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# EXPERIENCE OF OUTPATIENT FOLLOW-UP OF HEART TRANSPLANT RECIPIENTS AT SHUMAKOV CENTER

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Heart transplantation (HT) is considered the optimal therapy for end-stage heart failure. In recent years, the number of operations performed has been growing, which has led to a rise in the number of heart transplant recipients requiring outpatient follow-up. **Objective:** to evaluate the effectiveness of the model of dual personalized follow-up of heart transplant recipients in the consultative and diagnostic department of Shumakov National Medical Research Center of Transplantology and Artificial Organs. **Materials and methods.** The study included 1,436 patients under outpatient follow-up from January 2008 to December 2022. Recipient data, results of laboratory and instrumental examination methods, nature and frequency of complications at different follow-up periods were analyzed. **Results:** At the time of discharge from the hospital, 98.7% of patients had received triple-drug immunosuppressive therapy; 6 months later, methylprednisolone was discontinued in 72.2% of recipients. Mean tacrolimus level during the 1-year follow-up was 8.7 ± 2.7 ng/mL; in the period from 1 to 5 years of follow-up, the mean was 5.1 ± 2.4 ng/mL. At year 1 after transplantation, 23 (1.7%) recipients had been converted to everolimus; by the end of year 5 of follow-up, the number had increased to 8.6%. The most frequently detected complications during outpatient follow-up were: hypertension (48.65%), post-transplant diabetes mellitus (7.24%), nephropathy (35.97%), and malignant neoplasms (4.2%). Recipient survival, excluding in-hospital mortality, was 96.5%; and 88.0% at year 1 and 5 of follow-up, respectively. **Conclusion:** The dual personalized approach model for outpatient follow-up and treatment of heart transplant recipients will improve recipient survival and quality of life in the long-term post-HT period.

*Keywords: heart transplantation, vasculopathy, kidney failure, post-transplant diabetes mellitus, malignant neoplasms, hypertension.*

## INTRODUCTION

Heart transplantation (HT) is a high-tech medical care for patients with end-stage chronic heart failure. It is aimed at prolonging and improving the quality of life in this patient cohort [1]. In Russia, the first successful HT was performed on March 12, 1987 at Shumakov National Medical Research Center of Transplantology and Artificial Organs ("Shumakov Center"). Since that time, the research center has taken a leading role in providing transplantation care to patients with end-stage organ diseases, including the heart [2, 3]. Apart from surgical care, the ideology of the research center involves monitoring organ recipients in the long-term postoperative period, which allows to keep statistical records and analyze the survival rate in the post-transplant long-term period. Today, against the background of improving the organization of organ donation in our country, improving peri- and postoperative management of heart recipients, and the emergence of new effective immunosuppressive agents, the number of orthotopic heart transplant operations performed has doubled. This has led to a threefold increase in the number of recipients living with a transplanted heart. By early 2018, the number of such recipients had exceeded 800 [4]. Follow-up of heart transplant recipients after discharge from the hospital involves a multidisciplinary approach to improve their quality of life, prevent complications and ensure early detection of complications that emerge at different periods after surgical intervention. The outcomes of heart transplantation in the long-term follow-up period depend, among other things, on the professional management of the recipient at the outpatient follow-up stage. The role of the outpatient physician includes deciding on the frequency of visits, monitoring immunosuppressive therapy, determining indications for hospitalization, explaining certain treatment guidelines, encouraging adherence to treatment and lifestyle modification.

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In our country, Shumakov Center is the leading institution in providing this type of medical care [2]. Therefore, the center has unique experience in outpatient follow-up of heart transplant recipients.

The aim of our work is to evaluate the effectiveness of the model of dual personalized follow-up of heart transplant recipients at the Consultative and Diagnostic Department, Shumakov Center.

