I.A. PANOVA, A.V. KUDRYASHOVA, E.A. ROKOTYANSKAYA,
A.I. MALYSHKINA, V.V. PAREYSHVILI, I.K. BOGATOVA

CLINICAL VALUE OF CHANGES OF THE TRANSMIGRATION ACTIVITY OF LEUKOCYTES IN THE DIAGNOSIS OF SEVERE PREECLAMPSIA

V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia

Aim. *To identify additional criteria for the diagnosis of severe preeclampsia (PE) in pregnant women based on an investigation of the expression of the early adhesion molecules, chemokine receptors, and markers of endothelial dysfunction in venous blood neutrophils and monocytes.*

Material and methods. *One hundred and fifty patients with PE (74 with moderate PE, 76 with severe PE) and 70 women with a physiological course of pregnancy were tested for venous blood neutrophils and monocytes expressing adhesion molecules CD62L, CD11b, chemokine receptors CCR2 and CX3CR1, and the number of circulating endothelial cells (CECs).*

Results. *When compared with women having uneventful pregnancy and patients with moderate PE, patients with severe PE had significantly lower levels of CD62L+neutrophils, but higher levels of CX3CR1+monocytes and neutrophils, and a greater number of CECs. The diagnostic thresholds for these parameters are informative in the diagnosis of PE severity.*

Conclusion. *Measuring the relative levels of CD62L+, CX3CR1+ neutrophils and the number of CECs in the blood can be used for stratifying severity of PE with greater accuracy.*

Key words: *pregnancy, preeclampsia, venous blood, diagnostic criteria, adhesion molecules, chemokine receptors, desquamated endotheliocytes.*

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Preeclampsia (PE) is one of the most challenging problems in obstetrics. Severe PE remains the second leading cause of maternal mortality worldwide and the fourth leading cause of maternal death in the Russian Federation [1]. Moderate PE affects 3-8% of pregnant women in the second half of gestation, and 1-2% of them develop severe PE, worsening perinatal outcomes, and complicating the course of labor and the postpartum period [2]. Currently, variations in the clinical manifestations of PE make it difficult to diagnose and choose an appropriate management strategy. In many cases, PE has an atypical clinical presentation, including clinical surgical masks (acute necrotizing pancreatitis, acute liver dystrophy), renal failure without severe hypertension, hemorrhagic syndrome, pneumonia and pleuropneumonia, peripartum cardiomyopathy, fever of unknown origin, and transient ischemic attack without the hypertensive syndrome [3]. These diseases are relatively rare, their manifestations are almost identical, all of which can mimic severe PE, but the therapeutic approaches to managing such patients vary [4].

A particularly important component of the pathogenesis of PE is endothelial dysfunction leading to impaired vascular permeability and systemic inflammatory response. Systemic inflammatory response results in the dysregulated functional activity of leukocytes, the increased expression of adhesion molecules, and stimulation of cell migration into the inflammation site [5, 6]. Earlier, we found that in pregnant women the level of expression of leukocyte cell adhesion molecules participating in transendothelial migration varies in different types of hypertensive disorders [7]. According to our data, patients with essential hypertension had significantly elevated levels of CD99+ in neutrophils, while PE patients had increased levels of neutrophils expressing CD49b molecules [7, 8]. Probably, the character of expression of late-stage adhesion molecules by neutrophils is determined by the combination of various pathogenic mechanisms responsible for various forms of hypertension in pregnancy. However, in any case, the binding of neutrophils to vascular endothelial cell adhesion molecules may trigger a respiratory explosion activity of neutrophils in blood [9], causing damage to surrounding tissues and aggravating endothelial vascular dysfunction.

Endothelial dysfunction leads to destruction of endothelial cells, resulting in a release of various circulating markers of endothelial activation: thromboxane A2, endothelin 1, prostacyclin, vWF, fibronectin, endothelial relaxing factor, endothelial cells [10, 11]. According to the literature, circulating endothelial cells (CECs) are elevated in PE, and the number of cells correlates with disease activity. Therefore, circulating endothelial cells can be used as a

novel marker of vascular damage in patients with PE and the severity of this complication of pregnancy [11, 12].

