Diagnostic and prognostic markers of morphofunctional heart state impairment and long-term persistence of heart failure in patients with myocarditis

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DATA SHARING
Data are available upon reasonable request to corresponding author.

Introduction
Myocarditis is an inflammatory lesion of the heart muscle of various etiology and is characterized by a wide spectrum of nonspecific clinical symptoms with an unpredictable course. The disease most often has a viral etiology and can be associated with both the direct cytotoxic effect of viruses on the myocardium and the activation of immunopathological reactions, that leads to autoimmune heart damage and long-term persistence of the inflammatory process [2, 4, 11, 29]. In recent years, the problem of myocarditis has become especially relevant in connection with the COVID-19 pandemic and its consequences. By itself, the coronavirus infection can rarely become the direct cause of inflammatory heart damage - its specific weight in the structure of etiological factors among other viruses is up to 5% [6, 20]. However, it has been proven that COVID-19 is able to stimulate the replication of other viruses in the myocardium, or activate immunopathological reactions from the hypersecretion of pro-inflammatory cytokines with the development of the well-known phenomenon called “cytokine storm” [20, 25,
Another problem, which is relevant primarily for our country, is the active hostilities that continue on the territory of Ukraine as a result of Russian aggression, which lead to an increase in the incidence of myocarditis in the most vulnerable category of people - young and middle-aged men [3, 20]. So, to date, according to the received data, myocarditis occurs more often in men (about 2/3 of cases) and has a more severe course [18, 20, 31]. Moreover, the disease is most often observed in the age range of 30-45 years [22, 31]. Factors contributing to an increase in the likelihood of developing myocarditis in conditions of war, in particular in military personnel, internally displaced persons and persons injured as a result of hostilities, are the deterioration of living conditions and the quality of food, hypothermia, the influence of acute and chronic stress, the need for a long-term stay in stable team, which leads to activation of viral infections. In view of the above, the problem of myocarditis, in particular in Ukraine, has gained special relevance in recent years, therefore, the search for new diagnostic and prognostic markers of the adverse course of the disease is expedient for the timely appointment of optimal drug therapy, strengthening of regimen measures and adequate monitoring of the patient's clinical condition.

The purpose of the study - to establish laboratory and instrumental markers of morphofunctional heart state impairment and to develop a mathematical model for early prediction of long-term heart failure persistence in patients with myocarditis.

Material and methods

The study included 80 patients with acute myocarditis of a severe course, who at the time of inclusion had a reduced ejection fraction (EF) of the left ventricle - <40 % according to the recommendations of the European Society of Cardiology and II-IV functional class of heart failure according to the classification of the New York Heart Association [23]. The diagnosis of myocarditis and the determination of the criteria for the severe course of the disease were established on the basis of the Recommendations for the diagnosis and treatment of myocarditis and on the basis of the Standards for the diagnosis and treatment of cardiovascular diseases of the All-Ukrainian association of cardiologists of Ukraine for the year 2021 [16].

The study was conducted in accordance with the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles of Medical Research Involving Human Subjects" and the "Universal Declaration of Bioethics and Human Rights (UNESCO)", on the basis of the department of non-coronary heart diseases, rheumatology and therapy from June 2022 to March 2023. The research was approved by the ethics commission of the State institution "National Scientific Center "The M. D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Sciences of Ukraine", in order to determine:

- levels of pro-inflammatory cytokines - interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and anti-inflammatory interleukin-10 (IL-10) in blood serum by enzyme immunoassay;
- cardiospecific antibodies (CA) to cardiac L-myosin (CM) and beta1-adrenoceptors (β1-AR) by calculation of optical plane units (OPU) using the ELI-Viscerotest test system;
- expression of Toll-like receptors of the 2nd and 4th types on the surface of monocytes by the method of flow cytofluorimetry based on the study of the average fluorescence intensity (AFI).

