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Experience of solid organ transplantation in the Krasnodar Region

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The article discusses the development of solid organ transplantation in the Krasnodar Region. The clinical efficacy of kidney, liver, and heart transplantation performed in the in the leading regional multidisciplinary clinic, the Research Institute – Regional Clinical Hospital No.1 n.a. Prof. S.V. Ochapovsky has been demonstrated. The authors have analyzed the changing trends in donor population structure and waiting list dynamics, and also the early and long-term postoperative outcomes in the Krasnodar Region.

Keywords: organ transplantation, heart, kidney, liver, postoperative complications, recipient survival

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CHF, chronic heart failure

HT, heart transplantation

LV, left ventricle

MOF, multiple organ failure

OLT, orthotopic liver transplantation

RRT, renal replacement therapy

Despite the achievements in the field of pharmacotherapy for solid organ diseases, transplantation remains the only treatment method for a number of patients that significantly improves their prognosis and quality of life. The implementation of donor organ transplantation should be concentrated in the leading federal or regional medical centers that have an up-to-date material-and-technical base and qualified medical personnel [1]. The Research Institute - Regional Clinical Hospital (RI-RCH) No.1 (headed by its Chief Physician V.A.Porkhanov, Professor, Academician of the Russian Academy of Sciences) is the medical institution in Krasnodar Krai (an administrative territory in southern Russia) that since 2009 has been the first medical center providing the patients suffered from end-stage diseases of solid organs with the opportunity to receive a high-tech treatment of transplantation that is a vital surgery for irreversible heart, lung, kidney, liver, and pancreas diseases. This article summarizes the information on the results of using the transplantation technologies in RI-RCH No.1.

Total 673 transplantations have been performed in RI-RCH No.1 of the Krasnodar Krai within the programme of providing the population with the high-tech medical care: namely, 172 heart transplants, 138 liver transplants, 353 kidney, 6 lung, and 4 pancreas transplants. More than 50% of heart transplant recipients were operated on at the age of 50-59 years, 13% underwent such surgery at over 60 years old, about 40% were patients from 18 to 50 years old. Similar age parameters may be seen among liver

recipients: 12% were over 60 years old, 38% were from 50-59 years, and about 40% were 35-49 years of age. The majority of patients undergoing kidney transplantation belong to the age groups of 35-49 years old (37%), and 50-59 years old (38%), 24% were people over 60. According to literature reports [2], in the period from 2001 to 2005, the countries of the European Union were facing a 2.5% annual increase in patients over 65 years on the waiting list for transplantation. Therefore, taking into account the tendency towards "aging" of the population, the experience of working with age recipients is necessary for every transplant center.

The estimated number of donors per 1 million population in the Krasnodar Krai is significantly higher than the mean for Russia, which can probably be explained by the presence of the transplantation center per se in the regional city, as well as by the coordinated interactions of various services organizing the transplant care. Doctors of all medical and prophylactic institutions of the region are well aware of the Transplantation Center potential in RI-RCH No.1. Five regions of the Krasnodar Krai most actively participating in the transplantation process are Krasnodar, Temryuk, Slavyansk-on-Kuban, Kanevskaya, Gelendzhik. Patients with severe brain injury (in coma assessed as Glasgow Coma Scale [GCS] 3) from regional hospitals are transported by sanitary aviation to the Neurological Intensive Care Unit of the Transplantation Center, where they are monitored and their vital functions are corrected in attempts to improve their clinical condition. Worthwhile to note that the health status of about 25% of potential donors admitted in the Transplantation Center is clinically improved as a result of successful resuscitation and rehabilitation measures, with the subsequent discharge from the hospital. Specifically, in the period of the Transplantation Center functioning from 2010 to 2015, of 520 patients with severe brain

injury (in coma scored 3 by GCS), 124 patients were clinically stabilized and transferred for the treatment and follow-up to the therapeutic and prophylactic institutions of the region. For many years, the age over 55 years old was the criterion for exclusion from organ donation; nowadays many centers regularly work with donors of significantly older age [3-6]. In our Center there is also a distinct tendency to "aging" among the donor population. So, the age of donors averaged 36.8 years old in 2010, 43 years old in 2016. Since 2015, there has been a significant increase in the number of donors older 50 years (Fig. 1).

