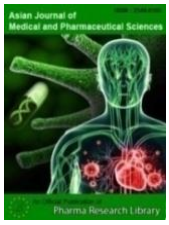

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Long-term Survival Rates of Recipients Post-Liver Transplantation in Acute Liver Failure: A Systematic Review and Meta-Analysis

Chetan Ramesh Kalal*[1], Harshad Joshi[1], Shankar Zanwar[1], Anil Singh[1], Ankush Golhare[1], Gaurav Patel[1], Vibhor Vinayak Borkar[1], Anurag Shrimal[1]

[1-8]*Nanavati Max Institute of Liver, Pancreas and Intestine Transplantation, Nanavati Max Super speciality Hospital, Vile Parle, Mumbai, India*

A B S T R A C T

Acute liver failure (ALF) poses significant morbidity and mortality challenges, with liver transplantation (LT) being the soleintervention for patients who fail to recover with medical management. However, LT outcomes, particularly beyond the 1st year, remain suboptimal. This study aimed to evaluate the long-term survival rates (SR)post-LT in adult ALF patients through a systematic review and meta-analysis (SRMA). The SRMA included seven studies published between January 2000 and December 2023, focusing on English language paper sreporting long-term SR (≥1 year) in adult ALF patients undergoing LT. The analysis, encompassing 9013 patients, revealed overall SR of 76%, 71%, 69%, and 62% at 1-, 3-, 5-, and 10-years post-LT, respectively. Aetiology of ALF did not significantly impact SR. The first year post-LT demonstrated the highest SR, with subsequent years showing a decline. Despite advancements in pre- and post-LT care, mortality rates remained high, underscoring the need for further research to improve patient outcomes.

Keywords: Liver failure, living donor liver transplantation, overall survival, patient mortality, transplantation outcomes.

A R T I C L E I N F O

***Corresponding Author:**
Chetan Ramesh Kalal
Nanavati Max Institute of Liver ,
Pancreas and Intestine Transplantation,
Nanavati Max super speciality Hospital.
Vile Parle, Mumbai, India

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C o n t e n t s

1. Introduction

Acute liver failure (ALF) is a critical condition in individuals without prior liver disease, characterised by liver injury(abnormal liver tests), coagulopathy (INR>1.5), and hepatic encephalopathy. ALF may have several aetiologies and early identification and treatment, including potential transplantation, can be life-saving.[1] The definition of ALF varies globally. In the US and Europe, ALF is defined as a liver illness lasting <26 weeks, without preexisting liver disease or cirrhosis, associated with any degree of encephalopathy and coagulopathy. According to the American Association for the Study of Liver Diseases, the King's College Criteria remain the most clinically useful, with a sensitivity of 68% to 69% and a specificity of 82% to 92%.[1-6]

In India, a1996 Delhi study involving 423 ALF patients revealed differing prognostic and etiological factors from those in the West.[7] Thus, the Indian National Association for the Study of Liver defines ALF as a "clinical syndrome characterized by encephalopathy, jaundice, and prolonged

prothrombin time (INR>1.5) developing in a patient without prior liver disease, severe acute liver injury can occur within four weeks of symptom onset. In some cases, particularly those involving drug-induced liver injury, encephalopathy may develop between four and eight weeks after symptoms begin.''[8]

Globally, liver transplantation (LT)remains the only definitive treatment for patients who do not recover with medical management. However, the 1-year survival rate (SR) aftera cadaveric LT for ALF is lower than that for chronic liver failure. ALF patients alsodemonstrate poor long-term survival. The use of living donor LT (LDLT) and auxiliary LT remains controversial.[5,9,10]

ALF carries a high morbidity and mortality without LT.[1,11-13] Although overall survival and transplant-free survival have improved over the last few decades,[1,14] timely diagnosis is imperative for the early referral of the patient to an LT centre. LT is a life-savingbut complex surgery with high post-LT complication rates.[15]

As per the European Association for the Study of the Liver Clinical Practical Guidelines on the management of acute (fulminant) liver failure, LT is done in only a minor proportion (18.2%) of patients with ALF.[3,16]LT use varies significantly between countries, across transplant centres within the same country, and liver failure causes.[3,11,17,18]

To date, a comprehensive global analysis of overall SR at 1-, 3-, 5-, and 10-years post-LT in patients with ALF has not been conducted.This study aims to address this gap by performing a systematic review and meta-analysis (SRMA) of studies published after 2000, focusing on long-term patient survival.

We will also explore sources of heterogeneity and potential inconsistencies in the results of the included studies. By thoroughly analysing current literature, this study aims to enhance understanding of long-term survival post-LT in ALF and guide future research.