Despite the worldwide attention to the problem of PE, there are many controversial issues in the diagnosis of this condition, and the differential diagnosis of this pregnancy complication seems to be an extremely important and often affects the outcome.

The study aimed to identify additional criteria for the diagnosis of severe PE in pregnant women based on an investigation of the expression of the early adhesion molecules, chemokine receptors, and markers of endothelial dysfunction in venous blood neutrophils and monocytes.

Material and methods

The study comprised 150 pregnant women at 22-36 weeks' gestation and PE of varying severity, who were examined at the obstetric clinic of V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood of Minzdrav of Russia. They were divided into group 1 (n=74) and group 2 (n=76) with mild to moderate PE (ICD 10 code O14.0), and severe PE (ICD 10 code O14.1), respectively. Seventy women with a physiological pregnancy made up a control group. Exclusion criteria were: secondary (symptomatic) hypertension (ICD 10 codes O10.1, O10.2, O10.3, O10.4), chronic arterial hypertension (CAG) (ICD 10 code O10.0), pre-existing hypertension with PE (ICD 10 code O11), gestational arterial hypertension (ICD-X O13 code), acute and exacerbation of chronic inflammatory diseases, allergic reactions at the time of examination, tumors of various locations, systemic connective tissue disorders, and chronic renal failure.

The diagnosis of PE was made according to clinical recommendations (protocol of treatment) "Hypertensive disorders in pregnancy, during childbirth and the postpartum period. Preeclampsia. Eclampsia" (2016).

The material for the study was peripheral venous blood. The expression of cell adhesion molecules on neutrophils and monocytes was measured by flow cytometry using a FACS Canto II flow cytometer (Becton Dickinson, USA).

The relative level of cells expressing adhesion molecules CD62L (L-selectin), CD11b (β2-integrin), the chemokine receptors CCR2 (receptor for MCP-1 monocyte chemoattractant), and CX3CR1 (fractalkine receptor) was determined in neutrophil (CD14-CD45 +) and monocyte (CD14 + CD45 +) gates. The number of CECs in peripheral blood (cells/μl) was determined by the J. Hladovec method using phase contrast microscopy with the MICMED-1 equipment (Russia) and by counting CECs in a Goryaev chamber.

Statistical analysis was carried out using Microsoft Office 2010, Statistica for Windows 6.0., and MedCalc 7.4.4.1. The descriptive statistical analysis was performed, including the calculation of the mean and standard error of the mean (M ± m) (normal distribution), median and quartiles (Me, C25-C75) (if the distribution was not normal). The significance of the differences between the variables was assessed using the Student t-test, Fisher and Mann-Whitney criteria (p values < 0.05 were considered statistically significant). To assess the diagnostic accuracy of the studied tests, ROC analysis was used. Relative risk (RR) and 95% confidence interval (CI) were calculated using the OpenEpi.

Results and discussion

The mean age of patients in PE groups was comparable with those in the control group [28 (25-33) years and 27 (24-31) years, respectively, (p = 0.07)] and did not differ between the groups with moderate and severe PE (p = 0.45). However, women aged over 36 years were more likely to develop severe PE during pregnancy than those in the control group (p = 0.03); RR 3.4 (95% CI 1.1-12.6). There were no differences between the groups regarding social status; all women had secondary or higher education, most of them were married and were employees (p>0.05in all cases). Compared with women in the control group, patients with PE were more likely to have chronic pyelonephritis and urolithiasis (p<0.05 in all cases); women with these diseases had 4.8 times (95% CI = 1.7-15.1) and 10.4 times (95% CI = 1.3-83.9) higher risk for developing severe PE, respectively.

