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Assessment of heart transplant recipients survival based on ultrasound diagnostic methods and immunological screening of antibodies to leukocyte donor antigens

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Aim. To create a mathematical model for predicting an assessment of the risk of antibody-mediated rejection (AMR) and analyze the survival of recipients with antibodies to leukocyte donor antigens.

Material and methods. A single-center study was conducted on the basis of S.V. Ochapovsky Regional Clinical Hospital № 1. During the 7 years 181 heart transplant recipients were observed. Based on the AMR crisis and detected antibodies to leukocyte donor antigens (HLA), 5 groups were identified: group 1 (n=10) — donor-specific antibodies (DSA) and AMR crisis, group 2 (n=7) — patients without DSA and AMR crisis, group 3 (n=17) — patients with antibodies to HLA, without AMR crisis, group 4 (n=11) — with AMR crisis, without identified antibodies to HLA, group 5 (n=87) — patients, not having antibodies to HLA and signs of both AMR and cell-mediated rejection (according to endomyocardial biopsy). The recipients underwent immunological tests, 2D-speckletracking echocardiography (2D-STE) and transthoracic echocardiography (TTEchoCG). Statistical methods were used to assess the results.

Results. Predictors of the severe form of AMR in TTEchoCG are: left ventricle enddiastolic diameter, interventricular septum thickness, ejection fraction, right ventricle volume. Predictors were determined using the 2D-STE method: global longitudinal peak strain, sensitivity (SE) — 86,2%, specificity (SP) — 90,4%; radial strain, SE — 75,8%, SP — 84,5%; circular strain, SE — 78,6%, SP — 84,4%. When taking into account the indicators of the global longitudinal peak strain of the left ventricle and the longitudinal peak strain of the right ventricle, SE increases to 91,9%, SP — 94,6%, with p<0,001. The survival rate of patients with identified post-transplant (*de novo*) donor-specific antibodies of the late period is 40%, without identified donor-specific antibodies — 68%. Dedicated predictors are used for mathematical prediction of AMR risk.

Conclusion. The relationship between immunological changes and data of TTEchoCG, deformation parameters and mechanics of a heart transplant was revealed. The presence of *de novo* DSA decline the survival, increases the risk of AMR, and contributes to the development of coronary artery disease. The proposed AMR risk prediction model will improve the long-term results of heart transplantation.

Key words: humoral rejection, antibodies to donor antigens, donor-specific antibodies, global longitudinal peak strain, 2D-speckle-tracking echocardiography, artificial neural network, survival.

Conflicts of Interest: nothing to declare.

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To date, the crisis antibody-mediated rejection (AMR) remains an important diagnostic and therapeutic problem in heart transplantation [1]. Clinical practice discusses the importance of early and late rejection, the effect of human leucocyte antigens (antibodies to HLA, HLA AB), donor-specific antibodies (DSA) and non-DSA identified in the post-transplant period (*de novo*) on the development of complications and long-term outcomes of heart transplantation (HT) [2, 3]. Researchers from different countries have concluded that *de novo* HLA AB have an adverse effect on the prognosis of heart recipients. At the same time, the presence of *de novo* HLA AB, without signs of transplant dysfunction, does not always associated with AMR crisis [4].

The use of easily available, non-invasive conventional transthoracic echocardiography (TTE), which is the first stage of the crisis diagnostics, allows us to identify changes in parameters that correlate with a detailed picture of heart transplant rejection. However, TTE and Doppler ultrasonography are not early predictors of rejection due to high variability in cardiac recipients. [5]. The use of more complex, applied 2D-speckle-tracking echocardiography (2D-STE) technique, which approved oneself since the beginning of the 20th century, helps to further quantify the function of longitudinal, circular and radial fibers of the left ventricle, longitudinal fibers of the right ventricle, as well as heart mechanics [6]. Many sources of literature indicate the relationship of morphological changes in the early stage of rejection and diagnostic parameters of the 2D-STE technique, which allows it to be used for a more in-depth study of cardiac transplant dysfunction [6].

In our study, artificial neural network was used to assess AMR risk. It allowed us to increase the accuracy of the results.

The aim of this study was to develop an artificial neural network to assess the AMR risk, based on important risk factors identified through routine studies in clinical practice, followed by predicting the survival of cardiac transplant recipients.

