

# Twenty Years of Experience in Liver Transplantation in Slovenia

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## ABSTRACT

Liver transplantation is a successful way of treatment for patients with liver cirrhosis with complications, acute (fulminant) hepatic failure, liver tumors, and liver-based metabolic disorders. 283 patients underwent liver transplantation in the University Clinical Center (UKC) Ljubljana, Slovenia, between 20. 6. 1995 and 31. 12. 2016. One-year survival of our patients is 84,2%, and five-year survival is 76,6%. Our results are comparable with results of other centers included in Eurotransplant.

## INTRODUCTION

The first successful liver transplantation in the world was performed in 1963 by Starzl in the United States (1). On 20. 6. 1995 the first liver transplantation by a Slovenian surgical team, led by French surgeon J. Belghiti, was performed in UKC Ljubljana, Slovenia. The patient is still alive today. In 1998 the national program for liver transplantation started and in 2000 we became a member of Eurotransplant. Slovenia has one transplant center, UKC Ljubljana. In the last years, we

performed 20 to 30 liver transplantations per year. Our liver transplant team discusses patients before and after liver transplantation at weekly liver transplant meetings. The transplant team includes hepatologists, liver surgeons, intensivists and other specialists contributing in liver transplantation. Patients who are candidates for liver transplantation are admitted to the Clinical Department of Gastroenterology UKC Ljubljana to be prepared for the procedure and for contraindications for liver transplantation to be excluded. These include advanced cardiopulmonary disease, uncontrolled sepsis, extrahepatic malignancy, untreated alcohol and drug addiction, body mass index (BMI) above 40, Acquired Immune Deficiency Syndrome (AIDS) and anatomical abnormalities that preclude liver transplantation. Patients who fulfilled liver transplant criteria are listed to the waiting list. After the transplantation procedure patients are hospitalized at the Surgical Intensive Therapy unit first and then at the Department of Abdominal Surgery. After hospital discharge patients are followed by hepatologists of the Department of Gastroenterology. Indications for liver transplantations are divided into four groups: chronic liver diseases, liver tumors, acute (fulminant) liver fail-

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ure and metabolic liver diseases (2) (3). **Chronic liver diseases** include: cholestatic liver diseases (primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and secondary biliary cirrhosis), hepatocellular liver diseases (alcoholic liver disease, autoimmune hepatitis (AIH), cryptogenic liver cirrhosis, chronic hepatitis B and C) and vascular liver diseases such as Budd-Chiari syndrome. The decision for liver transplantation in chronic liver diseases is made according to Child-Pugh classification, Model of End-stage Liver Disease (MELD) score and presence of complications of liver cirrhosis such as: variceal bleeding, refractory ascites, spontaneous bacterial peritonitis (SBP) and other infections, hepatic encephalopathy, hepatic-pulmonary syndrome (HPS), hepatorenal syndrome (HRS) and hepatocellular carcinoma (HCC) (4).

### **Liver tumors**

HCC is one of the most frequent indications for liver transplantation in the western world. Liver transplantation is a successful way of treatment of HCC in patients within Milan criteria (one nodule up to 5 cm in diameter, up to 3 nodules smaller than 3 cm in diameter, without vascular and lymph nodes invasion and extrahepatic metastases) (5). Other tumors in which liver transplantation is indicated include hepatic epithelioid hemangioendothelioma, isolated neuroendocrine tumor (NET) liver metastases after primary tumor removal and liver hemangiomas.

### **Acute (fulminant) liver failure**

Acute liver failure (ALF) is a sudden onset of hepatic encephalopathy with concomitant jaundice, coagulopathy and multiorgan failure in a patient without history of liver disease. Predominant causes of ALF are viral infections (hepatitis A, B, and E) in the eastern world and drug-induced liver injury (most often caused by paracetamol) in the western world. Other causes: acute ischemic liver injury due to systemic hypotension in sepsis or cardiac failure,

acute Budd-Chiari syndrome, neoplastic infiltration, heat-stroke, mushroom ingestion, autoimmune hepatitis, acute liver failure of pregnancy and acute Wilson's disease. The decision for emergency liver transplantation in ALF is made according to King's College Criteria. The presence of hepatic encephalopathy is a key indicator, with further consideration given to patient's age, etiology of liver disease and severity of liver dysfunction assessed by extent of coagulopathy and jaundice (6).

