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Clinical Research

LONG TERM SURVIVAL AFTER LIVER TRANSPLANTATION – A SINGLE CENTRE STUDY

KEY WORDS: Hepatocellular carcinoma (HCC), Liver transplant, Survival analysis

Mr Manish Kumar Singh — Senior Biostatistician, Medanta Institute of Education and Research, PhD Scholar - Department of Basic and Applied Sciences, GD Goenka University Gurugram, Haryana.

Ms Gargi Singh — Real World Evidence Fellow (CDM), Medanta Institute of Education and Research, Medanta – The Medicity, Gurugram, Haryana.

Dr Arvinder S. Soin — Chairman, Medanta Institute of Liver Transplantation and Regenerative Medicine, Medanta The Medicity, Gurugram, Haryana.

Dr. Naresh Sharma* — Professor & Head, Department of Basic and Applied Sciences, G.D. Goenka University, Gurugram, Haryana. *Corresponding Author

ABSTRACT

Background: The Medanta Institute of Liver Transplantation and Regenerative Medicine is one of the largest Institute offering liver transplantation and all other levels of treatment for liver diseases. The objective of the study is to estimate the long term survival rate and associated risk factors after liver transplantation. **Materials:** Data relates to 2616 adult patients, first-time liver transplant recipients transplanted between January 2003 and April 2023. Data were maintained in electronic hospital information system. **Results:** The median age of the patients was 50 year (IQR: 42 – 56 years). Female were 16.2%. The median length of hospital stay was 14 days (12 – 18 days). Overall median survival time was 15 years (95% C.I.: 14.7 – 16.1 years). Median survival time for male and female were 13.2 years and 16.5 years respectively. The survival rate at 1, 3, 5 and 10 years was 93.0%, 88.2%, 85.0% and 75.8% respectively. The most common significant risk factor for death of liver transplant patients were Emergency Colectomy (HR = 6.6), post-operative pneumonia (HR = 6.4) and post-operative re-ventilation (HR = 4.1). Male was more on risk for death (HR = 2.1). **Conclusion:** Post-operative pneumonia and re-ventilation are unfavorable predictors of survival outcomes after liver transplantation. This study provides a better view of the efficiency of medical cares, regarding liver transplantation. Medical care be enhanced to increase the survival of liver transplant patients.

INTRODUCTION

Liver disease accounts for around 2 million deaths annually on a global scale (Asrani et al.,2019). According to the latest data published by the World Health Organisation (WHO) in 2017, the number of deaths by liver disease in India is approximated to 259,749, constituting 2.95% of the overall mortality rate. This figure represents a significant proportion, specifically 18.3%, of the worldwide deaths resulting from cirrhosis (Mondal et al.,2022).

Despite significant improvements in the medical management of risk-factors related to liver disorders, liver transplantation remains the sole and definitive therapeutic intervention for individuals suffering from end-stage liver disease (Farkas et al.,2014). Indications for liver transplantation are manifold and can be classified into end-stage liver disease, acute liver failure, cirrhosis and certain benign and malignant liver tumours. Henceforth, Liver transplantation (LT) is a lifesaving and most preferred therapy for patients with end-stage liver disease and acute liver failure. LT has successfully conquered numerous obstacles in order to attain these exceptional long-term outcomes (Varma et al.,2011).

Over the past three decades, there has been a significant transformation in the field of liver transplantation, wherein it has evolved from a risk-laden last option to secure therapeutic approach for individuals suffering with end stage liver disease (Russo et al.,2016). Consequently, there has been a shift in the primary objective of liver transplantation, transitioning from prioritising short-term survival to emphasising long-term survival along with overall well-being of transplant recipients (Jain et al.,2000).

Liver transplantation has been widely acknowledged as a viable therapeutic intervention for people with end-stage liver disease since the year 1983 (Marroni et al.,2018). Over the years, there have been notable enhancements in patient survival rates, primarily attributed to advancements in immunosuppressive treatments and medical care, technical accomplishments, and improvements in the processes of procurement and preservation (Starzl T. E.,2000).

Indices for the prediction of survival play a crucial role in evaluating prognosis and establishing priority for liver transplantation (Botta et al.,2003). Although many significant evidences, including data from registries, have described short-term variables that affect survival, only few evidences have examined factors that affect long-term survival rate after liver transplantation (Nitski et al.,2021).