## MATERIALS AND METHODS

After discharge from the hospital, the patients' health status was monitored by a cardiologist at the Consultative and Diagnostic Department, Shumakov Center, as well as by health care specialists at the patient's place of residence. Physicians from Shumakov Center improve their professional level of training, undergoing regular training, on-the-job training, and also participate in Russian and foreign conferences and congresses. The procedure for follow-up of heart transplant recipients was developed empirically, based on long-term experience monitoring this patient cohort (see Table 1). Specialists from Shumakov Center conducted remote consultations with local physicians and/or heart transplant recipients by telephone or via the Internet. Annually and if there were indications for hospitalization, the recipients were hospitalized in the cardiology ward of Shumakov Center for more in-depth examination and correction of drug therapy.

All patients underwent routine general clinical examination: history taking, physical examination methods, as well as the necessary range of instrumental and laboratory methods of diagnosing graft function: echocardiography to assess graft function, electrocardiography to detect rhythm problems. Where necessary, additional examination methods were performed depending on the patient's current condition.

All patients received multicomponent immunosuppressive therapy including a combination of calcineurin inhibitors (tacrolimus, Tac), cytostatics (mycophenolic acid or mycophenolate mofetil (MMF)) or proliferative signaling inhibitors (everolimus, EV), methylprednisolone. Drug dosage depended on the time since the surgical intervention and graft rejection frequency. Delayed conversion to EV was performed in case of chronic graft rejection (cardiac graft vasculopathy), progression of renal failure on the background of long-term intake of calcineurin inhibitors (CNI) and detection of malignant neoplasms. The side effects of immunosuppressive therapy were evaluated based on glomerular filtration rate (GFR) level; assessment of neurological status; oncological screening and others.

Immunosuppressive therapy was monitored by assessing the target serum levels of immunosuppressive drugs on a Cobas e411 analyzer (Roche, Switzerland) by electrochemiluminescence immunoassay.

Coronary angiography and endomyocardial biopsies were performed during the first week after surgical intervention, then according to the examination schedule or as indicated. Acute cellular rejection was diagnosed based on the results of histochemical study of endomyocardial biopsies. The diagnosis of antibody-mediated rejection was made according to the ISHLT-2013 classification (M.E. Hammond et al., 2016).

Data are presented as arithmetic mean and standard deviation (M ± SD). The Kaplan–Meier survival regression analysis method (IBM SPSS Statistics 23) was used to estimate event-free survival.

## RESULTS

For the period from January 2008 to December 2022, 1,775 heart transplants were performed at Shumakov Center. This included 51 heart retransplants and 4 heart re-retransplants. Cases of heart retransplantation, hospital mortality, and recipients under 18 years of age were excluded from the study. Thus, the study included 1,436 heart transplant recipients who underwent outpatient follow-up at Shumakov Center from January 2008 to December 2022.

One of the tasks of outpatient follow-up is to assess the efficacy and safety of ongoing immunosuppressive therapy. The efficacy of therapy was evaluated based on the results of endomyocardial biopsies performed. Safety was assessed based on the obtained blood levels of CNI and proliferative signaling inhibitors, as well as detection of side effects on the background of long-term use of immunosuppressive drugs. At the time of hospital

Table 1

**Outpatient follow-up plan and planned admission of heart transplant recipients**

| | Post-HT timeline | | | | |
|---|---|---|---|---|---|
| | First 4 weeks | 1–3 months | 4 months – 1 year | 1–5 years | >5 years |
| Outpatient visit | Once a week | Once every 2 weeks | Once every 3 months | Once every 3–6 months | Every 6 months |
| Blood test | Once a week | Once every 2 weeks | Once every 3 months | Once every 3 months | Once every 6 months |
| Heart biopsy | – | – | Once every 6 months | Once a year | Once a year |
| ECHOCG | Once a week | Once every 3 months | Once every 3 months | Once every 6 months | Once every 6 months |
| Coronary angiography | – | Once a year | Once a year | Once a year | Once a year |

discharge, 98.7% of patients (n = 1,418) received triple-drug immunosuppressive therapy – Tac, MMF, and methylprednisolone; 1.3% (n = 18) of recipients received double-drug immunosuppressive therapy (Tac + MMF).

