotic-resistant pathogens significantly exceeds its prototype, where $\chi^2 = 47.33$ (CIRS-Obs) versus $\chi^2 = 30.19$ (CIRS) ($p < 0.001$). CIRS-Obs can be recommended for puerperas with endometritis after cesarean section and in pregnant women at the preoperative stage to assign

them a risk group and select the appropriate antibiotic to personalize the PPIC antimicrobial prevention and treatment.

CONCLUSIONS

1. Comorbidity statistically significantly worsens the prognosis of the course of endometritis after cesarean section. Higher CIRS index values are associated with a higher risk of carrying antibiotic-resistant microflora ($r = 0.562$; $p < 0.001$).
2. The most significant associated predictors with a high risk of isolation of resistant and multi-resistant pathogens in patients with endometritis were CIRS index of 4 points and higher, the emergency cesarean section in combination with prolonged labor and a long rupture to delivery interval, and the intake of antibiotics in trimester III of pregnancy or after cesarean section, as well as hospitalizations during pregnancy, invasive procedures, or surgeries.
3. The CIRS-Obs scale that we developed to assess the risk of isolation of resistant and multi-resistant pathogens in puerperas with endometritis after cesarean section, depending on the somatic status of the patient, antibiotic intake, and conditions of the surgery, is used to increase the accuracy of the prognosis for making rational therapeutic decisions.

ADDITIONAL INFORMATION

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