Several studies have been conducted to examine the survival results following liver transplantation, focusing on the short- to medium-term follow-up period. Nevertheless, there are fewer research evidences of long-term follow-up reports. The limited interpretation of these data is attributed to the heterogeneity of program practices, variations in the classification of aetiology of liver disease, and the absence of standardised and uniform follow-up procedures (Jain et al.,2000). The aim of this study is to analyse the long-term survival rate following liver transplantation in a large population of patients from a single centre, with consistent follow for duration of up to twenty years. Additionally, we aim to assess the mortality rate and factors contributing to death, taking into account variables such as age, diagnosis, gender, and year of transplantation.

MATERIAL & METHODS

A total of 2616 patients who had undergone liver transplantation during January 2003 - April 2023 period were reviewed. The records of such patients are maintained in electronic hospital information system at Medanta-The Medicity, Gurgaon. Patient with Hepatocellular carcinoma (HCC), retransplantation, and children (age < 18 years) were

excluded from the study. The investigation encompassed a comprehensive dataset, including demographic details, anthropometric measurements, personal habits, comorbidities, and the etiology of liver disease. Thorough information was gathered on pre-operative clinical features, while post-operative records encompassed details on complications, readmissions, culture findings, and other pertinent aspects. Importantly, the study tracked mortality and associated details for a period spanning up to 20 years for the included patients.

Statistical Methods

The analysis involved categorizing patients based on demographic, anthropometric, personal habits, comorbidities, and etiological factors. Profiling was conducted on pre-operative clinical and laboratory data, with results expressed as absolute numbers and percentages for categorical variables, and means with standard deviation for quantitative variables. Survival rates at different time points were computed using the life table approach, while Kaplan-Meier analysis was employed to determine patients' survival times. Cox regression analysis was utilized to identify potential risk factors for mortality. Gender and age-based differences in survival rates were compared using the log-rank test. A p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS software, version 24.0.

RESULTS

Demographic and Anthropometry

Majority of the patients were male 2193 (83.8%). The mean age of the patients was 49.1±10.3 (Range: 18 – 79) years. Importantly, around 2/3rd of the patients were in the age group 41 – 60 years. As per Body-Mass Index (BMI) classification, more than half of the total patients were overweight and obese. Only 3.4% patients were chronically energy deficient and rest 45% were normal.

Personal Habits

As to the personal habits, alcoholics were 8.8%, smokers – 3.9% and tobacco chewing – 1.6%.

Comorbidities

As high as 23.7% were diabetic and 13.3% were hypertensive. Those with Acute Kidney Injury (AKI) were 7.5% and hypothyroid as 4.2%.

Etiology of Liver Disease

This study showed that Acute Liver Disease (ALD) (33.2%), Hepatitis C virus (HCV) (22.4%), cryptogenic (16.9%) and Hepatitis B virus (HBV) (15.1%) have become the most common etiologies of liver disease without HCC. Nonalcoholic steatohepatitis/ Nonalcoholic Fatty Liver Disease (NASH/NAFLD) (8.3%) and Autoimmune (4.2%) were relatively less.

Pre – Operative Clinical Features

Gastrointestinal (GI) bleed (21.4%) and fever (10.4%) were common pre – operative clinical features. Pre-op intensive care unit (ICU) admission required was 2.4% patients. Further, pre-op culture was positive among 2.4% patients.

Post-Operative Complication

The most common post-operative complication observed was high TLC level (> 12000) – 29.4%. Re-exploration was observed in 6.3% patients and fever was in 3.9% patients. Cytomegalovirus (CMV) DNA positive and sepsis were 4.6% and 2.4% respectively.

Post – operative Readmission

Importantly, ICU readmission required in 1.5% patients, re-ventilation in 0.4% and tracheostomy required in 2.5% patients.

Post-Operative Culture

Post-operative, positives cultures were observed in blood (7.8%), body fluid (5.1%) and urine (4.7%).

Table 1 represents the patient characteristics.