Material and methods

In the "S. V. Ochapovsky Research Institute of Regional Clinical Hospital № 1" in Krasnodar, the analysis of heart recipients' (n=181) monitoring from 2010 to 2017 was conducted. There were more men — 82,87% (n=150), women accounted for 17,13% (n=31), and the average age of the recipients was 48±11 years. Patient survival over 7 years of follow-up was 72%. All heart recipients were examined according to the currently accepted algorithm in the medical center. Depending on the histological data of the AMR crisis and the detected *de novo* HLA AB, the studied recipients were divided into 5 groups: group 1 (n=10) — patients with DSA and AMR crisis, group 2 (n=7) — patients with non-DSA and AMR crisis, group 3 (n=17) — patients with HLA AB, without AMR crisis, group 4 (n=11) — patients with AMR crisis, without identified HLA AB at the time of the study, and group 5, control (n=87) — patients without HLA AB and signs of both AMR and cell rejection according to endomyocardial biopsy (EMB).

Immunology research. The screening and identification of HLA AB in the posttransplant period, *de novo*, was carried out in accordance with the schedule adopted at the medcial center: at 1-3-6 and 12 months, and also according to emergency indications in cases of suspected AMR crisis. Screening and identification was made by Luminex Multiplex Assays using LIFECODES reagents.

Conventional TTE. The conventional TTE was performed on Acuson Siemens SC 2000 and Philips IE 33 devices according to the standard protocol. The visualization was carried out in B-mode with the assessment of the left ventricular end diastolic volume (LV) (LVEDV, ml), left ventricular end systolic volume (LVESV, ml), ejection fraction (EF,%), LV wall thickness (PWT — posterior wall thickness, IVST — interventricular septal thickness , mm), dimension of the left atrium (LA, mm) and the right atrium (RA, mm). Determination of pericardial effusion and systolic pressure in the pulmonary artery (SPPA, mm Hg) were performed. Using pulse-wave tissue Doppler imaging (PW-TDI), peak early diastolic filling (E, cm/s), peak late diastolic filling (A, cm/s), peak ratio E/A, isovolumic relaxation time (IVRT) were estimated. Mitral valve ring velocities were also measured — LV Em (diastolic peak velocity of early diastolic filling during mitral ring movement), LV E/Em (ratio of peaks of early diastolic filling to early diastolic displacement of mitral ring tissues), S (cm/s) — systolic peak. They were evaluated using PW-TDI of the lateral part of the TV ring: peak velocities of RV Em, RV E/Em R, RV S. The averaged echocardiographic parameters of each of the recipients were calculated in the first observation period after the HT, at the time and after the AMR crisis, and at the last observation period.

2D-STE. During planned and emergency hospitalizations, with suspected AMR crisis, 2D-STE was performed for cardiac recipients. In the gray scale image, the obtained segments were evaluated using the Acuson Simens SC 2000 device. In order to

Table 1

Parameters of strain and mechanics in the last year of follow-up for 5 groups

	Group 1	Group 2	Group 3	Group 4	Group 5
LV GLS, %[1]	-15,57±0,59	-15,66±0,59	-17,82±1,49	-15,45±0,46	-18,26±1,48
RadS LV, %[2]	30,67±0,99	30,55±2,08	30,27±2,48	29,22±3,97	31,10±2,46
CirS LV, %[3]	-22,02±1,96	-20,09±1,25	-21,86±2,16	-21,71±1,83	-22,69±2,50
ROTAPEX°[4]	6,41±1,01	5,24±0,91	6,49±1,16	6,68±1,24	5,69±1,14
ROTBASE°[5]	-2,39±6,50	-5,91±1,09	-6,89±0,92	-6,23±1,30	-6,13±1,41
ROTMID°[6]	2,41±0,87	2,88±0,82	1,77±0,92	2,75±0,81	3,21±1,42
TWIST, %[7]	12,00±1,10	11,75±1,04	12,97±0,96	12,09±1,18	11,93±1,94
RV-FWS, %[8]	-18,59±1,03	-17,11±0,72	-18,29±1,23	-17,69±1,07	-17,86±1,20