24-hour (Holter) ECG monitoring was performed on a Philips Digitrack TM-plus 3100A device. The percentage of ventricular extrasystoles (VE) relative to the number of normal ventricular complexes, and the presence of paroxysms of non-sustained ventricular tachycardia (NSVT) were assessed. The presence of tachycardia with 3 or more ventricular complexes lasting up to 30 seconds according to the Standards for the diagnosis and treatment of cardiovascular diseases of the All-Ukrainian association
Transthoracic echocardiography (EchoCG) was performed on an Aplio Artida SSH - 880 CV ultrasonic diagnostic device, Toshiba Medical System Corporation (Japan). In the two-dimensional mode, during systole and diastole, the end-diastolic volume (EDV) of the left ventricle was calculated, which was related to the body surface area and an indexed indicator was obtained - left ventricular EDVi. Left ventricular EF was estimated by the biplane method of Simpson discs. With the help of the speckle-tracking (ST) technique, the indicator of left ventricular longitudinal global systolic strain (LGSS) was evaluated, to determine which video loops were recorded from three standard apical accesses: four-chamber, two-chamber and three-chamber positions, using the sixteen segmental model of left ventricle according to Lang R. [19]. Circumferential global systolic strain (CGSS) and radial global systolic strain (RGSS) were also assessed, for which determination was made by recording video loops along the short axis of the left ventricle at the level of the papillary muscles [24]. While calculating the average deformation and deformation rates of six segments were taken - one segment each of each left ventricular wall in the middle section [15, 24]. The analysis of deformation indicators was carried out using the Wall Motion Tracking software package. The results of ST Echocardiography are presented in the form of absolute indicators.

Cardiac magnetic resonance (CMR) imaging with the use of gadovist as a contrast agent was performed in the department of radiodiagnostics of the State institution "National Scientific Center "The M. D. Strazhesko Institute of Cardiology, Clinical and Regenerative Medicine of the National Academy of Medical Sciences of Ukraine". The Toshiba Vantage titan HSR 1.5 Tesla device (Japan) was used. Images were evaluated in 3 modes along the short and long axis of the heart: before the introduction of a contrast agent (T2 Black blood FSat mode) to detect the area of edema in the myocardium; within 3-5 min. after administration (T1 early contrast) to detect hyperemia in the zone of inflammatory lesions and the mode of T1 delayed enhancement after 10-15 min. from the introduction of a contrast solution to detect fibrotic/necrotic changes [7, 12]. To estimate the number of segments of the left ventricle affected by inflammatory or fibrotic/necrotic changes contemporary model of the 17-segment structure of the left ventricle was used [12]. Figure 1 shows an example of active inflammatory damage of myocardium as a result of diffuse myocarditis, which was accompanied by pronounced morphofunctional disorders: significant dilatation, eccentric remodeling, and severe systolic dysfunction of the heart.

Statistical processing of the received data was carried out using the software package of SPSS Advanced Statistics 27.0 license program number L-CZAA-BT2KCD (USA). The calculated quantitative indicators are given as the mean value and standard deviation of the mean (M ± m), the Student's t-test was used to compare the average indicators in all groups. For all types of analysis, the critical level of statistical significance was p<0.05. Limit values of indicators that served as predictors of the presence of certain clinical characteristics and confidence intervals were determined based on the Student's test using binary logistic regression. ROC analysis was used to assess the quality of binary classification. Mathematical models were built using discriminant analysis.
Results

The study of immune status indicators during dynamic observation of patients with myocarditis allowed to establish that the highest activity of immunopathological reactions was observed in the 1st month from the onset of the disease in the acute stage. This was confirmed by the highest levels of pro-inflammatory cytokines, a high content of cardiac-specific autoantibodies, in particular to cardiac myosin and β-adrenoceptor, which was observed on the background of high expression activity of type 2 and 4 TLRs (Table 1). After 6 and 12 months, there was a gradual decrease in the content of pro-inflammatory cytokines and an increase in the concentration of anti-inflammatory IL-10, which was combined with a decrease in the content of cardio-specific autoantibodies and a decrease in the activity of TLR expression.

When studying the structural and functional state of the heart with the help of echocardiography with speckle-tracking technique and the results of CMR with contrast, it was established that the most pronounced violation of the contractility of the left ventricle was noted in the first month after the onset of myocarditis (Table 2). After 6 months of observation, a gradual improvement of the left ventricular contractile capacity was determined, which was evidenced by a significant increase in the value of left ventricular EF, longitudinal and circumferential global systolic strain.