Table 1: Patient Characteristics

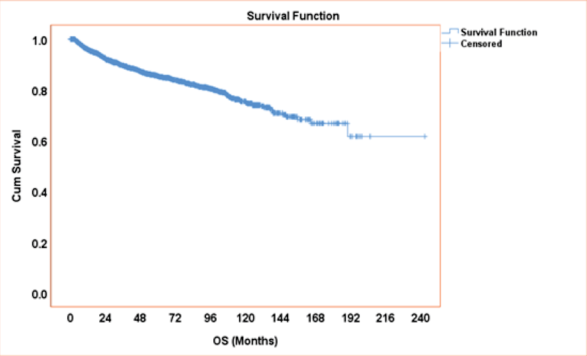
	Number of Patients (n=2616)	Percentage (%)
Demographic		
Age (Years)		
18 – 30	127	4.9%
31 – 40	386	14.8%
41 – 50	833	31.8%
51 – 60	938	35.9%
> 60	332	12.7%
Mean ± SD (Range)	49.1±10.3 (18 – 79)	
Median (IQR)	50 (42 – 56)	
Gender		
Male	2193	83.8%
Female	423	16.2%
BMI (Kg/m2)		
Chronically energy deficient (Below 18.5)	90	3.4%
Normal (18.5 – 24.9)	1186	45.3%
Overweight (25.0 – 29.9)	888	34.0%
Obese (≥ 30)	452	17.3%
BMI (Kg/m2)	25.3±4.3 (14.2 – 40.9)	
Personal Habits		
Alcoholic	229	8.8%
Smoker	101	3.9%
Tobacco chewing	42	1.6%
Comorbidities		
DM	619	23.7%
HTN	349	13.3%
AKI	196	7.5%
Hypothyroid	111	4.2%
CAD	50	1.9%
Etiology of Liver Disease		
ALD	869	33.2%
HCV	586	22.4%
Cryptogenic	442	16.9%
HBV	394	15.1%
NASH/NAFLD	217	8.3%
Autoimmune	109	4.2%
Emergency Colectomy	76	2.9%
Pre – Operative Clinical Features		
GI Bleed	560	21.4%
Fever	271	10.4%
High TLC > 12000	66	2.5%
Pre op ICU admission Required	63	2.4%
Pre-op positive Culture Positive	62	2.4%
Post-Operative Complication		
Pneumonia	3	.1%
UTI	1	.0%
Fever	101	3.9%
High TLC > 12000	770	29.4%
Re-exploration	164	6.3%
CMV DNA positive	121	4.6%
Body fluid high cell count	10	.4%
Sepsis	64	2.4%
High drain output > 1000 on POD7	50	1.9%
Post-op high drain output > 1000 on POD14	12	.5%
Tracheostomy	66	2.5%
ICU readmission	40	1.5%
Re-ventilation	11	.4%
Fever with high TLC	8	.3%

Retransplant procedure	1	.0%
Post-Operative Culture (Positive)		
Blood	205	7.8%
Body Fluid	134	5.1%
Urine	123	4.7%
Sputum	36	1.4%

Survival Analysis

Survival Time and Rate

Overall mean survival time was 15 years (95% C.I.: 14.7 – 16.1 years) (Graph 1).



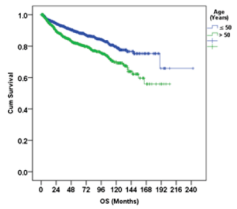
Graph 1: Kaplan Meier Curve for Overall Survival

The survival rate at 1, 3, 5 and 10 years was 93.0%, 88.2%, 85.0% and 75.8% respectively (Table 2).

Table 2: Survival Rate at different time points

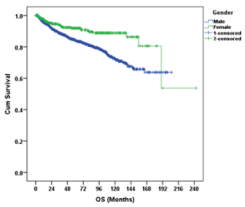
Time Interval (Months)	Number Entering Interval (n)	Number of Terminal Events (d)	Number Withdrawing during Interval	Survival Rate
0	2616	99	365	96.2%
12	2152	71	274	93.0%
24	1807	52	218	90.4%
36	1537	37	204	88.2%
48	1296	27	221	86.4%
60	1048	17	162	85.0%
72	869	16	145	83.4%
84	708	13	157	81.9%
96	538	15	139	79.6%
108	384	10	106	77.5%
120	268	6	94	75.8%
132	168	5	56	73.5%
144	107	3	44	71.4%
156	60	1	20	70.3%
168	39	0	14	70.3%
180	25	1	13	67.4%
192	11	0	8	67.4%
204	3	0	2	67.4%
216	1	0	0	67.4%
228	1	0	0	67.4%
240	1	0	1	67.4%

Survival time showed declining trend with age of the patients. The survival time for patients under 50 years (OS = 16.2, 95% C.I.: 15.3 – 17.2 years) was significantly higher as compared to those above 50 years (OS = 12.6, 95% C.I.: 11.9 – 13.2 years) (log rank = 24.823, p = 0.001) (Graph 2).



Graph 2: Kaplan Meier Curve for Overall Survival – Age Group

Mean survival time for female (OS = 16.5, 95% C.I.: 14.4 - 18.6 years) was significantly higher as compared to male (OS =13.2 years; 95% C.I.: 12.8 - 13.6 years) (log rank = 16.897, p = 0.001) (Graph 3).