Abbreviations: LV GLS, % — LV global longitudinal strain, [2]LV RadS, % — LV radian systolic strain, [3]CirS LV, % — circular systolic strain, [4]ROTAPEX° — rotation of apical segments, [5]ROTBASE° — rotation of basal segments, [16]ROTMID° — rotation of medial segments, [8]RV GLS, % — RV global systolic strain, group 1 — patients with DSA and AMR crisis, group 2 — patients with non-DSA and AMR crisis, group 3 — patients with HLA AB, without AMR crisis, group 4 — patients with AMR crisis, without identified HLA AB at the time of the study, group 5 — control, patients without AMR crisis and HLA AB.

evaluate global longitudinal strain (LV GLS, %), the apical two-chamber (A2C), three-chamber (A3C) and four-chamber (A4C) positions were used [7]. Radian strain (LV Rad S, %) was determined for the basal area along the short LV axis in the parasternal position. Circular strain (Cir S LV, %) was determined at the level of the basal area along the short LV axis. To assess twisting (twist, %), we used images along the short axis at the base (Rotbase°) and the apex of the LV (Rotapex°). Assessment of the right ventricle free wall strain (RV-FWS) was determined by A4C projection [7].

Statistical methods. To describe the clinical parameters, the arithmetic mean was used together with the confidence interval, standard deviation (M±σ), standard error, median with upper (75%) and lower quantiles (25%). To compare the means in more than 2 groups, the Kruskal-Wallis test was used. Comparison of the averages during repeated measurements was carried out using the sign and Wilcoxon tests. When analyzing the degree of correlation between clinical indicators, groups of patients Spearman's rank correlation coefficient was used. Analysis of the relationship structure was conducted using contingency tables in conjunction with the Pearson's chi-squared test, ML (maximum likelihood) Chi-square, F-test, coefficient of contingency, Spearman's correlation coefficient [8]. Kaplan-Meier curves were used to analyze patient survival and the development of AMR. Diagnostic efficacy was assessed by ROC analysis. In order to predict the AMR crisis, an artificial neural network has been built. The architecture of the neural network consists of a two-layer perceptron. The first number indicates the quantity of variables in the network model — input data, the second and third ones — the quantity of hidden and output neurons in the model. The greater the performance, the more accurate the prediction is. The maximum possible performance is 100%.

Statistical processing was conducted by STATISTICA 10 (Tibco, USA) software.

Results

According to endomyocardial biopsy data, out of 132 recipients, 28 patients (21,2%) showed signs of AMR in accordance with the criteria for working formulations of the International Society for Heart and Lung Transplantation (WF-ISHLT from 2005 and revision from 2015). Among patients with AMR crisis — 57% were dead, without AMR crisis — 14% were dead. The largest percentage of deaths in group 1 was 60%, followed by group 2 — 57%, group 4 — 55%. Group 5 (without HLA AB, signs of AMR and cell rejection) had only 17% of deaths, in group 3 there were no deaths.

At the first stage, the heart recipients underwent dynamic TTE observation. First, an estimate of the arithmetic mean and standard error (standard deviation divided by the sample size) was determined for the TTE parameters in the first year of observation, then at the time of the AMR crisis and the last observation period. Intergroup differences in the parameters of the first observation year, using the Kruskal-

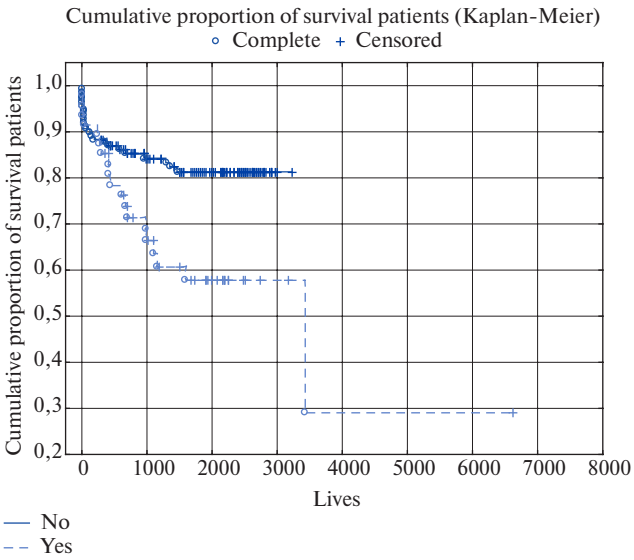

Fig. 1. AMR risks for patients with and without HLA AB.