Positive dynamics were maintained and after 12 months of follow-up, it was also characterized by reverse remodeling of the left ventricle, which was evidenced by a significant decrease in the left ventricular EDVI. Improvement of the contractile capacity and reverse remodeling of the left ventricle was observed on the background of a decrease in the volume of the inflammatory lesion - according to CMR, the number of segments of the left ventricle with the presence of inflammatory changes significantly decreased after 6 months, and after 12 months their number was 2.3 times less than in the first month from the onset of the disease. After 12 months we also observed the reduction of left ventricular segments number in which delayed enhancement was present, that became a sign of regression of myocardial fibrotic/necrotic changes.

According to the results of 24-hour ECG monitoring, a decrease in the average number of ventricular extrasystoles was established from 3.640±0.412 % in the 1st month to 2.217±0.312 and 1.714±0.269 after 6 and 12 months, respectively (p<0.01). The frequency of NSVT paroxysms detection decreased from 27.50 % at the onset of the disease to 17.50 and 12.50 %, respectively, after 6 and 12 months of observation.

After 12 months of observation, the frequency of cardiovascular events was analyzed and it was established that two patients died (2.50 %), one patient (1.25 %) developed a cerebral circulation disorder due to cerebral vessel thromboembolism of cardiac origin, and 15 patients (18.75 %) required hospitalization due to decompensation of heart failure. It should be noted that the cases of planned hospitalization for routine examinations and correction of therapy, which is provided by the Standards of the All-Ukrainian association of cardiologists of Ukraine for patients with myocarditis, were not classified as cardiovascular events.

On the basis of 12-month follow-up period, we assessed the impact of the studied indicators on the development of cardiovascular events, which included cases of cardiac death, development of a stroke, and the need for hospitalization due to decompensation of heart failure. For this purpose, a search for independent predictors of the development of cardiovascular events in patients with acute myocarditis was conducted based on statistical analysis using the binary logistic regression method. The most significant in this aspect were the following indicators determined in the first month from the onset of the disease: value of left ventricular EF ≤30 %, value of LGSS ≤7.0 %, the presence of unstable ventricular tachycardia paroxysms, inflammatory changes affecting ≥6 segments of the left ventricle, the presence of delayed enhancement (fibrotic/necrotic changes) in ≥5 segments of the left ventricle (Table 3).

Next, we constructed a ROC curve reflecting the relationship between the development of cardiovascular

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Value of indicator (M±m)</th>
<th>Referent values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st month</td>
<td>After 6 months</td>
<td>After 12 months</td>
</tr>
<tr>
<td>IL-1β, pg/ml</td>
<td>6.213±0.432</td>
<td>4.201±0.408*</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>14.29±1.32</td>
<td>12.22±0.92</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>17.20±1.11</td>
<td>9.284±0.803*</td>
</tr>
<tr>
<td>IL-10, pg/ml</td>
<td>12.13±1.10</td>
<td>24.12±2.28**</td>
</tr>
<tr>
<td>Antibodies to CM, OPU</td>
<td>5.123±0.571</td>
<td>3.445±0.343**</td>
</tr>
<tr>
<td>Antibodies to β1-AR, OPU</td>
<td>2.07±0.212</td>
<td>1.828±0.174</td>
</tr>
<tr>
<td>TLR2, AFI</td>
<td>9.304±1.012</td>
<td>7.923±0.932</td>
</tr>
<tr>
<td>TLR4, AFI</td>
<td>12.92±1.43</td>
<td>9.730±1.329*</td>
</tr>
</tbody>
</table>

Note: difference in indicators is significant compared to those in the 1st month from myocarditis onset: * - p< 0.05; ** - p<0.01.
Therefore, we can state that independent predictors of the development of cardiovascular events within 12 months from the onset of myocarditis with reduced left ventricular EF are the simultaneous presence in the first month from the onset of the disease of a complex of the following pathological changes: left ventricular EF < 30%; value of LGSS < 7.0%; presence of NSVT paroxysms; presence of inflammatory changes in > 6 segments of the left ventricle; presence of delayed enhancement in > 5 segments of the left ventricle.