Graph 3: Kaplan Meier Curve for Overall Survival - Gender

Risk Factors for Death

Based on the univariate cox regression model, the most common significant risk factor for death of liver transplant patients were Emergency Colectomy (HR = 6.6), post-operative pneumonia (HR = 6.4) and post-operative re-ventilation (HR = 4.1). Other significant risk factors include age > 50 years (HR = 1.7), HTN (HR = 1.4), DM (HR = 1.5), ALD (HR = 1.3), post op high TLC (HR = 1.3), post op INR < 1.4 (HR = 1.8), pre op Bilirubin (Total) < 2.2 (HR = 1.8), CTP worst > 10 (HR = 1.6), calculated MELD > 14 (HR = 1.8), Hospital Stay > 14 days (HR = 1.4), pre – operative INR > 1.4 (HR = 1.8). Male were more on risk for death as compared to female (HR = 2.1) (Table 3).

Table 3: Univariate Cox Regression Model For Prediction of Death

	Beta Coefficient	HR	95% CI for HR		p-value
			Lower	Upper	
Male	0.7	2.1	1.4	2.9	0.001*
Age > 50 years	0.5	1.7	1.4	2.1	0.001*
HTN	0.4	1.4	1.1	1.9	0.012*
DM	0.4	1.5	1.2	1.9	0.001*
ALD	0.3	1.3	1	1.6	0.016*
Emergency Colectomy	1.9	6.6	1.6	26.6	0.008*
Post op Pneumonia	1.9	6.4	1.6	25.8	0.009*
Post Op high TLC	0.3	1.3	1.1	1.6	0.011*
Post Op Re Ventilation	1.4	4.1	1.5	11.1	0.005*
Post Op INR > 1.4	0.6	1.8	1.4	2.3	0.001*
Pre Op Bilirubin (Total) < 2.2	0.6	1.8	1.4	2.3	0.001*
CTP Worst > 10	0.5	1.6	1.3	2.1	0.001*
Calculated MELD > 14	0.6	1.8	1.3	2.5	0.001*
Hospital Stay > 14 days	0.3	1.4	1.1	1.7	0.004*
Hypothyroid	-0.2	0.9	0.5	1.6	0.600
Alcoholic	0.0	1.0	0.6	1.6	0.925
Smoker	-0.2	0.8	0.4	1.7	0.536
Tobacco chewing	-0.4	0.7	0.2	2.8	0.612
Pre-op Fever	0.0	1.0	0.8	1.4	0.771
Pre-op ICU admission	0.1	1.1	0.6	2.1	0.807
AKI	0.3	1.3	0.9	2.1	0.193
GI Bleed	-0.2	0.9	0.6	1.1	0.270
Post-op UTI	-3.0	0.0	0.0	104597.9	0.686
Post-op Fever	0.0	1.0	0.6	1.8	0.866
Post-op Fever with high TLC	0.2	1.2	0.2	8.6	0.850
Blood culture positive	0.1	1.1	0.7	1.6	0.689

Urine culture positive	0.0	1.0	0.6	1.7	0.912
Sputum culture positive	-0.2	0.8	0.3	2.0	0.648
Body Fluid Culture positive	0.3	1.4	0.9	2.1	0.127
Post-op Sepsis	0.1	1.1	0.6	1.9	0.715
Re-exploration	0.0	1.0	0.7	1.5	0.932
Post-op ICU readmission	0.5	1.6	0.8	3.2	0.205
Graft Weight (gms)	0.0	1.0	1.0	1.0	0.529
CIT	0.0	1.0	1.0	1.0	0.382
WIT	0.0	1.0	1.0	1.0	0.486
PRBC	0.0	1.0	1.0	1.0	0.341
Apheresis	0.0	1.0	0.9	1.0	0.533
PRP	0.0	1.0	0.7	1.3	0.996
FFP	0.0	1.0	1.0	1.0	0.117

*p – value < 0.05, statistically significant

On multivariate cox regression model, Emergency Colectomy (HR = 7.2), post op Pneumonia (HR = 6.6) and post op Re-Ventilation (HR = 35.1%) were the significant risk for death of the post liver transplant patients (Table 4).