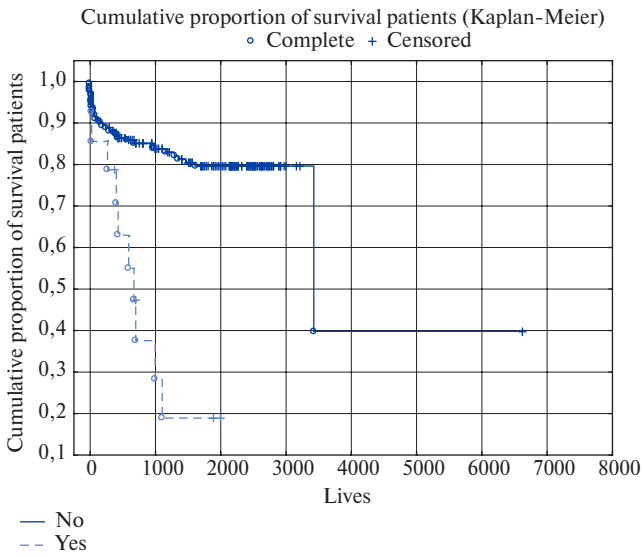

Fig. 2. The risks of AMR for recipients with and without DSA.

Wallis test, revealed the homogeneity of the five studied groups in almost all parameters ($p<0.05$). Group 5 includes recipients who did not have episodes of AMR and cell rejection during the observation period. Thus, TTE parameters of group 5 correspond to the standard values of heart transplant recipients. Groups 1, 2, 4 included recipients, who had AMR crisis. The intergroup differences of the last observation year revealed the statistical significance of the averages for 14 parameters ($p<0,05$), for 7 parameters there were no statistically significant changes ($p>0,05$). So, in group 1, when comparing the parameters of the first and last observation years, the following statistically significant changes can be noted: change in LV dimension ($p=0,004$), IVST ($p=0,045$), PWT ($p=0,026$), E/A ($p=0,036$), LV S ($p=0,012$), RV S ($p=0,004$), SPPA ($p=0,004$), RA ($p=0,004$), $p <0,05$. In group 2, differences were noted: LA ($p=0,023$), IVST ($p=0,023$), PWT ($p=0,041$), E/A ($p=0,023$), RV S ($p=0,023$), SPPA ($p=0,023$). In group 4, there were following changes: LA ($p=0,015$), LV end-diastolic dimension (EDD) ($p=0,045$), IVST ($p=0,044$), PWT ($p=0,002$), A ($p=0,026$), LV E/Em ($p=0,036$), SPPA ($p=0,045$), RA ($p=0,045$), IVRT ($p=0,026$), DT ($p=0,026$).

In order to identify AMR predictors, a correlation analysis was performed for the parameters of the standard TTE, which showed a statistically significant ($p<0,05$) difference in the crisis groups for LA, LV EDD, IVST, RV and EF. All parameters with statistically significant correlations can be used as predictors in models.

At the second stage, recipients were examined using the 2D-STE technique. First, the arithmetic and standard errors were estimated for the parameters of strain and mechanics in the first observation period, then at the time of the AMR crisis and the last observation period. The results of group 5 correspond to the normative values of heart transplant recipients without crisis. The Kruskal-Wallis test did not reveal a statistically significant difference in average values of the parameters in the groups for the first year of observation ($p>0,05$).

At the time of the AMR crisis, significant changes in the strain parameters and mechanics were revealed: LV GLS was 9,94±1,37%, LV Rad S — 19,36±3,66%, LV Cir S — 17,83±4,89, ROTAPEX° — 4,51±1,46, ROTBASE° — 4,75±2,12, ROTMID° — 1,94±1,41, TWIST — 8,90±1,85%, RV-FWS — 15,89±0,89%.

The possible diagnostic criteria for AMR crisis were: global peak systolic strain, sensitivity (Se) 86,2%, specificity (Sp) — 90,4%; radian systolic strain, Se — 75,8%, Sp — 84,5%; circular systolic strain, Se — 78,6%, Sp — 84,4%; LV twisting, Se — 66,7%, Sp — 94,2%, $p<0,001$, When LV GLS and the longitudinal peak strain of the right ventricle are taken into account, Se increases to 91,9%, Sp to 94,6%, and $p<0,001$ in the diagnosis of AMR crisis.