The further step was the creation of a mathematical model for predicting the long-term persistence of heart failure, which was based on the most informative immunological markers and morphofunctional indicators. The mathematical model was built using discriminant analysis. The model included indicators with the highest odds ratio (OR) values for persistence of II or higher functional class of heart failure or its absence after 12 months: Y1 - for the presence of II or higher functional class of heart failure after 12 months, Y0 - for the presence of functional class I of heart failure or its absence after 12 months:

\[
Y_1 = 3.021 \times \text{IL-1} + 9.247 \times \text{CA to CM} + 15.40 \times \text{CA to } \beta_1 - \text{AR} + 3.105 \times \text{TLR2} + 4.653 \times \text{TLR4} - 0.422 \times \text{EF of left ventricle} - 1.489 \times \text{LGSS} - 1.414 \times \text{CGSS} + 0.170 \times \text{EDVi of left ventricle} + 17.32 \text{ in presence of } > 6 \text{ SIL} + 14.92 \text{ in presence of } > 5 \text{ SDE} - 66.54;
\]

Table 2. Results of echocardiography and cardiac magnetic resonance during dynamic observation of patients with myocarditis.

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Value of indicator (M±m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF of left ventricle, %</td>
<td>33.13±2.24</td>
</tr>
<tr>
<td>EDVi of left ventricle, ml/m²</td>
<td>105.7±7.2</td>
</tr>
<tr>
<td>LGSS, %</td>
<td>8.213±0.736</td>
</tr>
<tr>
<td>CGSS, %</td>
<td>8.993±0.754</td>
</tr>
<tr>
<td>RGSS, %</td>
<td>15.37±1.73</td>
</tr>
<tr>
<td>Amount of left ventricular segments with inflammatory lesions</td>
<td>6.641±0.630</td>
</tr>
<tr>
<td>Amount of left ventricular segments with late gadolinium enhancement</td>
<td>4.755±0.437</td>
</tr>
</tbody>
</table>

Table 3. The role of pathologic changes detected in the first month from the onset of myocarditis in relation to the development of cardiovascular events during 12 months of observation.

<table>
<thead>
<tr>
<th>Pathologic changes detected in the first month from the onset of myocarditis</th>
<th>Odds ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF of the left ventricle ≤ 30%</td>
<td>2.021 (CI 1.710-2.322; p=0.021)</td>
</tr>
<tr>
<td>LGSS ≤ 7.0%</td>
<td>1.794 (CI 1.590-2.034; p=0.032)</td>
</tr>
<tr>
<td>Presence of NSVT</td>
<td>2.152 (CI 1.851-2.602; p=0.018)</td>
</tr>
<tr>
<td>Presence of inflammatory changes affecting &gt; 6 segments of left ventricle</td>
<td>1.663 (CI 1.452-1.939; p=0.041)</td>
</tr>
<tr>
<td>Presence of delayed enhancement in ≥ 5 segments of left ventricle</td>
<td>1.712 (CI 1.401-1.993; p=0.029)</td>
</tr>
</tbody>
</table>

Fig. 2. ROC curve showing the relationship between the simultaneous presence of a complex of pathologic changes and the development of cardiovascular events in patients with acute myocarditis during a 12-month observation period.

Note: CI - confidence interval.
Y = -2.236 x IL-1β + 9.447 x CA to CM + 16.01 x CA to β1-AR + 3.039 x TLR2 + 4.553 x TLR4 - 0.515 x EF of left ventricle - 1.528 x LGSS - 1.322 x CGSS + 0.161 x EDVI of left ventricle + 16.53 in presence of ≥5 SIL + 15.94 in presence of ≥5 SDE - 53.20.

Note: CA - cardiospecific antibodies, SIL - segments with inflammatory lesions, SDE - segments with delayed enhancement.

The probability of having II or higher functional class of heart failure after 12 months is estimated by the formula: Y/(Y + Y0) x 100 %.

The probability of having functional class I of heart failure or its absence after 12 months is estimated by the formula: Y / (Y + Y0) x 100 %.

The sensitivity of the model for predicting the persistence of heart failure is 84.20 %, the specificity is 78.94 %. Positive predictive value - 82.49 %, negative predictive value - 75.92 %. The practical significance of this model is obvious, since with its help, already in the first month from the debut of myocarditis with reduced EF of the left ventricle, the further course of the disease can be predicted with high reliability and the prospects of regression of heart failure clinical symptoms after 12 months can be estimated on the early stage of the disease.