The family history of hypertension was identified in 30.5% and 22.9% of women with and without the PE, respectively (p = 0.31). Patients with both moderate and severe PE more often had a history of hypertensive disorders in previous pregnancies than women in the control group (p = 0.001). More than half of women in the whole cohort were primiparous (p = 0.52). However, PE patients more often had a history of perinatal loss and spontaneous miscarriage in early pregnancy (p = 0.01 in all cases). A history of a miscarriage was associated with 3.1 higher risk of developing severe PE (95% CI = 1.1-10.1). Compared with the control group, PE patients had a higher incidence of uterine myoma (p = 0.001); the presence of uterine myoma was associated with 6.4 times greater relative risk of developing severe PE (95%CI = 1.4-29.6). A significantly higher proportion of women with than without PE had body mass index >30 (p = 0.001), which was associated with 2.4 times greater relative risk of developing severe PE (95%CI = 1.1-7.3). At baseline, the mean arterial pressure (BP) was 84.8 ± 0.8 mmHg and 78.5 ± 0.6 mmHg in the PE groups and the control group, respectively (p = 0.001). Patients, whose pregnancy was complicated by PE, significantly more often had baseline diastolic blood pressure above 80 mmHg than women without PE (p = 0.01). Patients with severe PE were more likely to have baseline diastolic pressure above 80 mmHg than patients with moderate PE (p = 0.02). The relative risk of developing severe PE in patients with baseline diastolic blood pressure above 80 mmHg was 5.4 (CI = 1.5-19.9). At the time of hospital admission, the mean BP was 116.1 ± 0.9 mmHg, 110.1 ± 0.7 mmHg., and 86.3 ± 0.6 mmHg in women with severe PE, moderate PE, and physiological pregnancy, respectively (p = 0.001 in all cases).

At hospital admission, PE patients had significantly higher levels of proteinuria than women in the control group (p = 0.001); levels of proteinuria in patients with severe and moderate PE were 3.01 ± 0.3 g/l and 1.1 ± 0.2 g/l (p = 0.0001), respectively. PE patients were more likely to deliver at an earlier gestation (33.8 ± 0.4 weeks)

than women in the control group (39.2 ± 0.1 weeks) (p = 0.001). The term of delivery was 32.7 ± 0.4 and 35.1 ± 0.3 weeks in patients with severe and moderate PE, respectively (p = 0.001). Compared with the controls, children born to mothers with PE significantly more often had neonatal depression and hypotrophy, so they were more often referred to the neonatal intensive care unit (p <0.05 in all cases).

Changes in the level of cells expressing early-stage adhesion molecules were detected only in the neutrophil population. Compared with women in the control group, PE patients had significantly lower relative levels of CD62L+ neutrophils (p = 0.01) and higher levels of CD11b+ neutrophils (p = 0.04) (table).

Patients with moderate and severe PE had similar levels of neutrophils expressing CD11b molecules (p> 0.05 in all cases). However, pregnant women with severe PE had a significantly lower level of CD62L+neutrophils compared both with women in the control group (p = 0.01) and patients with moderate PE (p = 0.04).

The relative level of monocytes expressing early-stage adhesion molecules (CD62L, CD11b) in the groups of women with moderate and severe PE did not differ significantly from the control group (p> 0.05 in all cases). Also, these parameters were similar in patients with moderate and severe PE (p> 0.05).

Recent studies indicate that the development of gestational hypertension is initiated by endotheliosis, which contributes to increased leukocyte transmigration through the endothelial monolayer [13]. Previously published studies have shown that in women with preeclampsia maternal systemic vasculature, including the intima and the muscle layer is infiltrated by neutrophils, but not lymphocytes or monocytes [14, 15]. Probably, in women with preeclampsia endotheliosis and infiltration of the maternal systemic vasculature are mediated mainly by neutrophils, but not a pool of monocytes.

The contact interaction of L-selectin (CD62L) with corresponding endothelial ligands ensures cell flattening onto the endothelium. The observed decrease in CD62L+ neutrophils in severe PE could be caused both by a true decrease in the level of such cells and by rapid recruitment of CD62L-positive cells from blood flow. The latter assumption seems more likely, as according to some researchers, pregnant women with PE have high serum levels the soluble form of L-selectin [16, 17]. The increase in the serum level of L-selectin molecules in women with PE can be due to the elution of CD62L molecules from the cell membrane after interaction with the corresponding endothelial ligand [18], caused by growing levels of inflammatory mediators [19] or by exposure to angiotensin II cells [20].