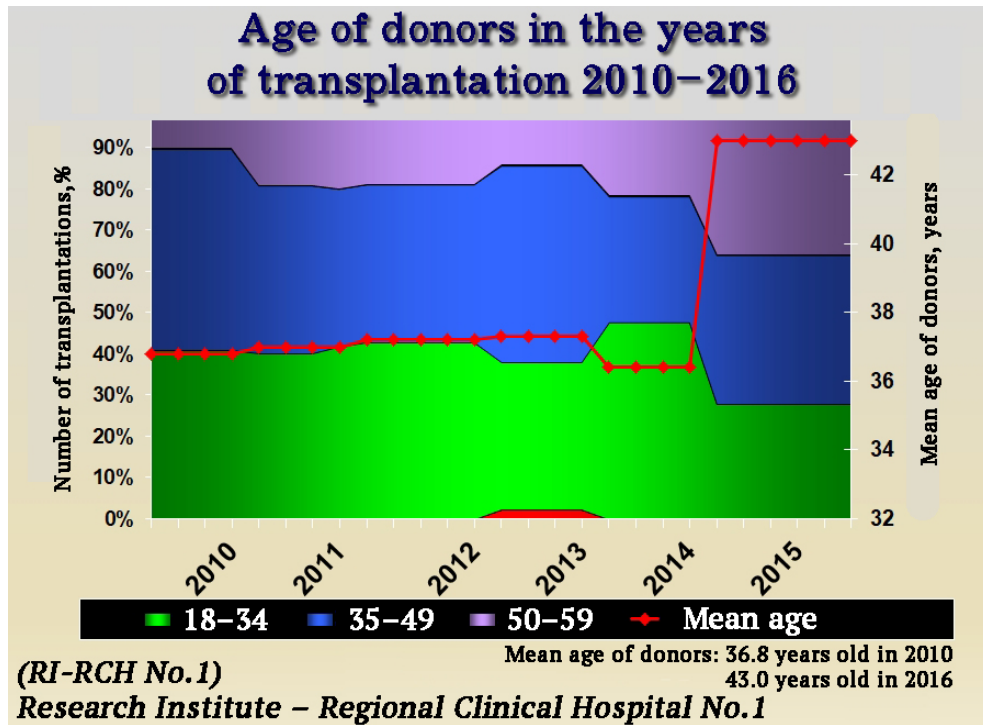


Fig.1. Age of donors in the years of transplantation 2010-2016

In Russia, there are more than 40 medical institutions where organ transplantations are performed with different degrees of activity: from several to 200 or more surgical interventions per year. The kidney

transplantation rate per 1 million population of Krasnodar Krai significantly exceeds the mean statistical level in our country (Fig. 2).