### **Metabolic liver diseases**

Metabolic liver diseases that may occur with chronic liver disease and require liver transplantation due to liver cirrhosis and its complications include genetic hemochromatosis, alpha one antitrypsin deficiency and Wilson's disease. Indications for liver transplantation also include some metabolic disorders originating in liver, affecting other organs but not involving liver: type 1 hyperoxaluria, familial homozygous hypercholesterolemia and familial amyloidosis (7). The most common complications after liver transplantation include: infections, biliary complications (most commonly stenosis of biliary anastomosis and leakage) that occurred in up to 32% (8), vascular complications (mostly hepatic artery and portal vein thrombosis) in 7% (9), acute rejection in 25%, chronic rejection in 5% and malignancy. HCC recurrence rate after liver transplantation is up to 20% (10). De novo cancers ranging up to 19% and 34% at 10 and 15 years, respectively, following liver transplantation (11) (12).

## **PATIENTS AND METHODS**

283 patients underwent liver transplantation in UKC Ljubljana, Slovenia, between 20. 6. 1995 and 31. 12. 2016. Of those 186 (65,7%) were men and 97 (34,3%) women. The average age at transplantation was 50,2 years. (Indications for liver transplantation are shown in Figure 1.) 208 (73,5%) patients, of which 139 (66,8%) men and 69 (33,2%) women, were transplanted due to chronic liver diseases: 59 because of cholestatic liver diseases (26: 4 men and

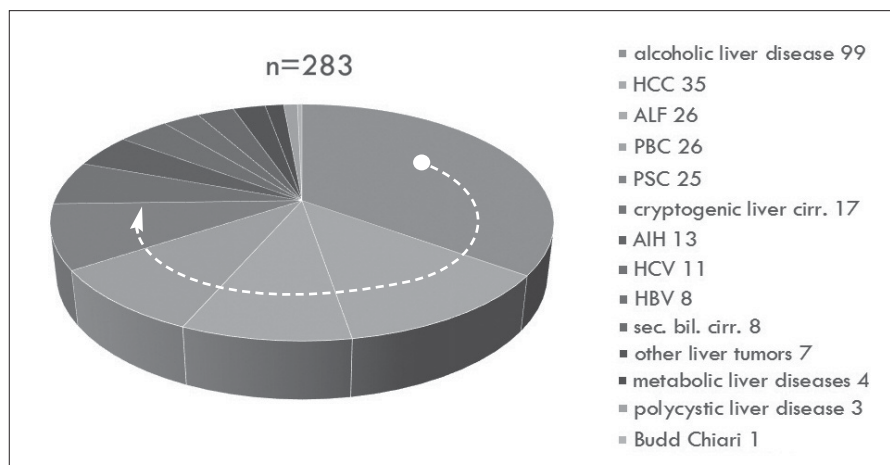


Figure 1: Indications for liver transplantation in Slovenia 20. 6. 1995 – 31. 12. 2016.

22 women, because of PBC, 25: 19 men and 6 women, because of PSC and 8: 4 men and 4 women, because of secondary biliary cirrhosis), 148 due to hepatocellular liver diseases ( 99: 80 men and 19 women because of alcoholic liver disease, 13: 3 men and 10 women, because of AIH, 17: 12 men and 5 women, because of cryptogenic liver cirrhosis, 8: 7 men and 1 woman, because of chronic B hepatitis and 11: 10 men and 1 woman, because of chronic hepatitis C). 1 woman was transplanted because of Budd-Chiari syndrome. 42 (14,8%) patients, of which 35 (83,3%) men and 7 (16,7%) women, were transplanted due to liver tumors: 35: 30 men and 5 women, because of HCC, 4: 3 men and 1 woman, because of hepatic epithelioid hemangioendothelioma, 2 men because of isolated neuroendocrine tumor (NET) liver metastases after primary tumor of terminal ileum removal and 1 woman because of liver hemangiomas. 26 (9,2%) patients, of which 7 (26,9%) men and 19 (73,1%) women, were transplanted due to ALF: 4: 2 men and two women, because of acute Budd-Chiari syndrome, four women because of acute Mb. Wilson, 4: 2 men and two women, because of drug-induced ALF, four women because of acute AIH, two women because of fulminant hepatitis B, one woman because of mushroom poisoning and one woman because of ALF in pregnancy. In 6 transplanted patients, three men and three women, the cause of ALF remained unknown. 4 (1,4%) patients: 3 men (75%) and one woman (25%), were transplanted due to metabolic

liver diseases: 2: 1 man and one woman, because of Mb. Wilson, one man because of familial homozygous hypercholesterolemia and one man because of familial amyloidosis.