Interacting with CECs, activated neutrophils release toxic substances, such as reactive oxygen species (ROS), interleukins, tumor necrosis factor-alpha (TNFα), thromboxane, myeloperoxidase, all of which can cause endotheliosis and hemorheological disorders [9, 14]. In our study, we observed a slight increase in the level of CD11b+ neutrophils in the peripheral blood of PE patients. According to the literature, women with preeclampsia show increased expression of endothelial ICAM-1, which are ligands for this integrin [21]. Perhaps, in PE the tight attachment of neutrophils to the endothelium is determined by the activated endothelial cells themselves. The interaction of the chemokine receptors expressed by the cells with the chemokines produced in the affected area is one of the key mechanisms of inflammation. This process regulates the mobilization of certain populations of leukocytes in damaged tissues through the vessel wall, under the influence of chemokines contained in the endothelium and perivascular space [9]. When studying chemotaxis of neutrophils and monocytes of venous blood, we found that the levels of CCR2+ in leukocyte populations in patients with moderate and severe PE did not differ significantly from those of the control group (p> 0.05 V all cases) (table).

The relative level of CX3CR1+ in peripheral monocytes in the PE group did not differ statistically significantly from those in the control group (p> 0.05 in all cases). At the same time, in the neutrophil population, the level of CX3CR1+ in cells was significantly lower

Table. Indicators of the relative level of cells expressing early-stage adhesion molecules and chemokines receptors in peripheral blood in pregnant women with moderate and severe PE

Variable, % Me (C25–C75)		Control, *n*=70	PE, *n*=150	Moderate PE, *n*=74	Severe PE, n=76
CD62L+	neutrophils	71,8 (60,6–83,2)	60,4^{xxx} (47,2–72,4)	65,8 (57,6–76,2)	56,6xxx,y (45,6–69,5)
	monocytes	68,0 (44,0–80,9)	55,6 (42,7–72,5)	55,7 (38,6–69,3)	56,6 (45,2–76,1)
CD11b+	neutrophils	84,2 (72,2–90,9)	89,3^{x} (81,5–93,2)	90,2 (81,5–94,5)	88,2 (78,6–91,4)
	monocytes	83,1 (76,3–91,9)	83,1 (77,5–88,6)	83,3 (78,2–88,4)	83,1 (75,4–90,3)
CCR2+	neutrophils	22,0 (12,3–41,2)	30,2 (16,3–55,2)	31,2 (19,2–46,6)	28,3 (15,1–58,1)
	monocytes	80 (68,3–88,7)	85,2 (74,4–91,3)	86,3 (76,7–93,3)	82,4 (73,8–90,4)
CX3CR1+	neutrophils	53,3 (43,0–73,6)	31,6^{xxx} (23,8–47,4)	28,9^{xxx} (22,8–39,5)	41,9x,y (28,5–57,4)
	monocytes	71,2 (35,2–89,9)	61,5 (36,0–80,4)	46,8^{x} (36,0–62,8)	70,5y (42,3–87,4)

Note: x - statistical significance of the differences compared to the control group (x = *p* = 0.04, xxx - *p* = 0.01), y - statistical significance of the differences compared to the group with moderate PE (y = *p* = 0.04).

in the groups of women with moderate and severe PE, compared with the control group (p = 0.001, p = 0.001, p = 0.04, respectively). A distinctive feature of women with severe PE was a significantly higher relative level of CX3CR + monocytes and neutrophils than in women with moderate PE (p = 0.04 in both cases).

Earlier, we showed that the development of PE is accompanied by a significant increase in the serum level of fractalkine [22]. Its production is stimulated by the inflammatory cytokines, such as TNF-α, IFN-γ, and IL-1 [23], which levels are significantly increased in PE [24]. CX3CL1 is synthesized as a membrane-bound molecule with the chemokine domain presented on a mucin-like stalk which mediates the direct capture of circulating leukocytes and supports integrin-independent leukocyte adhesion [25]. Cleavage at the base of this stalk by a protease, namely the tumor necrosis alpha-converting enzyme, generates a soluble chemokine, which functions as a potent chemoattractant of target cells [26].