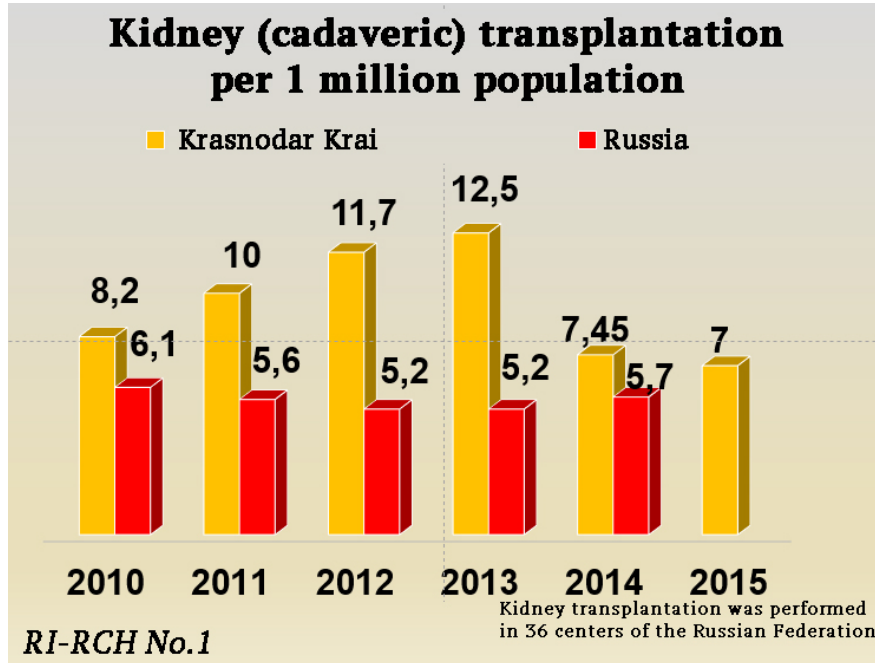


Fig. 2. Dynamics of kidney transplantation in 2010-2015

Liver transplantation in those years was performed in 14 centers of the Russian Federation. The numbers of operations per 1 million population of Russia, and Krasnodar Krai were 0.9, and 2.4 in 2010, 0.9 and 4.5 in 2011, and 3.7 and 1.2 in 2014, respectively. Similar rates were noted in the heart transplantation percentage of when compared to 9 centers of the Russian Federation performing such transplant operations in the studied period from 2010 to 2015 (Fig. 3).