3 (1%) patients, two men, and one woman were transplanted because of polycystic liver disease. 29 (10,2%) patients, of which 16 (55,2%) men and 13 (44,8%) women were re-transplanted, 13: 5 men and

8 women, underwent urgent and 16: 11 men and 5 women, underwent elective re-transplantation. One man had two elective re-transplantations.

## RESULTS

On the date 31. 12. 2016 out of 283 transplanted patients 207 were alive.

76 (26,8%) patients: 51 men and 25 women, died. Causes of death are shown in Table 1.

Table 1. Causes of death in liver transplant patients in Slovenia 20. 6. 1995 – 31. 12. 2016

Cause of death	Number of patients	%
infection	26	34,2%
cancer	15	19,7%
graft failure	9	11,8%
cardiovascular	7	9,2%
intraabdominal hemorrhage	4	5,3%
intracranial hemorrhage	4	5,3%
trauma	1	1,3%
complication of tx	1	1,3%
unknown	9	11,8%
SUM	76	99,9%

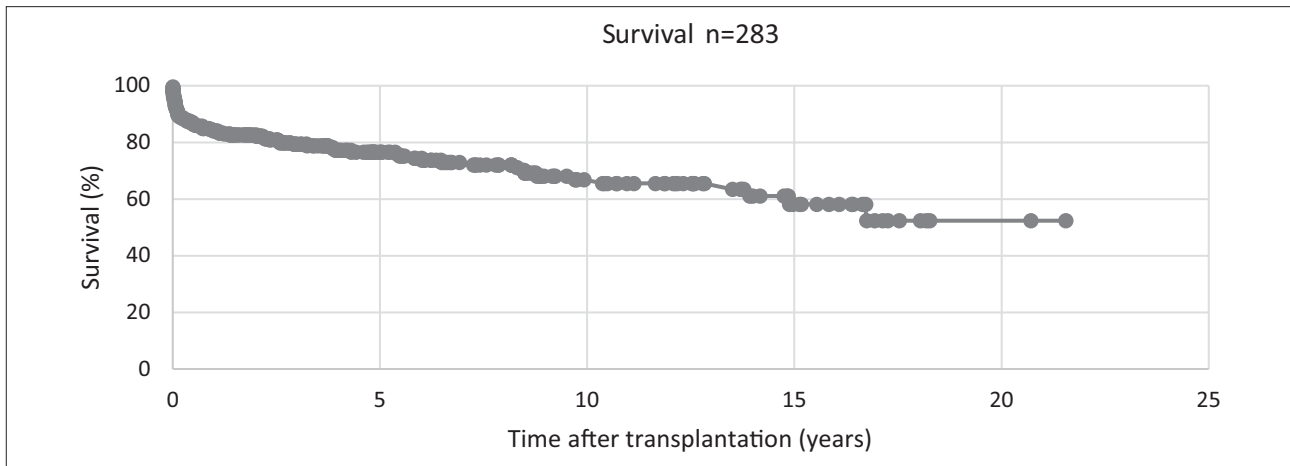


Figure 2: Survival curve after liver transplantation in Slovenia 20. 6. 1995 – 31. 12. 2016

1-year survival of our liver transplanted patients is 84,2%, and 5-year survival is 76,6% (Figure 2). In the same period 1- and 5-year survivals after liver transplantation in Eurotransplant are 82 and 70%, respectively.

1-year survival of our patients transplanted due to chronic liver disease is 87,7%, and 5-year survival is 81,3%.

1-year survival of patients transplanted because of liver tumors is 76%, and 5-year survival is 57%.

1- and 5-year survival of patients transplanted due to ALF is 72,1%.