Discussion

According to the world's leading experts on the problems of diagnosis and treatment of myocarditis, the in-depth study of the morphofunctional state of the heart, taking into account its changes in dynamics, nowadays might be the main approach to predicting the clinical course of the disease, preventing the development of complications and choosing the optimal tactics of drug therapy [11, 18, 29]. The results of dynamic monitoring of patients with severe myocarditis, obtained in our study, indicate a gradual recovery of the contractility of the heart after 6 and 12 months of treatment, which occurs on the background of left ventricular dilation decrease and attenuation in the activity of the inflammatory process. A gradual decrease in the concentration of pro-inflammatory cytokines, the content of cardiospecific antibodies and the expression of type 2 and 4 TLRs after 6 and 12 months had a clear association with a reduction of left ventricular segments number affected by inflammatory changes according to CMR data. A decrease in the activity of the inflammatory process and the volume of the inflammatory lesion of the left ventricle during dynamic observation was accompanied by an improvement in the morphofunctional state and contractility of the left ventricle, and the most informative indicators characterizing this process were the values of longitudinal and circumferential systolic strain. The high informativeness and prognostic value of the LGSS in patients with myocarditis and its comparability with the results of CMR was also proven in several foreign studies [9, 15, 28]. In our study, in addition, an associative relationship was shown between the improvement of the contractile capacity, the reduction of left ventricular dilatation and the reduction of the number of segments affected by inflammatory changes on CMR not only with the value of LGSS, but also with the values of CGSS and RGSS, although the value of the latter increased significantly only after 12 months of observation.

In patients with non-coronary heart diseases, in particular with myocarditis, a high prognostic value has been proven today regarding the future development of cardiovascular events, sudden cardiac death and long-term persistence of heart failure in the presence of delayed contrast on CMR, reduced EF and significant left ventricular dilatation [1, 10, 14, 17, 21]. In addition, a significant role in the development of cardiovascular events has been proven for ventricular rhythm disorders, in particular paroxysms of non-sustained and sustained ventricular tachycardia, which develop in patients with myocarditis both on the background of the influence of stress factors and as a result of morphofunctional changes in the myocardium of inflammatory and fibrotic origin [8, 13, 26, 27]. In the mathematical model created based on the results of our research and according to the data of ROC analysis, in addition to the above indicators, results of speckle tracking echocardiography, in particular LGSS and CGSS, as also immunological biomarkers - IL-1β, CA to CM and β1-AR, demonstrated a high prognostic value, as well as TLR type 2 and type 4 expression activity. Evidence of the prognostic value of active TLR type 4 expression in patients with myocarditis regarding the outcome of the disease and response to immunosuppressive therapy was also obtained by a team of Italian authors led by Chimenti C. [5]. In our study, using statistic analysis it was possible to combine a complex of laboratory and instrumental indicators characterizing the morphofunctional state of the heart, the determination of which already at the onset of myocarditis makes it realistic to assess the risk of cardiovascular events development and calculate the probability of long-term persistence of heart failure.

Nevertheless, the problem of diagnosing and predicting the clinical course of myocarditis, as well as preventing the development of complications remains one of the most difficult for both Ukrainian and foreign cardiology [3, 12, 17, 23]. Currently, the issue of creating recommendations and unified clinical guidelines for the diagnosis and treatment of myocarditis is acute, because this disease remains almost the only common nosology for which, given the complicity of the problem, no appropriate recommendations have been created by the European Society of Cardiology and the American Heart Association. Taking into account the complexity of the problem, it is obvious that there is a need for prospective investigations devoted to the study of morphofunctional heart state in patients with myocarditis, which should include laboratory tests, a wide range of imaging methods and endomyocardial biopsy. A possible way to solve this problem is to conduct multicenter randomized clinical trials dedicated to improving approaches to diagnosis, prognosis, and treatment of myocarditis.
because contemporary approaches to the problem of myocarditis are based mostly on the results of single-center studies with a small number of patients.

