

Преживување кај нашите пациенти изнесува 92.1%, а петгодишното преживување е 82.75%. Најчеста причина за развој на терминална цирнодробна болест кај нашите трансплантирани пациенти е цироза, асоцирана со ХБВ инфекција (кај 33.3% од пациентите), потоа следуват среќава тромбоза на хепатичната артерија, а билијарните компликации типот на стеноза на анастомозата се најчести во подоцнежниот период. **Клучни зборови:** Црнодробна трансплантација, следење, рани и касни компликации

**FOLLOW-UP OF PATIENTS AFTER LIVER TRANSPLANTATION WITH EMPHASIS ON THE OCCURRENCE OF SHORT-TERM AND LONG-TERM COMPLICATIONS - SINGLE CENTER EXPERIENCE**

**B. Todorovska<sup>1</sup>, K. Grivcheva Standelova<sup>1</sup>, N. Joksimović<sup>1</sup>, M. Genadieva-Dimitrova<sup>1</sup>, M. Trajkovska<sup>1</sup>, R. Porova<sup>1</sup>, Jovanovska<sup>1</sup>, G. Deriban<sup>1</sup>, F. Lichoska Josifovikj<sup>1</sup>, V. Andreevski<sup>1</sup>, E. Surakova Ristovska<sup>1</sup>, E. Nikolovska Trpchevska<sup>1</sup>, A. Volkanovski<sup>1</sup>, Nikolovska<sup>1</sup>, A. Karadzova Dzatbaz<sup>1</sup>, Adem Dz<sup>1</sup>, G. Krstevski<sup>1</sup>, F. Nikolov<sup>1</sup>, S. Antovic<sup>2</sup>**

<sup>1</sup>University Clinic of Gastroenterohepatology, Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, RN Macedonia  
<sup>2</sup>University Clinic of Digestive Surgery, Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, RN Macedonia

**Introduction:** Liver transplantation is the only curative method for the treatment of end-stage liver disease, acute liver failure or hepatocellular carcinoma within the Milan criteria. It was first performed more than 55 years ago. The survival rate after liver transplantation has increased over time, it is now 96% after the first year, and 71% after ten years. The better survival rate is due to several achievements: effective immunosuppressive drugs, new solutions for preservation, improved surgical techniques, as well as early diagnosis and successful management of post-transplant complications. There are short-term and long-term complications after liver transplantation. The short-term complications include:

1. Allograft primary non function (usually needs re-transplantation)
2. Hepatic artery thrombosis (prompt intervention - thrombectomy can save the graft and prevent the need for retransplantation)
3. Biliary leakage or obstruction
- 4 Hemorrhage

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1. Intra-abdominal sepsis
  2. Thrombosis of the portal vein or VCI,
  3. Acute cellular graft rejection, etc.
- Long-term complications after liver transplantation are following:
1. Chronic allograft dysfunction-CAD
  2. Renal dysfunction (mostly caused by CNJ-based immunosuppressants)
  3. Cardiovascular diseases
  3. Diabetes mellitus
  1. Dyslipidemia
  2. Obesity
  3. Osteoporosis

Infections, most commonly CMV infections, most commonly CMV infections, most commonly CMV infections, followed by post De novo malignancies (skin tumors-most common, followed by post transplant lymphoproliferative disease (PTLD), etc).  
 Recurrence of underlying liver disease (hepatitis C infection-in 90%, PBC- 20-50%, autoimmune hepatitis-in 20-30%, PSC-in 20-30%, hepatitis B infection-in 10%, NAFLD -at 20-40%)  
 De novo liver disease (NAFLD-due to the presence of HTA, DM, dyslipidemia, HIV-most common in the pediatric population, Hepatitis B and C

**aim of the study:** To review the follow-up of liver transplant patients in our country with an emphasis on the occurrence of short-term and long-term complications after liver transplantation.

**Material and methods:** Liver transplant patients (42 in total) are followed-up regularly at the University Clinic for Gastroenterohepatology in Skopje, regardless of whether they were operated on in our country or abroad. In the past, most of the patients were sent abroad for living donor liver transplantation (34 patients in total), and the remaining eight patients underwent cadaveric transplantation (six patients in another country). In November 2022, the first deceased donor liver transplantation was performed in our country, and soon after the second one, thus starting a new chapter in our healthcare system in terms of treating patients with end stage liver disease.