Table 4: Multivariate Cox Regression Model for Prediction of Death

	Beta Coefficient	HR	95% CI for HR		p-value
			Lower	Upper	
Male	1.0	2.8	0.6	12.8	0.173
Age > 50 years	0.1	1.1	0.5	2.3	0.770
HTN	0.0	1.0	0.4	2.5	0.965
DM	0.5	1.7	0.8	3.5	0.152
ALD	0.3	1.4	0.7	2.8	0.403
Emergency Colectomy	0.6	7.2	2.8	19.3	0.039*
Post-op Pneumonia	1.9	6.6	0.8	52.5	0.045*
Post-op high TLC	0.3	1.4	0.7	2.8	0.357
Post-op Re Ventilation	3.6	35.1	6.4	192.1	0.001*
Post-op INR > 1.4	0.3	1.3	0.5	3.5	0.618
Pre-op Bilirubin (Total) < 2.2	-0.8	0.5	0.2	1.3	0.139
CTP Worst > 10	0.8	2.1	0.9	5.1	0.087
Calculated MELD > 14	0.0	1.0	0.3	3.1	0.996
Hospital Stay > 14 days	-0.1	0.9	0.4	1.8	0.737

DISCUSSION

The present study is the long-term follow-up of liver transplant patients from a single tertiary care centre. The findings of this study offer valuable insights into the demographic and clinical characteristics of liver transplant recipients and their impact on long-term survival. The majority of patients in this single-centre study were male. These findings were consistent with existing literature suggesting a higher prevalence of liver diseases in males (Sarkar et al.,2015). The mean age of the patients was 49.1 years and patients ranging between 41–60 age group showed significant liver transplantation.

The observed high prevalence of overweight and obese individuals among liver transplant recipients is a concerning trend, as per evidences from associations between obesity and liver diseases (Klaassen et al.,2017). Addressing lifestyle factors, such as diet and physical activity, in the post-transplant period may play a crucial role in optimizing long-term outcomes. The prevalence of alcohol use, smoking, and tobacco chewing among the study patients highlights the continued importance of addressing these modifiable risk factors in liver transplant recipients (Choudhary et al.,2021). Integrating targeted interventions for substance use cessation into the post-transplant care plan may contribute to better overall outcomes.

The study's documentation of comorbidities, such as diabetes, hypertension, AKI, and hypothyroidism, emphasizes the complexity of the patient population undergoing liver transplantation. Personalised management strategies addressing these comorbidities in the pre- and post-transplant phases are crucial for optimizing patient health (Guo et al.,2020). The etiological distribution of liver diseases, with ALD, HCV, cryptogenic, and HBV emerging as the leading causes, aligns with global trends (Spengler et al.,2017). Understanding the underlying causes informs preventive measures and therapeutic approaches to mitigate the risk of liver disease progression. The pre-operative clinical features, including GI bleed and fever, shed light on the challenges faced by patients prior to transplantation (Guo et al.,2020). Timely identification and management of these issues are pivotal for optimizing transplant outcomes. The low percentage of positive pre-operative cultures suggests effective pre-transplant screening and infection control measures in the studied center.

Post-operative complications, particularly the high TLC levels, re-exploration, fever, CMV DNA positivity, and sepsis, underscore the need for vigilant post-transplant care (Azevedo et al.,2015). Identifying and addressing these complications promptly may contribute to improved patient outcomes and reduced long-term morbidity. The post-operative readmission rates, especially ICU readmission, re-ventilation, and the requirement for tracheostomy, indicate the complexity of post-transplant care (Klaassen et al.,2017). Further research and quality improvement initiatives may be warranted to enhance the efficiency of post-transplant care protocols and reduce readmission rates. The positive cultures post-operatively in blood, body fluid, and urine highlight the ongoing risk of infections in the post-transplant period. Implementing rigorous infection control measures and monitoring for signs of infections are crucial components of post-transplant care. The long-term survival analysis revealed an overall mean survival time of 15 years, with survival rates at 1, 3, 5, and 10 years indicating favourable outcomes. However, the declining trend in survival with increasing age suggests the need for tailored strategies for older transplant recipients (Farkas et al.,2014). The significant disparity in mean survival time between genders warrants further investigation into potential gender-specific factors influencing outcomes. The identification of risk factors for mortality, including emergency colectomy, post-operative pneumonia, and post-operative re-ventilation, provides valuable insights for risk stratification. Factors such as age, hypertension, diabetes, alcoholic liver disease, and various clinical and laboratory parameters further contribute to the multifaceted nature of risk assessment in liver transplantation. The elevated risk observed in males underscores the importance of gender-specific considerations in post-transplant care.

CONCLUSION

In conclusion, this comprehensive study sheds light on the multifaceted landscape of long-term survival after liver transplantation. The demographic and clinical characteristics of the patient population, coupled with detailed analyses of complications and survival outcomes, provide a robust foundation for understanding the complex dynamics involved in post-transplant care. The identified risk factors for mortality offer valuable insights for refining pre- and post-transplant management strategies, ultimately contributing to improved patient outcomes in the evolving field of liver transplantation.

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