2. Materials and Methods

The SRMA was performed in compliance with PRISMA guidelines with no patient participation.

Search strategies

Studies investigating the SR of patients post-LT were identified through searches across multiple databases, including Pub Med, Google Scholar, Cochrane Library, ClinicalTrials.gov, and the Clinical Trials Registry – India. The search was conducted from November 21, 2023, through December 09, 2023. The search terms used were "liver transplantation,""liver transplantation in acute liver failure," "acute liver failure," "liver transplant", "liver transplant acute liver failure", "liver transplant in acute liver failure", "Living Donor Liver Transplantation for Acute Liver Failure", "Causes of death after liver transplantation",and "Liver transplantation, acute liver failure, single, centre". Specific filters were applied in each data base. In ClinicalTrials.gov, "liver transplantation" and "liver transplant" were used in the "intervention" category. In Cochrane Library, advanced searches were doneusing " acute hepatic failure" for PICO; "liver transplant" for intervention; and "Liver Failure, Acute" for medical terms (MeSH) with "Liver Transplant" for subheadings. In Google Scholar, the year of publication, i.e., 2000 to 2023 was used as the filter. In PubMed, the filters used were for English language, type and year of publication, and full-text availability. Additionally, related articles and reference lists from the retrieved articles were manually reviewed to identify further data and avoid omission.

Each identified study was independently reviewed by two reviewers to determine its eligibility for SRMA. An SRMA flow chart (Figure 1), based on the eligibility criteria mentioned below, was made after a preliminary review of each title.

Eligibility criteria

Studies that fulfilled all of the following criteria were included: (1) Published between 2000andDecember 09, 2023 (2) Focused onLT in ALF (3) Reported long-term (≥1 year) survival data (4) Involved adult patients (≥18 years) (5) Published in English (6) Available as full text.

Studies were excluded if they: (1) Were animal studies, editorials, commentaries, conference reports, case reviews, review articles, and other similar literature (2) Were not in English (3) Lacked relevant or sufficient survival data (4) Focused only on liver re-transplantation (5) Had fewer than 15 patients (6) Were SRMAs(7) Included combined transplantation.

Quality assessment and risk of bias assessment

The quality of included studies was assessed with the ROBINS-I[19] tool for non-randomised studies or RoB 2 tool for cluster-randomised trials.[20] Two reviewers independently conducted the assessments with discrepancies resolved by author consensus.

Data extraction

Data were extracted by two reviewers separately and included author names, publication year, number of LT patients with ALF, recipient age, and overall survival. Disagreements between reviewers were resolved through discussion with a third reviewer.

Outcome

The primary outcome of interest was the overall patient survival at 1 year. The secondary outcomes of interest were patient survival at 3, 5, and 10years.

Statistical analysis

Data entry was done using Microsoft Excel 2019. Forest plots were generated using R version 4.3.0, software provided by the R foundation for statistical computing. All statistical analyses were performed using "R software."

To assess heterogeneity, the I2 procedure was employed. If the P-value >0.1 or the I2 was ≤50%, indicatingno significant heterogeneity, a fixed-effects model was used. Conversely, if the P-value was <0.1 or the I2 value >50%, indicating substantial heterogeneity, the source was

investigated, and a random-effects model was used. To ensure consistency, measurement units from all articles were standardised, and events were converted to proportions before conducting the meta-analysis.For overall survival estimates, pooled proportion and 95% confidence interval were utilised. P-value <0.05 was considered statistically significant.

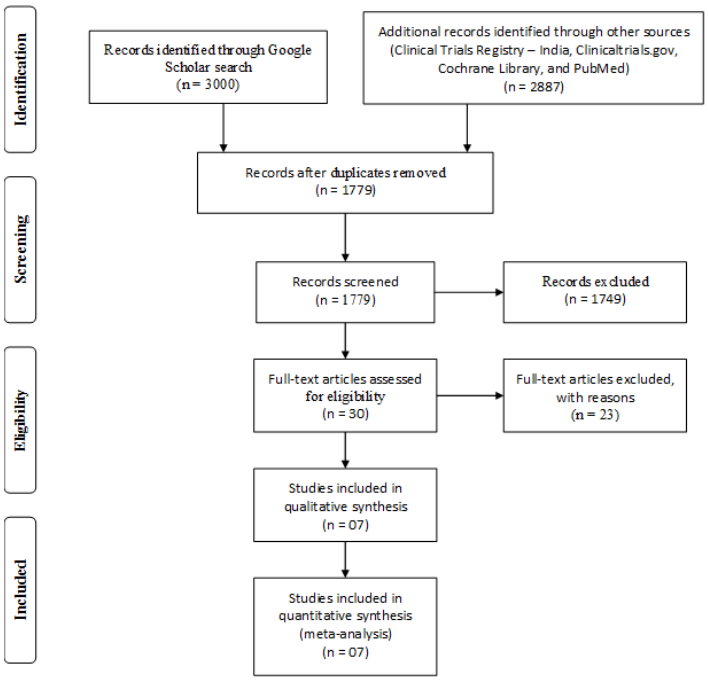

Figure 1 Systematic review and meta-analyses flowchart

3. Results and Discussion

Included studies: The literature search using the aforementioned parameters yielded 5,887 studies; however, only 7 studies met the eligibility criteria for our SRMA.[21-27] Some eligibility criteria data were obtained from supplementary and previously published materials.[2,28,29]