Table 1 presents the parameters of strain and mechanics in 7 years' follow-up. Patients of groups 1, 2 and 4 at this point had an AMR crisis. In group 1, a change was found in the following parameters: LV GLS ($p=0,004$), ROTBASE ($p=0,045$). In group 2, there were statistically significant changes: LV GLS

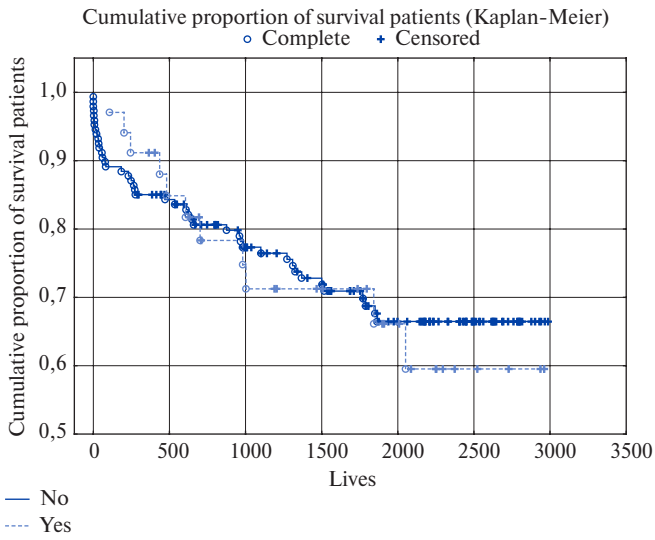

Fig. 3. Survival of patients with identified HLA AB *de novo*.

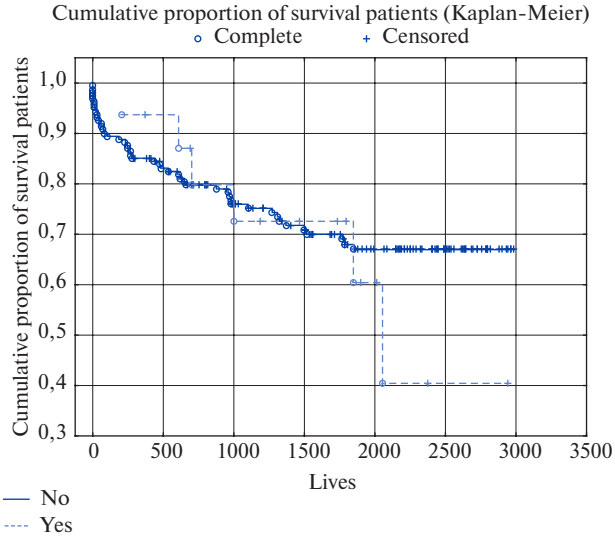

Fig. 4. Survival of patients with identified DSA *de novo*.
Abbreviation: DSA — donor-specific antibodies.

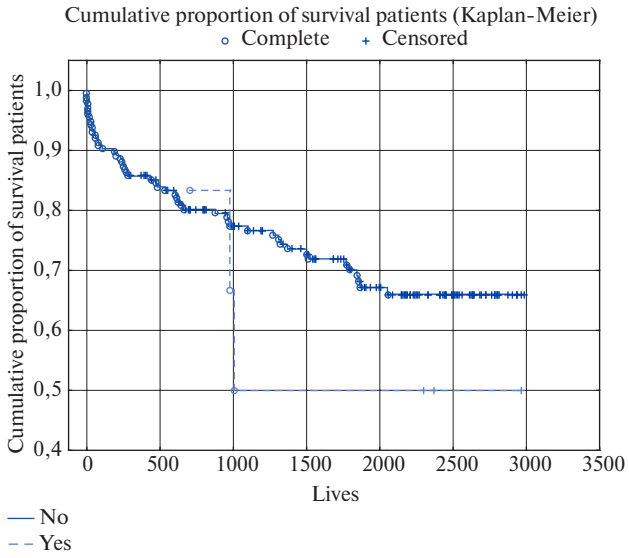

Fig. 5. Survival of patients with identified AB in the late period after HT.