As with the evaluation of leukocyte expression of CD62L molecules, no unambiguous conclusions can be drawn about the role of a higher level of CX3CR1+ neutrophils and monocytes in the pathogenesis of severe PE. On the one hand, the interaction of CX3CL1-CX3CR1 markedly increases the affinity of cells with integrin molecules, which results in much denser adhesion. It has been established that the co-expression of CX3CL1 and integrin ligands, such as the ICAM-1 intercellular adhesion factor and VCAM-1 vascular adhesion molecule, significantly increases cell adhesion compared to the mono interaction of each ligand with the corresponding receptor [27]. On the other hand, it is possible that the combination of a high level of soluble fractalkine and an increase in the expression of its receptors by monocytes and neutrophils keep some of the activated cells in the systemic circulation, contributing to the progression of systemic inflammatory response.

Patients with PE had significantly higher levels of CECs in venous blood, than women in the control group (12 (8-18) cells/μL and 4 (3-6) cells/μl, respectively, p = 0.0001), and in patients with severe PE levels of CECs were significantly higher than in patients with moderate PE (14 (9.5-22) cells/μL and 9 (6-16) cells/μL, respectively) = 0.04). CECs are the immediate most specific marker of damage to the inner lining of blood vessels. Under physiological conditions, a certain number of the endothelial cells slough from the vessel wall in a concentration not exceeding 4×10^4 cells per 1 ml of blood.

In women with gestational hypertensive disorders, the increase in CECs in the blood reflects the process of endotheliosis, caused by endotoxins, superoxide radicals, homocysteine, histamine and other damaging factors [12]. In the literature, an increase in CECs was associated with gestational hypertensive disorders [11].

Our findings on the increase in the CECs level of in severe PE indicate that manifestations of endotheliosis are intensified in the severe form of this pregnancy complication, which leads to disruption of the endothelial barrier and the appearance of intracellular openings increasing the permeability of the endothelial monolayer [28].

The ROC analysis revealed that the most accurate, sensitive and specific criterion for diagnosing severe PE is the relative level of CD62L+ neutrophils in venous blood (AUC = 0.852, sensitivity 81.5%, specificity 88.9%, diagnostic threshold 57%) (Fig. 1).

Thus, the relative levels of CD62L+ neutrophils in venous blood less than or equal to 57% and greater than 57% allow the diagnosis of severe and moderate PE, respectively, to be made.

Based on these diagnostic thresholds, a "Method for the diagnosis of severe preeclampsia" was developed (Patent No. 2587781 dated May 27, 2016).

Another informative criterion for severe PE was the percentage of neutrophils expressing fractalkine receptors (CX3CR1) (AUC = 0.873, precision 81.2%, sensitivity 100.0%, specificity 66.7% borderline 26.2%) (Figure 2).

Fig. 1. ROC-curve demonstrating sensitivity and specificity of the relative level of CD62L+neutrophils of venous blood in women with moderate (0) and severe (1) PE