In case of planned postoperative period, low immunologic risk and absence of data on acute graft rejection crises. Immunosuppressive therapy was adjusted 6 months after operation. So, methylprednisolone was withdrawn in 1,123 (72.2%) recipients, the rest 313 (21.8%) continued to receive triple-drug immunosuppressive therapy.

Analysis of Tac serum levels showed that mean serum level of the drug at year 1 of follow-up was 8.7 ± 2.7 ng/mL. Subsequently, the drug dose was reduced, which resulted in lower Tac levels – 5.1 ± 2.4 ng/mL in the period from 1 to 5 years of follow-up. In several cases, outpatient examination revealed reasons for late conversion to proliferative signaling inhibitors in order to reduce CNI doses. The reason for conversion in 23 (1.7%) recipients was progressive nephropathy and early development of cardiac graft vasculopathy. By the end of year 5 of follow-up, the proportion of patients converted to EV increased to 8.6. The mean serum EV levels during the observation period were 3.8 ± 2.1 ng/mL. Despite daily administration of immunosuppressants, development of acute cellular and antibody-mediated rejection in this patient cohort cannot be ruled out. Outpatient detection of first-occurring cardiac rhythm disturbances, decreased left ventricular ejection fraction, as well as decreased tolerance to physical exertion, were a reason for hospitalization of recipients in order to rule out acute transplant rejection response.

Between January 2008 and December 2022, 5,274 endomyocardial biopsies were performed. Acute cellular rejection developing during the first year of follow-up was diagnosed in 841 (27.5%) recipients. According to the international classification, mild rejection (R1G) was diagnosed in 786 (25.7%) cases, moderate rejection (R2G) was diagnosed in 48 (1.57%) recipients, and severe (R3G) cardiac graft rejection was detected in 0.23% (n = 7) of cases. One year after HT, there was a decrease in the incidence of acute cellular graft rejection crises development, which was confirmed by the results of biopsy material examination. Thus, in the period from 1 year to five years, R1G rejection was diagnosed in 55 (2.48%) and R2G in 13 (0.59%) recipients. No severe degree of cellular rejection, according to endomyocardial biopsies, was revealed. The incidence of antibody-mediated rejection at different follow-up periods was 7.17%.

Annual hospitalization of heart transplant recipients to assess the coronary artery and diagnose cardiac graft vasculopathy is mandatory when monitoring this category of patients. The absence of innervation of the donor heart and clinical manifestations of angina makes it difficult for early detection of myocardial ischemia, which may lead to irreversible consequences.

Cardiac graft vasculopathy was diagnosed in 286 recipients. Percutaneous coronary intervention was required in 47% (n = 134) of cases at different follow-up periods. Indications for myocardial revascularization were coronary lesions with stenosis >70% with the possibility of balloon angioplasty with stenting. In the remaining 152 patients, graft vasculopathy was characterized by obliteration of the distal channel, which technically did not allow to perform myocardial revascularization. After one year of follow-up, cardiac graft vasculopathy was diagnosed in 2.3% of patients. After 3 and 5 years of follow-up, chronic graft rejection was diagnosed in 12% and 17% of recipients. The data obtained indicate that in the period from 3 to 5 years of follow-up, there is a tendency for graft vasculopathy to progress.

Among the heart transplant recipients observed, high blood pressure (HBP) was one of the modifiable risk factors for adverse events, including cardiac graft dysfunction. During the first year of outpatient follow-up, HBP of varying severity was diagnosed in 37.87% of heart transplant recipients. At year 5 of follow-up, the number of patients with HBP had increased to 48.65%; by year 9 of follow-up, the proportion of recipients suffering from HBP was 60.4%. Fig. 1 shows the dynamics of HBP detection depending on the period after the surgical intervention.

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), slow calcium channel blockers (CCBs), diuretics (thiazide or loop diuretics, depending on the GFR) were prescribed as antihypertensive therapy. Drug doses were titrated individually depending on blood pressure fluctuation during the day. Fig. 2 shows the main groups of antihypertensive drugs prescribed for heart transplant recipients.