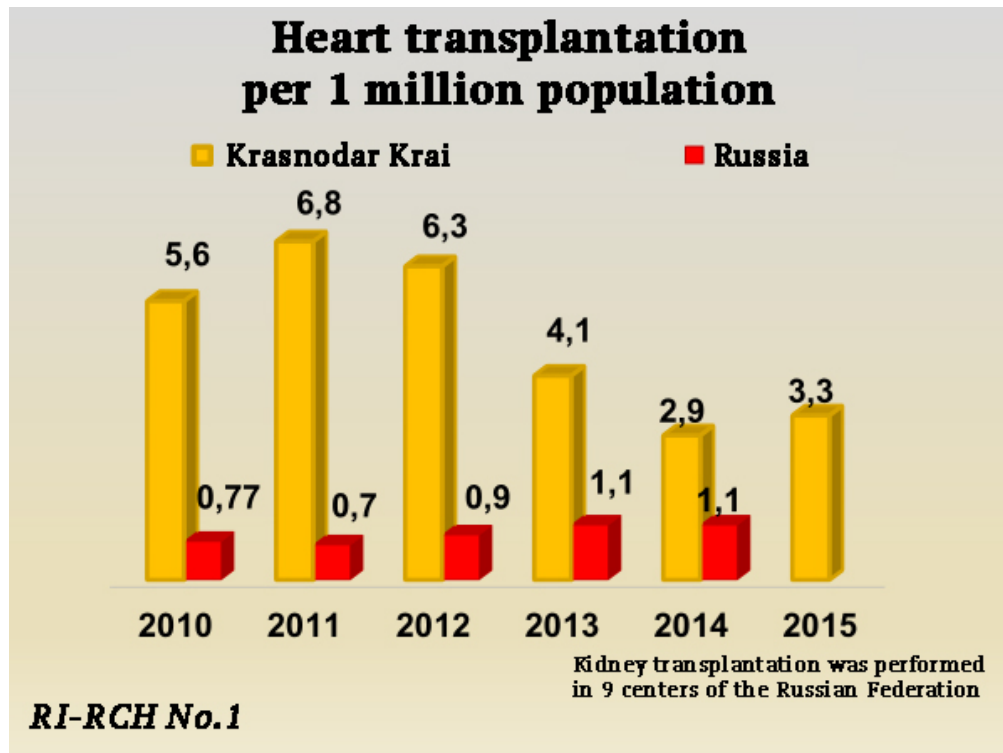


Fig. 3. Dynamics of heart transplantation in 2010-2015

Currently, there are 11 heart transplant centers in Russia, but only 4 of them make more than 10 transplantations a year. The analyzed dynamics of visceral organ transplantation confirms the steady growth of high-tech medical care potential both in the entire country and in Krasnodar Krai. This has been achieved as a result of using scientific, technological, and financial potential, as well as developing various options for working with donor bases. The decision on placing a potential candidate for transplantation on the waiting list is made by a multidisciplinary selection committee that includes surgical transplantologists, anesthesiologists, experts on other medical specialties (pulmonologist, cardiologist, hepatologist, gastroenterologist, nephrologist). It is well known that the waiting lists for organ transplantation are characterized by a high mortality rates and the increase due to adding new patients [7-8]. At present, the waiting list of the

RI-RCH No.1 includes 15 potential heart recipients, 250 potential kidney recipients, 29 liver and 11 lung recipients.

During the studied period, 332 kidney transplants were performed, 32 patients were switched to another renal replacement therapy (RRT). Four renal allograft recipients successfully carried out the pregnancy and gave birth. The main reasons for switching to another type of RRT were the renal allograft thrombosis (35%), the infectious process (35%), and chronic graft rejection (19%); 15 renal allograft recipients died, including 6 who died as a result of unfavorable infection course. Malignancies were verified in 3 recipients: the development of skin blastoma over the left frontal bone and interscapular area in 2, thyroid cancer in 1. The RI-RCH No.1 has the experience of a single-stage transplantation of the cadaveric kidney and pancreatoduodenal complex to 4 patients aged from 29 to 32 years. The first surgery was performed in 2012; 2 of 4 recipients currently have a satisfactory kidney and pancreas functions. The female patient operated on in 2014 returned to hemodialysis as a result of an early postoperative complication (thrombosis of vascular anastomoses). In a 29-year-old patient who underwent transplantation in 2012, the function of the transplanted pancreas was lost after an episode of intoxication with smoking compounds and alcohol in 2015; he was switched to insulin therapy, his kidney transplant functions satisfactorily.

The development of early postoperative complications often becomes fatal for a recipient survival. A particular problem is the bacterial invasion in the presence of immunosuppressive therapy. Since 2011, 6 lung transplants have been performed in our Center, 4 of them developed septic complications in the first 3 months post-surgery, which resulted in deaths. At present, 2 of 6 lung transplant recipients are alive. One patient underwent a

successful bougienage for cicatricial bronchial stenosis in the long-term postoperatively.

The first liver transplantation in RI-RCH No.1 was performed on May 7, 2010. Indications for transplantation included the end-stage viral invasion (54%), toxic hepatitis (7%), primary biliary cirrhosis (15%), malignant neoplasms (14%), including hepatocellular carcinoma resulted from viral cirrhosis, and cholangiocarcinoma. In 10% of cases, the etiology of the disease that caused severe hepatic insufficiency was not specified. In 4 cases, liver retransplantation was performed for fibrosing cholestatic viral hepatitis C of the graft. The results of liver cancer treatment (n=19, 14.7%) are as follows: 76% of patients were operated on in conformity with Milan Criteria; a further progression of the malignant disease after orthotopic liver transplantation (OLT) as observed in 42%, 6 patients died. Thirty-four patients had surgical complications after OLT, the most common being intra-abdominal bleeding (9.2%), stricture of biliary (9.2%) and arterial (4.5%) anastomoses, a small intestine perforation, intestinal fistula (2.5 %), and biloma of the abdominal cavity (2.5%). The dynamic postoperative observation of liver recipients demonstrated the following results: acute graft rejection occurred in 10.2%, and was controlled successfully with pulse therapy using immunosuppressants in all the cases; the recurrent autoimmune diseases were verified in 3 patients; 4 retransplantations were performed. In general, the survival rate of liver recipients operated on in RI-RCH No.1 is high, a 5-year recipient and graft survival was 113 of 136, respectively, which made 83.1%.