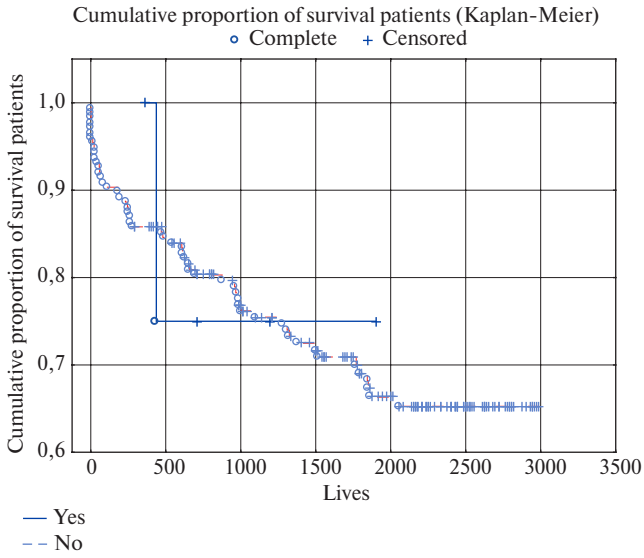

Fig. 6. Survival of patients with identified AB in the early period after HT.

(p=0,023), LV Rad S (p=0,042), LV Cir S (p=0,023); in group 4 — LV GLS (p=0,015), Rad S LV (p=0,046).

Patients with a history of AMR crisis had a statistically significant change in the following parameters: LV GLS, LV Rad S, LV Cir S. These indicators can be good predictors of an adequate prediction model for AMR crisis.

Further, the analysis of recipients with identified *de novo* HLA AB at different times after HT was performed. An assessment of the survival of recipients with HLA AB in the early and late posttransplant period, risk of transplant coronary artery disease (TCAD), a comparative characteristic of survival in patients with the AMR crisis and cell rejection.

Of the 34 recipients with HLA AB, DSA was identified in 16 (47,06%), 18 (52,94%) recipients had non-DSA.

Using Spearman's rank correlations, statistically significant (p<0,05), moderate associations between DSA and AMR crisis (rs=0,325) were revealed. We identified weak associations between DSA and TCAD (rs=0,224), weak associations between DSA and cell rejection crisis (rs=0,162).

The next stage, in order to assess the survival of heart recipients with identified HLA AB and prob-

ability of the recipient living for more than the specified period of time without AMR crisis and other complications of the posttransplant period, Kaplan-Meier survival curves were applied. We consider the development of a crisis or other complication as a complete event, no development — as censored event. Therefore, AMR risk (TCAD, cell rejection) will be called the probability that the patient could live longer than the specified time without this event.

To identify the risk of AMR developing in patients with HLA AB, Kaplan-Meier survival curves were constructed (Fig. 1). In patients with *de novo* HLA AB, the probability to live without an AMR crisis for more than 5 years, or rather 3,500 days, is only 29%. In the first 1000 days after HT, the survival curve decreases rapidly and from 1500 days to 3400 days, the curve stabilizes, and from 3400 days the risk of AMR sharply increases. At the same time, the probability of patients without HLA AB to live more than 3000 days without an AMR crisis is higher and equal to 80%. Figure 2 shows the ability to live longer than the specified time period without an AMR crisis in patients with *de novo* DSA and without DSA. It is seen that the risk of AMR crisis in patients with DSA is even higher than for patients with HLA AB *de novo*. The probability of living without AMR for more than 1000 days is only 0,19. That is, only 19% of recipients have a chance to live without AMR for more than 1000 days. At the same time, the risk of AMR in patients without DSA is much lower, so the probability of living more than 1,500 days is 80%, and the probability of living more than 3,400 days is 40%.

Analysis of the Kaplan-Meier curves for patients with DSA and other complications of the posttransplant period showed that the risk of cell rejection and TCAD in patients with DSA is lower compared to AMR. So, 78% of recipients are able to live without cell rejection for more than 1000 days, 62% can live more than 1800 days without TCAD. Figure 3 shows the survival graphs of recipients with and without HLA AB. Until 2000 days, survival is about the same. But, for a period of more than 2000 days, the survival rate of patients with HLA AB (59%) is lower than in patients without it (66%).

Survival of patients with and without DSA is shown in Figure 4. The graph shows that the probability of surviving more than 2000 days for patients with DSA is lower and equal to 40%, compared with patients without circulating DSA, in which the survival rate is 68%.

For a comparative analysis of the survival of patients with identified antibodies in the late period (three or more years after HT) and patients without HLA AB, Kaplan-Meier curves were constructed (Figure 5). The graph shows a sharp decrease in the survival curve after 1000 days for patients with antibodies detected in the late period. At the same time, the probability of surviving more than 1000 days for patients with HLA AB is 50%, for patients without HLA AB this probability is significantly higher and equal to 78%. In patients without HLA AB, there is a gradual decrease in survival function and by 6800 days is 68%, which is higher than survival rate in the same period of patients with HLA AB — 50%.