In our observation, the proportion of patients who required triple-drug antihypertensive therapy was 18% of recipients.

Post-transplant diabetes (PTDM) is a pathognomonic feature of the course of the long-term postoperative period and a risk factor for cardiovascular complications in patients with transplanted heart. Fig. 3 shows the frequency of detection of posttransplant diabetes in outpatient recipients.

All patients with PTDM (n = 298) received therapy to maintain normal blood sugar levels. Discussions on the importance of lifestyle modification and dietary adherence were also conducted on an outpatient basis. Of the 298 recipients with PTDM, 11.4% (n = 34) received insulin therapy; in the remaining 88.6%, maintenance of normal blood sugar levels was achieved by taking tablet forms of sugar-lowering drugs. Therapy effectiveness was evaluated by the level of glycated hemoglobin.

One of the aims of outpatient follow-up of heart transplant recipients is to assess renal function in order to rule out nephropathy against the background of long-term use

of CNIs. At the time of discharge from the hospital, the average rate of GFR was 89.11 ± 24.28 mL/min/1.73 m$^2$. At control outpatient visits during year 1 of follow-up, stage 3a chronic kidney disease (CKD) (GFR 53.15 ± 3.68) was diagnosed in 132 patients, stage 3b in 92 (GFR 39.07 ± 4.61), stage 4 in 48 (GFR 23.87 ± 3.87) and stage 5 was detected in 18 (GFR 8.3 ± 0.82) patients.

By the end of year 5 of follow-up, mean GFR was 74.92 ± 19.54 mL/min/1.73 m$^2$. Thus, after 5 years of follow-up, the proportion of patients with CKD increased