The first orthotopic heart transplantation (HT) in the Krasnodar Krai was performed in the RI-RCH No.1 in March 2010 in accordance with the

programme of providing the population with high-tech medical care. Currently the operative technique and perioperative support measures for the heart transplant recipients are being refined. In the period of 2010-2017, 172 HTs were performed, including as many as 17 in 2016; 13 patients were operated on for the expired period of 2017. The etiology of end-stage chronic heart failure (CHF) leading to making the decision on transplantation included the dilatation cardiomyopathy in 79 recipients (58.3%) and ischemic cardiomyopathy in 53 (38.2%), valvular pathology in 4 (3.5%). Earlier, 15 patients underwent heart surgery (11%). At the time of surgery, the condition of 98 patients (72%) was assessed as New York Heart Association Functional Class IV (1964). The echocardiography demonstrated a marked decrease of the left ventricle (LV) myocardial contractility (LV ejection fraction $16.7 \pm 4.9\%$, 6-27%), cardiomegaly (LV end-diastolic dimension 71.3 ± 9.8 mm, 35 -95 mm; LV end-diastolic volume 273.3 ± 84.2 ml, 52-724 ml), severe pulmonary hypertension (mean pulmonary artery pressure 55.6 ± 13.3 mm Hg, from 25 up to 82 mm Hg). The right heart catheterization demonstrated a high pulmonary artery pressure of 51.1 ± 14.3 mm Hg (from 17 to 58 mm Hg), high pulmonary capillary wedge pressure of 22.4 ± 13.9 mm Hg (ranging 4-41 mm Hg), high pulmonary vascular resistance making 4.2 ± 2.1 (from 2.1 to 10.7) Wood units, and a low cardiac index of 1.8 ± 0.5 l/min/m² (0.9-2.6 l/min/m²). An inhaled nitric oxide test was performed to all the patients in our center to determine if their pulmonary hypertension was reversible.

The most common causes of early mortality in heart transplant recipients were the infectious-septic complications and multiple organ failure (MOF) in 8 (80% of the deaths); 3 patients (30%) died due to the combination of sepsis and MOF, and 2 (20%) died of sepsis. In one case

(10%), the cause of death was pulmonary embolism on the 4th day after HT. Right ventricular failure in combination with other complications was noted in 17 patients (12.5%). Postoperative renal dysfunction was detected in 40 patients (29.4%). The kidney function in 10 recipients completely recovered after hemodialysis. Infectious complications during the hospital stay included pneumonia of bacterial etiology in 14 patients (10.3%), viral infections in 4 (3%). Suppuration of soft tissue in the postoperative wound was observed in 4 patients (3 %). An acute rejection reaction during hospital stay was diagnosed in 17 recipients (12.5%). Three patients (2.2%) had the permanent pacemaker implanted for the posttransplant third degree AV block and a sinus node weakness syndrome. Thromboembolism in the postoperative period was seen in 2 patients (1.5%). One of them developed massive pulmonary embolism (PE) with a fatal outcome on the 4th day after surgery. Seventeen recipients died in the long-term period; one patient died of myocardial infarction at 2 years after HT. In 1 case, the cause of death was the acute impairment of cerebral circulation developed at 4 months after HT. One patient died after 1.5 years due to the heart tumor development (highly-malignant non-Hodgkin's lymphoma). Another recipient had poorly differentiated non-keratinizing squamous cell carcinoma of the corpus spongiosum of the penis at 8 months after HT. In the long-term (up to 5 years), 95.04% of recipients were malignancy-free.