Figure 6, which shows the survival of patients with HLA AB that appeared in the early period (first month after HT), and without HLA AB, shows that the survival curve of patients with HLA AB, after about 300 days, sharply decreases by 400 days and reaches 75%. For patients without HLA AB, by 400 days there is a higher survival rate — approximately 85% of patients can live more than 400 days after HT, but overall, with an increase in the number of days lived, the survival rate decreases and reaches 65% by 1800 days, from 2000 days the survival rate stabilizes by level of 50%.

Thus, a comparison of the survival of patients with identified antibodies at different time periods after HT showed that HLA AB in the late period after HT lead to worse survival of recipients — 50%, compared with antibodies in recipients in the early posttransplant period — 75%

Neural network. Identified predictors can be used in the construction of an artificial neural network to determine the AMR risk. The program generated about 400 networks, from which a network with the best predictive efficiency was selected. The architecture of the two-layer perceptron consists of three layers. The first indicates the number of variables in the network model — 14, corresponds to the input parameters: eight quantitative — LV GLS, LV Rad S, LV Cir S, RV GLS, LV EDD, IVST, EF, RV and three qualitative parameters — DSA, non-DSA, HLA AB. Each can take on two values (yes, no), all in all qualitative variables take on 6 values. The intermediate layer contains 16 elements. On the last layer there are 2 neurons (yes, no) that predict the risk of AMR crisis. The fractions of correctly classified patients in the training, control and test samples took on the highest values — 100%, 100%, 89,47%, therefore we can consider the network acceptable for solving the problem of predicting the risk of AMR crisis. The total predictive capability of the network is 98,49%

Discussion

The study showed a low survival rate for patients with *de novo* HLA AB, especially with DSA — 40%, compared with recipients without DSA — 68%, which is comparable with data from other researchers. Smith JD, et al. performed a retrospective analysis of a group of recipients with *de novo* DSA and revealed low recipient survival (HR=3,198), which is comparable with the results of our study [9]. Similarly, by examining the survival of cardiac recipients with DSA, Coutance G, et al. found that 15-year survival was highest among recipients without DSA compared with those who identified DSA (70% versus 47%). Therefore, the screening and identification of HLA AB, in particular, *de novo* DSA, provides the most comprehensive information for the clinical observation of recipients with risk of AMR [10, 11].

The values of strain and heart mechanics in our study coincide with the normative range in healthy patients presented by the European Association of Echocardiography (EAE) [12, 13]. It was shown that AMR crisis in patients with and without antibodies to HLA, global peak systolic strain (-9,94±1,37%) can be used as predictor; Se — 86.2%; Sp — 90.4% radian systolic strain (19,36±3,66%); Se — 75,8%; Sp — 84,5%; circular systolic strain (-17,83±4,79%); Se — 78,6%; Sp — 84,4%, global stein of the right ventricle (-15,89±0,89%) at $p<0,001$. When LV GLS and longitudinal global strain of the right ventricle are taken into account, Se increases to 91,9%, Sp — to 94,6% ($p<0,001$) in the diagnostics of AMR.

Having carried out a multivariate analysis of the TTE parameters in the first observation period and before the development of severe rejection crisis, we were able to identify the predictors of the severe AMR; statistically significant changes at $p<0,05$ [14] were revealed for the parameters of LV EDD, LV IVST, EF and RV. Changes are most significant in patients with DSA.

The present study showed the relationship between changes in the parameters of strain and the mechanics of the heart transplant, parameters of TTE (volume of the left and right ventricles, ejection fraction, thickness of the interventricular septum) and immunopathological data, such as detection of HLA AB.

Conclusion

Screening and identification of *de novo* DSA with the aim of risk assessing and monitoring of AMR, provides the most comprehensive information for the clinical observation of heart recipients. Identified late HLA AB lead to AMR crisis and a decrease in survival.

A neural network model for determining the risk of AMR including the TTE predictors, 2D-STE, posttransplant HLA AB, age and gender of the recipient (the fractions of correctly classified patients took on the highest values — 100%, 100%, 89,47%). The total predictive capability of the network is 98,49%. A neural network may be acceptable for solving the problem of predicting the risk of AMR crisis.

Conflicts of Interest: nothing to declare.

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