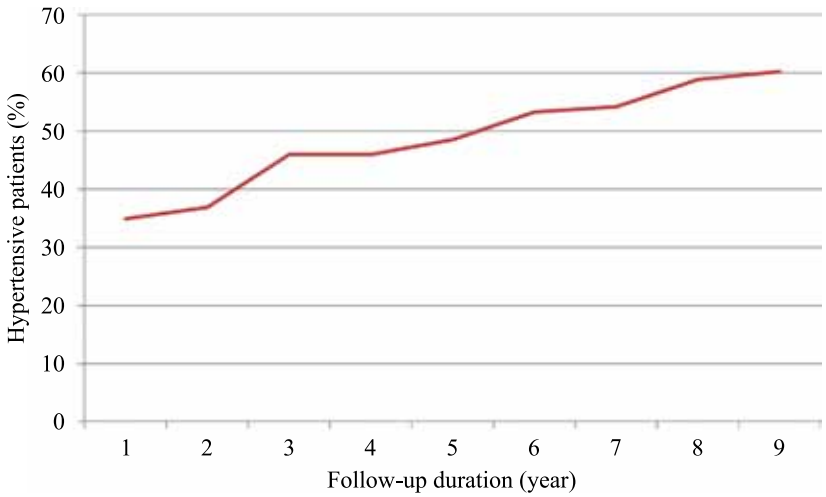


Fig. 1. Frequency of HBP detection depending on follow-up duration

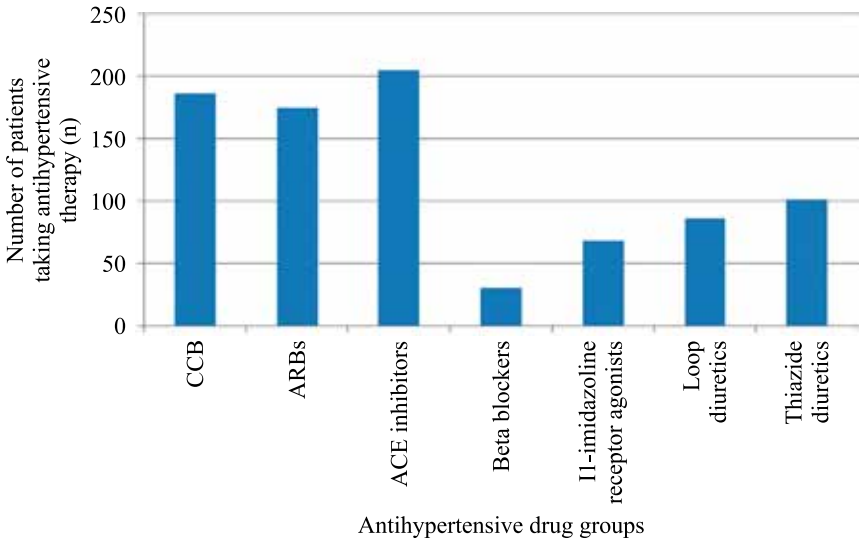


Fig. 2. Antihypertensive drug groups. CCB, slow calcium channel blockers; ARBs, angiotensin receptor blockers; ACE inhibitors, angiotensin-converting enzyme (ACE) inhibitors; I1-imidazoline receptor agonists

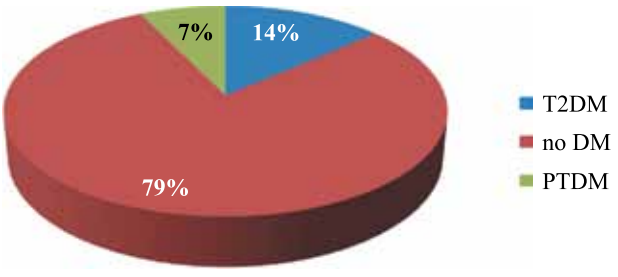


Fig. 3. Type 2 diabetes mellitus and post-transplant diabetes mellitus in heart transplant recipients. T2DM, type 2 diabetes mellitus; PTDM, post-transplant diabetes mellitus

with this patient cohort. Studies conducted in different periods of time at Shumakov Center have shown that complex therapy, including immunosuppressive therapy in combination with adjuvant therapy, significantly improves long-term survival in heart transplant recipients [4–6]. The personalized approach led to improvements in survival curves between time intervals 2007–2009, 2010–2012, 2013–2015, 2016–2018 and 1986–1991; 1992–1997, 1998–2003, and 2004–2006. However, since 2007, long-term survival rates have reached a plateau, and the median survival rate is 10.3 years, which requi-

and was distributed as follows: 260 recipients with stage 3a CKD (GFR 54.12 ± 4.75), 160 patients suffered from stage 3b CKD (GFR 38.45 ± 4.43), 68 recipients had stage 4 CKD (GFR 26.52 ± 2.84), end-stage CKD was diagnosed in 25 patients (GFR 8.1 ± 3.54). Twenty heart transplant recipients required long-term renal replacement therapy. After clinical and instrumental examination, 11 heart transplant recipients were included in the kidney transplant waiting list, seven of them underwent successful kidney transplantation within 6 months to one year.

When assessing the incidence of malignant tumors, it was found that at the follow-up period of 5–6 years after surgery, oncopathology was diagnosed in 61 recipients. The most common cancers were skin cancer (19.7%), lung cancer (16.4%), gastric cancer (16.4%), colorectal cancer (14.7%), oral cancer (9.8%), prostate cancer (6.6%), hepatocellular carcinoma (4.9%), thyroid cancer (4.9%) and others (6.6%).

Most recipients suffering from oncopathology were persons of working age from 40 to 65 years old.

When analyzing the causes of adverse events among outpatient recipients, it was shown that the main cause of mortality in the first year of follow-up was acute graft rejection. During the next 5 and 10 years of follow-up, most deaths were due to graft dysfunction on the background of coronary vasculopathy and oncologic diseases (see Table 2).

Survival analysis of heart transplant recipients, excluding in-hospital mortality, showed that survival at year 1, 5, and 10 of follow-up was 96.5%;, 88.0%, and 53.4%, respectively (see Fig. 4).

Median survival, excluding in-hospital mortality, is 10.5 years.