1-year survival of only four patients transplanted due to metabolic liver diseases is 75%, and 5-year survival is 50%.

In 83 (29,3%) patients after liver transplantation biliary tract complications occurred, most frequently stenosis of biliary anastomosis; the majority were treated endoscopically. In 51 (18%) of transplanted patients, vascular complications occurred that were mostly solved surgically. In 95 (33,6%) of patients acute and 24 (8,5%), chronic rejection occurred, both proven by liver histology.

Cancer is one of the leading causes of morbidity and mortality after liver transplantation. In 41

(14,5%) patients, 32 men and nine women, transplanted in our center, 44 occurrences of cancer were found (Figure 3). HCC recurs in 3 of 35 (8,6%) patients transplanted because of HCC and NET reappears in 1 of 2 patients transplanted due to NET liver metastases. Three patients had two cancers: 1 skin and lung cancer, one skin cancer and hypernephroma and one osteosarcoma and bladder carcinoma. 15 (5,3%) patients: 12 men and three women, died because of cancer, which makes it with 19,7% the second leading cause of death in liver transplant recipients, following infections. (Figure 4) Analysis of infections after liver

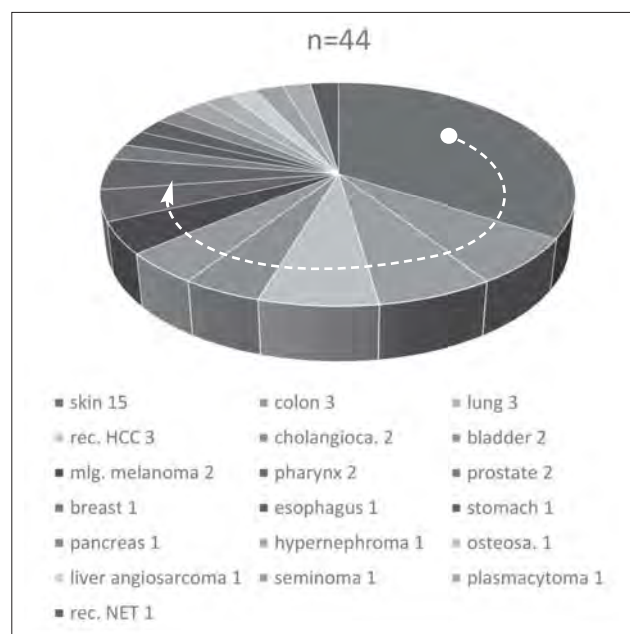


Figure 3: Cancer after liver transplantation

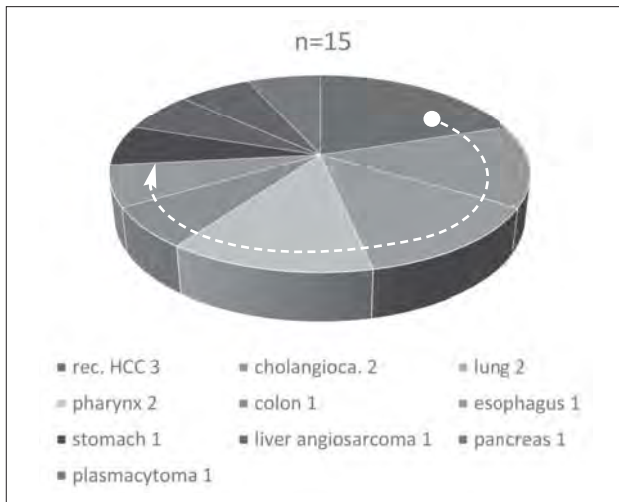


Figure 4: Mortality due to cancer after liver transplantation

transplantation in our cohort was impossible to make because of shortage of data.

## CONCLUSION

Liver transplantation is a successful way of treatment for patients with advanced chronic liver disease and its complications as well as for patients with acute liver failure. 1- and 5-year survival of our patients after liver transplantation is comparable to survival rates of other centers included in Eurotransplant. According to published data, our complication rate is quite high, which is mostly due to procedures performed in first years of our program. Our goal for the future is to improve our results using better patient selection and optimization of patient care using multidisciplinary approach, aiming to detect and treat complications following liver transplantation as soon as possible.

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