Among therapeutic complications after HT, there prevailed hypertension disease, myocardial infarction, coronary artery disease, pneumonia. The main cause of death in the long-term period was the rejection reaction in 13 cases (81%), and in combination with MOF in 5 cases. Therefore, the question of monitoring the cardiac allograft function and the early detection of rejection reactions remain invariably topical. In

most recipients, the graft rejection displays no clinical signs, which makes appropriate to perform regular endomyocardial biopsy examinations.

At present, there is a trend to reduce the number of control heart biopsies in favor of preferring non-invasive criteria to assess the graft rejection degree. A non-invasive, easy-to-use screening method was implemented in clinical practice of RI-RCH No.1. With the development of new EchoCG technologies and as a result of searching for objective quantitative measures to assess the local and global contractility, the speckle-tracking echocardiography technique has been developed, which improved the early diagnosis of cardiac allograft rejection and long-term prognosis in heart transplant recipients. This technique reflects the myocardium contractile properties on the subendocardial, myocardial, sub-epicardial levels, shows a preclinical impairment of systolic and diastolic functions and for the first time allows the heart mechanics parameters to be assessed. Using this technique for monitoring the recipients has demonstrated that the speckle-tracking echocardiography parameters are characterized by good prognostic value even in first degree rejection; the prognostic value increasing with the increase in rejection degree. When the speckle-tracking echocardiography was compared with the endomyocardial biopsy, the diagnoses coincided in 98% of cases in the recipient group without heart transplant rejection, 62% in those with the first degree of cellular rejection, in 88% of those with the second degree, and 87% of humoral rejection cases. A mathematical model for predicting the risk of heart transplant rejection by creating an artificial neural network allowed the recipients to be classified according to the degree of rejection identified by endomyocardial biopsy results.

At current stage of transplantation development, the recipient and cardiac graft survivals in the long-term are limited both by rejection reaction, and also by coronary artery disease and infectious complications. Vasculopathy after HT was seen in 9 cases (7.3%) in a planned endomyocardial biopsy; in all the cases, stenting of coronary arteries was performed. In the long-term (up to 5 years), 84.3% of our patients were vasculopathy-free. In the long-term period, the rejection reaction was observed in 10 cases making 7.8%; the infectious complications in the form of specific origin pneumonia (of mainly pneumocystis etiology) were seen in 12 cases (9.5%). At 1 year after HT, pulmonary actinomycosis was identified in 1 patient that was confirmed by its typical pattern at computed tomography, and by studying the tracheobronchial lavage contents. The lower lobe of the lung was resected. Some authors reported the most severe renal damage occurring in the first 6 months after HT, which is highly correlated with serum levels of calcineurin inhibitors. In our center, the renal dysfunction occurred in 3 patients in the first 6 months after HT, and in 5 more patients at a later stage. In the long-term (5-year) period, 77.5% were reported free from renal dysfunction, which is comparable to the ISHLT-reported data. In general, the recipient survival after HT was 72% as of 03.2017, which is comparable with the data reported by national and foreign transplantation centers.

The patients operated on in RI-RCH No.1 are generally followed-up by the Transplantation Center experts and receive the necessary medical care in medical facilities at their place of residence. The management of solid organ recipients is characterized by a number of specific factors that include the recipient's immunological response to the transplanted graft, the need in a lifelong immunosuppressive therapy, the specific course of the underlying

disease, and the individual aspects of the psychological, physical, and social adaptation. After transplantation, all patients receive the immunosuppressive therapy that is chosen to minimize the toxic effects of drugs on the recipient; routine pharmacokinetic studies are performed. Basing on the results of multi-center randomized trials, and clinical recommendations of leading foreign and Russian transplantologists, we prescribed the patients a two-component immunosuppressive therapy and, in some cases, a three-component treatment regimen adding glucocorticoids. According to current approaches, an early withdrawal of glucocorticoids or their dose reduction was attempted because of the significant undesirable reactions of this class of drugs; specifically, only about 10% of the liver transplant recipients received glucocorticoids. Unfortunately, besides this pharmacological class of drugs, virtually all immunosuppression effects are associated with a number of serious undesirable reactions, and therefore, additional diagnostic resources should be used to identify increased risks of graft rejection.