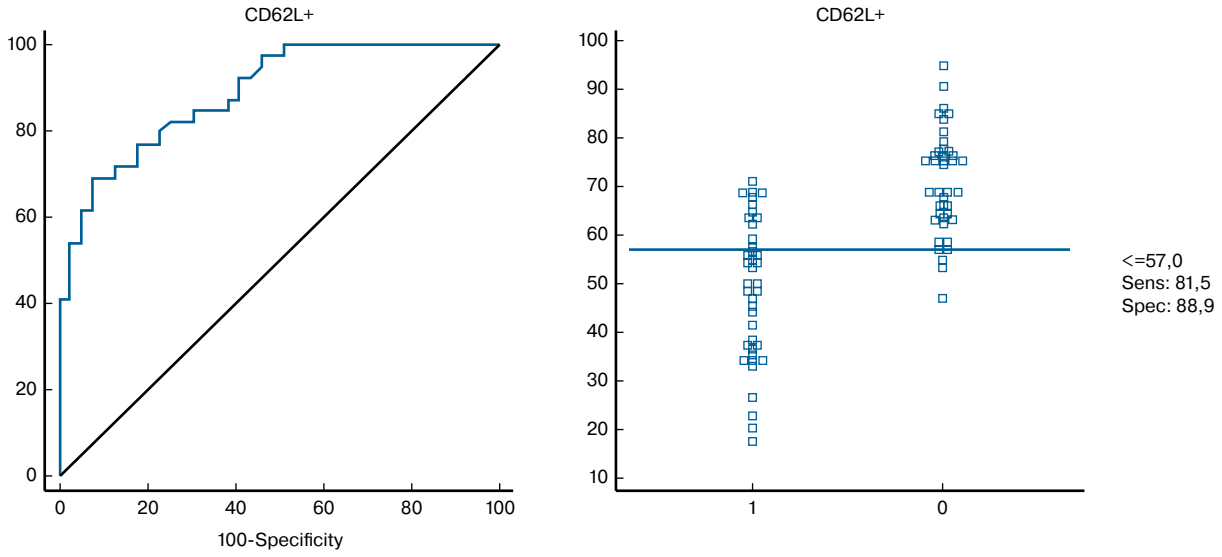


Fig. 2. ROC- curve demonstrating sensitivity and specificity of the relative level of CX3CR1+neutrophils in venous blood in women with moderate (0) and severe (1) PE

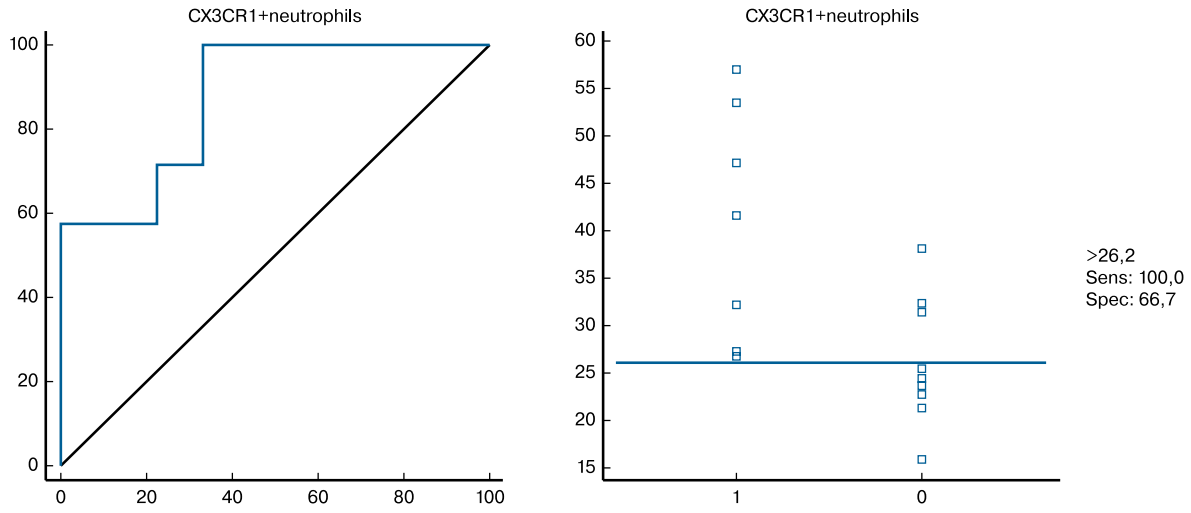
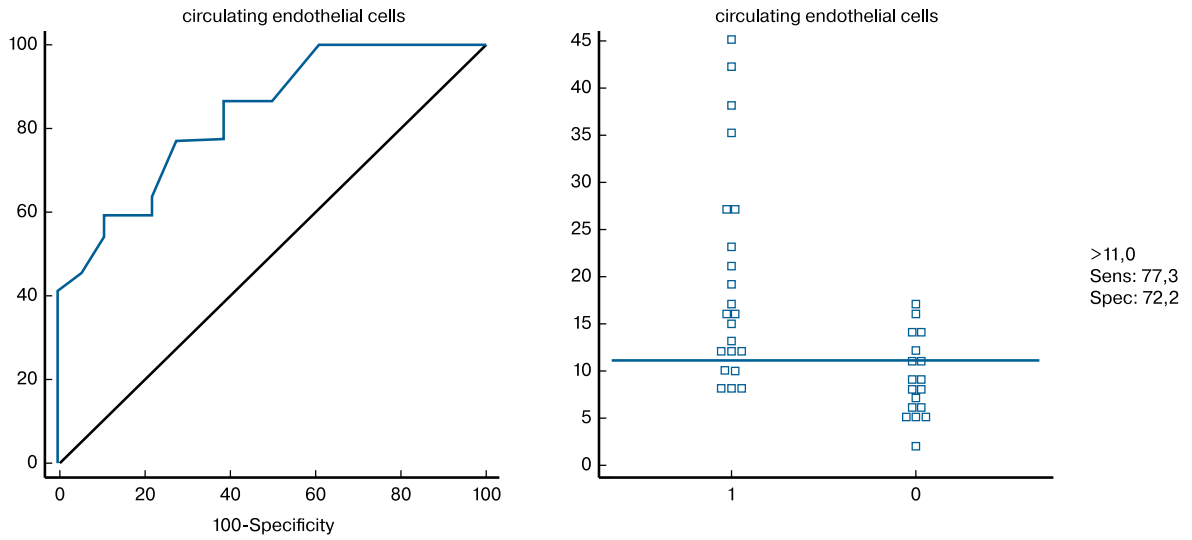