## DISCUSSION

Results of this study have shown that outpatient follow-up of heart transplant recipients within the framework of personalized approach to medical care with the involvement of specialists from Shumakov Center and primary outpatient physicians allows for early correction of immunosuppressive therapy and detection of complications developing at different follow-up periods. The dual control model allows for professional consultations of patients at the transplant center. It also facilitates better professional training of local specialists working

Table 2

**Causes of mortality at different follow-up periods after heart transplantation**

| Cause of death | 1-year follow-up (n = 50) | 5-year follow-up (n = 122) | ≥10-year follow-up (n = 74) |
|---|---|---|---|
| Cardiac allograft vasculopathy | 10 (4.06%) | 45 (18.29%) | 23 (9.35%) |
| Rejection | 23 (9.35%) | 23 (9.35%) | 10 (4.06%) |
| Cancer | 2 (0.81%) | 16 (6.5%) | 10 (4.06%) |
| Infection | 6 (2.44%) | 16 (6.5%) | 18 (7.32%) |
| Multiple-organ failure | 8 (3.25%) | 11 (4.47%) | 9 (3.66%) |
| Cerebrovascular complications | 1 (0.41%) | 4 (1.63%) | 2 (0.81%) |
| Other causes | – | 5 (2.03%) | 2 (0.81%) |

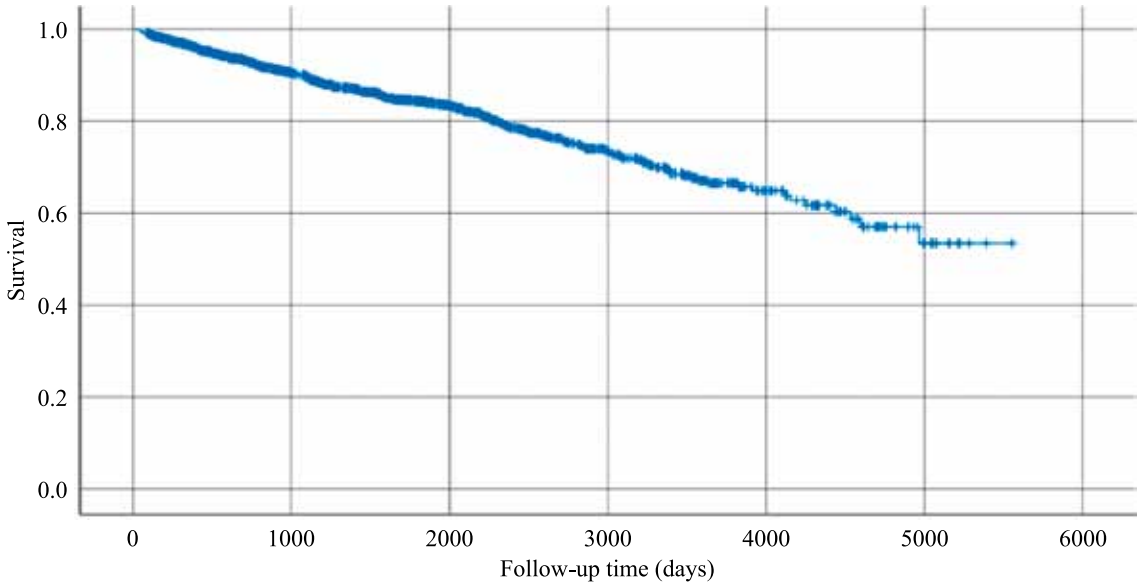


Fig. 4. Recipient survival

res further improvement and the development of new algorithms for outpatient care for heart transplant recipients, taking into account the increasing number of heart transplants performed annually [7].

## CONCLUSION

The main objective of the Consultative and Diagnostic Department, Shumakov Center, is to implement a personalized approach to the monitoring and treatment of patients after HT. This includes individual immunosuppressive therapy regimens, laboratory and instrumental diagnostic methods that are aimed at early detection of complications and determination of further treatment tactics. We believe that this approach will improve survival and quality of life of heart transplant recipients in the long-term post-HT period.

*The authors declare no conflict of interest.*

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