Conclusions

1. According to the results of dynamic monitoring of patients with myocarditis, it was established that the onset of the disease is characterized by a pronounced activation of immunopathological reactions with a significant increase in the concentration of proinflammatory cytokines, cardiospecific autoantibodies on the background of active expression of Toll-like receptors of the 2nd and 4th types, which causes involvement in the inflammatory process of a significant number of segments of the left ventricle and is accompanied by a violation of its morphofunctional state with dilation, significant impairment of contractility and development of ventricular arrhythmias. After 6 and 12 months of observation, on the background of a decrease in the activity of immunopathological reactions, there is a gradual restoration of the systolic function of the left ventricle, an early marker of which is an increase in the indicators of its longitudinal and circumferential global strain.

2. A set of instrumental indicators determined within the 1st month from the onset of myocarditis, which can serve as predictors of cardiovascular events during the next 12 months, was established: left ventricular ejection fraction \(< 30 \%\); index of longitudinal global systolic strain \(< 7.0 \%\); the presence of paroxysms of non-sustained ventricular tachycardia; the presence of inflammatory changes in \(> 6\) segments and delayed enhancement in \(> 5\) segments of the left ventricle. A mathematical model has been created, with the help of which within the first month from the onset of myocarditis it is possible to predict the adverse course of the disease with long-term (at least 12 months) persistence of heart failure.

References


ДИАГНОСТИЧНІ ТА ПРОГНОЗІЧНІ МАРКЕРІЇ ПОРУШЕННЯ МОРФОФУНКЦІОНАЛЬНОГО СТАНУ СЕРЦЯ ТА ДОГОВІРЛІВОї ПЕРСЕВІСТІ СЕРЦЕВОї НЕДОСТАТНОСТІ У ХВОРОХ З МІОКАРДИТОМ

Черніюк С. В., Марченко К. С.

Проблема міокардіту в останні роки набула особливої актуальності, тому пошук нових діагностичних і прогностичних маркерів несприятливого перебігу захворювання є доцільним для своєчасного призначення оптимальної медикаментозної терапії, пошукення режимних заходів та адекватного моніторингу клінічного стану хворого. Мета дослідження: встановити лабораторні та інструментальні маркери порушення морфофункціонального стану серця та розробити математичну модель для раннього прогнозування довготривалої персистенції серцевої недостатності у хворих з міокардітом.

Матеріали і методи

Усім пацієнтам здійснювали імунологічне дослідження серцево-судинних захворювань, серцево-судинні захворювання класифікація, критерій Стьюдента для порівняння середніх значень показників, пареметри та інформативні характеристики ехокардіограми, спектральні та мапінг-реєстри, метаболику та імунокомплекси, серцеві антитела, імуноглобулини, аминотрансферази, креатинін-нуклеотидфосфат кіназу, глутаміноксидазу, неоксонат і аль-карофанол.

Результати

У 30 % пацієнтів навчальних груп виявлено пароксизмів нестійкої шлуночкової тахікардії, яка вимагала посилення режимних заходів та адекватного моніторингу клінічного стану хворого.

Заключення

Серцево-судинні захворювання класифікація, критерій Стьюдента для порівняння середніх значень показників, пареметри та інформативні характеристики ехокардіограми, спектральні та мапінг-реєстри, метаболику та імунокомплекси, серцеві антитела, імуноглобулини, аминотрансферази, креатинін-нуклеотидфосфат кіназу, глутаміноксидазу, неоксонат і аль-карофанол.
Diagnostic and prognostic markers of morphofunctional heart state impairment and long-term persistence ...

контрастування у 3 б сегментах лівого шлуночка. Створено математичну модель, за допомогою якої впродовж першого місяця від дебюту міокардиту можна прогнозувати несприятливий перебіг захворювання з тривалою (не менше 12 місяців) персистенцією серцевої недостатності.

Ключові слова: міокардит, діагностика, прогнозування, морфофункціональний стан серця, імунний статус, ехокардіографія, магнітно-резонансна томографія серця.

Author's contribution

Cherniuk S. V. - conceptualization of the study, formal analysis and verification of data, writing of the original draft and editing of the article.
Marchenko K. S. - creating a database, statistical processing and formal data analysis, writing an original project.