Frequency of patient follow-up depended on how much time had passed after transplantation. Thus, at the beginning or the first month after discharge from the transplant center, patients are monitored more frequently or once a week, then every two weeks after 2-3 months of discharge, and once a month after the fourth month to the end of the first year. After the first year from transplantation, the follow-up is extended to six months. Necessary analyzes for follow-up the patient are the following:  
 Blood count, hepatogram with bilirubin, INR, protein status, degradation products, creatinine clearance, electrolyte status, 24 hour proteinuria, urine

СЕСИЈА 5

- culture, lipid status, glycemia with HbA1c, TSH, FT4
- Concentration of the immunosuppressant in the blood
- Abdominal ultrasound examination with Doppler of the abdominal blood vessels
- HBsAg and AntiHBs titer for HBV positive patients
- HCV RNA for HCV positive patients
- Evaluation of patients after 1, 5, 10, 15, 20...years after transplantation includes more extensive analyzes besides the basic ones, such as:
- Tumor markers: CEA, CA 19-9, CA 125
- Autoantibodies: ANA, AMA, ASMA, LKM, PANCA
- Virological profile for HAV, HBV, HCV, CMV, EBV, HIV, Herpes, Toxoplasmosis, Syphilis
- ECG and cardiac examination
- X-ray of lungs and pulmonary examination
- Liver biopsy under US control (only in patients with HCV infection is done every year)
- CT of abdomen and lungs
- Dermatovenereological examination
- Gastroscopy
- Colonoscopy

**Results:** So far, starting from 1997, 42 transplanted patients have been monitored (8 from a cadaver and 34 from a living donor). Of them, a total of 9 have died, namely: two died during transplantation (4.76%), two died after retransplantation (one after 9 years from the first transplantation, the other after 4 years from the first transplantation) - 4.76%, one died during the first year of transplantation (due to postoperative complications with the biliary anastomosis), one died after 4 years (due to COVID, but with many associated comorbidities), two died after 10 years (as a result of ABI and massive upper digestive bleeding due to marked portal hypertension), one died after 12 years (due to lung cancer).

One-year survival (of 38 patients - 3 deceased) is 92.1%, and five-year survival (of 29 patients - 5 deceased) is 82.75%

From the etiological point of view, the largest number of transplanted patients (14 in total) had cirrhosis associated with HBV infection, seven had immunogenic cirrhosis, four had alcoholic liver disease, three patients had cryptogenic cirrhosis, primary sclerosing cholangitis and Budd Chiari's syndrome. Two patients each, had cirrhosis associated with HCV infection and primary biliary cirrhosis and one patient each had acute M. Wilson, HCC, HCC with portal simultaneous presence of cirrhosis associated with HCV infection and biliary atresia (Table No.1)

**Table No 1 (Etiology of previous liver disease)**

Etiology of previous liver disease	Number of patients (%)
Alcoholic cirrhosis	4 (9,5)
Cirrhosis associated with HBV infection	14 (33,3)
Cirrhosis associated with HCV infection	2 (4,7)
PBC	2(4,7)
PSC	3(7,2)
M. Wilson	1(2,4)
Budd Chiari Sy	3(7,2)
Immunogenic cirrhosis	7 (16,6)
Cryptogenic cirrhosis	3 (7,2)
HCC	1 (2,4)
HCC+HCV	1(2,4)
Biliary atresia	1(2,4)
	42 (100)