Summary

Data from the literature, as well as the analysis of our own experience of solid organ transplantation, have indicated the efficacy of this high-tech treatment technique and demonstrated the high graft and recipient survival rates in the patients operated on in RI-RCH No.1. Further increase in the number of transplantations, the improvements in the management of patients on the waiting list, the studies to find the ways of early diagnosis and treatment of complications in the early and long-term posttransplant periods are needed.

Conclusions

1. The donation coordinating system established in Krasnodar Krai is an effective regional system that implies both the existence of the transplantation center functioning in the regional city and the highly-coordinated interaction of various services in organizing the transplant care.

2. The positive experience of our center in raising the age of the donor pool allows us to hope for further expansion of donor programs, a more active use of the older age group donors, and the emergence of expanded criteria donors.

3. Data from the literature, as well as the analysis of our own experience of solid organ transplantation, have indicated the efficacy of this high-tech treatment technique and demonstrated the high graft and recipient survival rates in the patients operated on in RI-RCH No.1. The lethality and mortality rates do not exceed the figures presented in the world registries. It is necessary to improve the protocols of recipient's and donor's transplantation stages, to accumulate one's own experience, which would improve the quality and speed-up the development of this care in the Krasnodar Krai.

Conflict of interests. Authors declare no conflict of interest.

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References

1. Gautier S.V. Clinical transplantology as an independent direction of medicine. *Medical almanac*. 2008;(5 Special Issue):14–19. (In Russian).

2. Frei U., Noeldeke J., Machold-Fabrizii V. Prospective age-matching in elderly kidney transplant recipients – A 5-year analysis of the

Eurotransplant Senior Program. *Am J Transplant.* 2008;8(1):50–57. PMID:17973969 DOI:10.1111/j.1600-6143.2007.02014.x

3. León Díaz F.J., Fernández Aguilar J.L., Sánchez P.B., et al. Results of Liver Transplantation With Donors Older than 75 Years: A Case-Control Study. *Transplant Proc.* 2016;48(7):2499–2502. PMID:27742334 DOI:10.1016/j.transproceed.2016.08.021

4. Franco C.C., Martínez J.M., Bellido C.B., et al. Results of liver transplants from donors aged 70 plus: analysis of Andalusian transplant register. *Transplant Proc.* 2013;45(10):3647–3649. PMID:24314984 DOI:10.1016/j.transproceed.2013.10.024.

5. Grazi G.L., Cescon M., Ravaioli M., et al. Successful liver transplantation from a 95-year-old donor to a patient with MELD score 36 and delayed graft arterialization. *Am J Transplant.* 2008;8(3):725–726. PMID:18294175 DOI:10.1111/j.1600-6143.2007.02114

6. Poptsov V.N, Spirina E.A., Koloskova N.N., et al. Heart transplantation from older donors. *Russian Journal of Transplantology and Artificial Organs.* 2017;(1):89–102. (In Russian). DOI:10.15825/1995-1191-2017-1-89-102

7. Gerasimova O.A. Non-surgical aspects of liver transplantation: analysis of the waiting list of A.M. Granov Russian Scientific Center for Radiology and Surgical Technologies in 2000-2007. *Russian Journal of Transplantology and Artificial Organs.* 2008;5(43):8–12. (In Russian).

8. Khubutiya M.Sh., Andreytseva O.I., Zhuravel' S.V., et al. Procedure for drawing up and keeping a liver transplantation waiting list. *Transplantologiya. The Russian Journal of Transplantation.* 2009;(1):13–18. (In Russian).