Fig. 3. ROC-curve demonstrating sensitivity and specificity of the number of CECs in venous blood in women with moderate (0) and severe (1) PE



At the same time, the percentage greater than 26.2% corresponds to the diagnostic criterion for severe PE, while at the percentage of less than 26.2% the severity of PE is defined as moderate.

Another criterion reflecting severity of PE was CECs number (AUC = 0,830, sensitivity – 77.3% and specificity – 72.2%, borderline value - 11 cells/μl) (Fig.3). Severe and moderate PE can be diagnosed at CECs numbers of more or less than 11cells/μl, respectively.

Conclusion

The established diagnostic thresholds for the levels of CD62L+ in neutrophils, neutrophils, expressing fractalkine receptors, and the number of CECs in venous blood can serve as additional criteria for stratifying severity of preeclampsia, which allow timely selection of appropriate management strategy in PE patients.

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Authors' information:

Panova, Irina A., Dr.Med.Sci., Associate Professor, Head of Department of Obstetrics and Gynecology, V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia. 153045, Russia, Ivanovo, Pobedy str. 20. Tel.: +74932351862. E-mail:ia_panova@mail.ru

Kudryashova, Anna V., Dr.Bio.Sci., Senior Researcher at the Laboratory of Clinical Immunology, V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia. 153045, Russia, Ivanovo, Pobedy str. 20. Tel.: +74932336928. E-mail:niimid.immune@mail.ru

Rokotyanskaya Elena A., Ph.D., Associate Professor at the Department of Obstetrics and Gynecology, Neonatology, Anesthesiology and Reanimatology, V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia.
153045, Russia, Ivanovo, Pobedy str. 20. Tel.: +74932351862. E-mail: rokotyanskaya.ea@mail.ru

Malyshkina Anna Ivanovna, Dr.Med.Sci., Director, V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia.
153045, Russia, Ivanovo, Pobedy str. 20. Tel.: +74932338320. E-mail: ivniimid@inbox.ru

Pareyshvili Violetta Vasilevna, Dr.Med.Sci., Professor at the Department of Obstetrics and Gynecology, Neonatology, Anesthesiology and Reanimatology, V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia. 153045, Russia, Ivanovo, Pobedy str. 20. Tel.: +74932351862. E-mail: ivniimid@inbox.ru

Bogatova Irina Konstantinovna, Dr.Med.Sci., Professor, Chief Researcher of the Department of Obstetrics and Gynecology, V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ministry of Health of Russia. 153045, Russia, Ivanovo, Pobedy str. 20. Tel.: +74932351862. E-mail: ivniimid@inbox.ru