СЕСИЈА 5

**Short-term complications (Table No. 2) after liver transplantation in our group were as follows:** Thrombosis of the hepatic artery, in a total of 4 patients, in which one patient underwent retransplantation, and in the remaining three, revascularization with thrombectomy, placement of a vascular stent and creation of a new arterial anastomosis were successfully performed. Occurrence of biliary bilomas detected in three patients, which subsequently spontaneously resorbed. In two patients, primary dysfunction of the graft was present with the need for retransplantation, one was successful, and the second was fatal. A biliary stent was placed in one patient due to biliary obstruction in the early postoperative period. Occurrence of intra-abdominal bleeding was observed in two patients and both were successfully reoperated. One patient had a complicated postoperative course, with the appearance of an ischemic non-anastomotic biliary stricture, for which percutaneous biliary drainage was performed, but despite the intervention, the development of cholangitis, with a subsequent septic condition, multi-organ failure and ultimately fatal outcome. After the first month of transplantation, one patient had an episode of acute graft rejection that was successfully resolved with methylprednisolone pulse therapy. One patient developed portal vein thrombosis three months after transplantation, which was resolved with anticoagulant therapy (low molecular weight heparin-LMWH).

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**Table No. 2 (Short-term complications after liver transplantation)**

Short-term complications after liver transplantation	Number of patients
Hepatic artery thrombosis	4
Biliary obstruction /	1
Biloma	3
Allograft primary non function	2
Acute cellular graft rejection	1
Intraa-abdominal hemorrhage	2
Sepsis	1
Thrombosis of the portal vein	1

CECИJA 5

The most frequent of the long-term complications (Table no. 3), in a total of patients, are stenoses of the biliary anastomosis, which are usually solved by plad a biliary endoprosthesis endoscopically, and less often by percutaneous bilia drainage or surgically by creating a hepatic-jejunal anastomosis. This is followed cardiovascular diseases in a total of seven patients, with a predominant appearer of arterial hypertension, who are treated with regular antihypertensive therap immunosuppressive therapy often leads to obesity (in 6 patients) despite dieta advice. Type 2 diabetes mellitus, treated either with oral antidiabetics or insul therapy, was noted in five patients. Renal dysfunction due to immunosuppressi therapy was present in five patients, and four patients suffered from dyslipidem treated with statins. De novo malignancy was diagnosed in four patients, of whi two patients were successfully operated for skin cancer, one patient was successfu treated according to the CHOP protocol + Rituximab for Non Hodgkin Lymphor (diffuse large B cell) after which she went into remission, and one patient endi fatally after the appearance of squamous cell carcinoma of the left lung treat with chemotherapy. De novo liver disease was detected in four patients, in one the NAFLD type, in two of the secondary biliary cirrhosis type, one patient had th occurrence of De novo hepatitis B virus infection, treated accordingly with antivir therapy, and there was a recurrence of viral C infection at one patient, cur adequately with the new DAA drugs. Three patients were treated with Allopurin therapy due to hyperuricemia. Osteoporosis was noted in one patient, and due an increased risk of infections as a result of immunosuppression, one patient ha a CMV infection successfully treated with virostatic and one patient received dep penicillin due to recurrent erysipelas.

**Table No. 3 (Long-term complications after liver transplantation)**

Long-term complications after liver transplantation	Number of patients
Stenosis of biliary anastomosis	10
Cardiovascular diseases	7
Obesity	6
Diabetes mellitus	5
Renal dysfunction	5
Dyslipidemia	4
De novo malignancies	4
Skin tumors	2
Squamous cell carcinoma of the lung	1
Non Hodgkin Lymphoma (diffuse large B cell)	1
Recurrence of underlying liver disease	1
Hepatitis C infection	1
De novo liver disease	4
NAFLD	2
Secondary biliary cirrhosis,	1
Hepatitis B infection	1
Hyperuricemia	3
Osteoporosis	1
Infections	2
CMV infections	1
Recurrent erysipelas	1

SESSION 5

**Conclusion:** Follow-up of patients after liver transplantation is of particular importance, with the aim of early detection and appropriate treatment of both, short-term and long-term complications. One-year survival in our patients is 92.1%, and five-year survival is 82.75%. The most common reason for the development of end-stage liver disease in our transplanted patients is cirrhosis associated with HBV infection (in 33.3% of patients), followed by immunogenic cirrhosis, in 16.6%. Thrombosis of the hepatic artery is the most common short-term complication, and biliary complications such as stenosis of the anastomosis are most common in the later period.

**Key words:** liver transplantation, follow-up, short-term and long-term complication