Characteristics of included studies: The included studies comprised 9013 patients who underwent LT for ALF. Table 1 provides detailed study characteristics of these patients.

Table 1: Details of study characteristics

Author/year and Study Design	Key inclusion criteria	Key exclusion criteria
Barshes NR, 2006[21]: Randomised	• Adult patients • FHF: Onset of encephalopathy ≤8 weeks of hepatic symptoms in the absence of preexisting liver disease	• The time interval between initial listing and LT was more than 30 days • History of organ transplant
Rajekar H, 2008[22]: Non-randomised	• Adult patients who underwent LDLT for ALF	• Not available
Bernal W, 2009[23]: Non-randomised	• ALF: As described by Trey and Davidson	• Chronic liver disease
Park SJ, 2010[24]: Non-randomised	• ALF: As per AASLD • Sudden development of severe coagulopathy • INR≥ 1.5 • Mental alteration with an illness duration ≤26 weeks	• Liver cirrhosis
Yuan D, 2012[25]: Non-randomised	• ALF: As per AASLD	• Patients with cirrhosis identified by histologic examination of the liver explants • Donors with known medical disorders that significantly

		increased perioperative risk or contraindicated donation
Germani G, 2012[26,29]: Non-randomised	• LT	• Simultaneous transplant of another organ with no information on outcome
Urrunaga NH, 2014[27]: Non-randomised	• Adult patients who underwent LDLT or DDLT for ALF	• LTs performed ≤12 months of the data creation date by the United Network for Organ Sharing

AASLD: American Association for the Study of Liver Diseases; ALF: Acute liver failure; DDLT: Deceased donor liver transplantation; FHF: Fulminant hepatic failure; INR: International normalised ratio; LDLT: Living donor liver transplantation; LT: Liver transplantation.

Characteristics of included patients: *Table 2 provides detailed characteristics of the patients included in this SRMA.*

Table 2: Baseline characteristics of patients

Author/year	**Number of patients (N) and Age (years)**	**INR**	**MELD score**
Barshes NR, 2006[21]	N: 1458; Age: >18	NA	NA
Rajekar H, 2008[22]	N: 15; Age: 27-65	Median (IQR): 2.2 (1.6-3.8)	Median (IQR): 32 (25-48)
Bernal W, 2009[23]	N: 236; Age: 19-49	NA	NA
Park SJ, 2010[24]	N: 44; Age: 18-59	Median (IQR): 3.1 (2.7-4.2)	Median (IQR): 30.7 (26.8-38)
Yuan D, 2012[25]	N: 20; Age: 29-63	Mean±SD: 4.18±3.42	Mean±SD: 37.1±8.6
Germani G, 2012[26]	N: 4903; Transplantation era (Mean±SD; age):1988-1993: 37.6±13, 1994-1998: 38.9±13.7, 1999-2003: 40.4±13.8, 2004-2009: 41.7±13.9	NA	NA
Urrunaga NH, 2014[27]	N: 2337; Type of donor (Median age):LDLT: 31 years; DDLT: 38	Type of donor (Median): LDLT: 3.3; DDLT: 2.9	Type of donor (Median):LDLT: 37; DDLT: 35

DDLT: Deceased donor liver transplantation; INR: International normalised ratio; IQR: Interquartile range; LDLT: Living donor liver transplantation; MELD: Model for end-stage liver disease; SD: Standard deviation.

Excluded studies

A total of 23 full-text articles were excluded,[30-52]for not meeting the eligibility criteria.

Quality assessment

The quality of all included studies was assessed with ROBINS-I or RoB 2)tool.[19,20]

All 6 non-randomised studies assessed with ROBINS-I had a 'low' overall risk of bias. One randomised study assessed with RoB 2tool had an 'unpredictable' overall risk of bias.

Overall survival at 1-year

The 1-yearoverall SR was 76%, with about 6,834 out of 9,013 patients surviving post-LT with high heterogeneity between studies (I^2 = 79%, t^2 = 0.0010, P<0.01) (Figure 2).

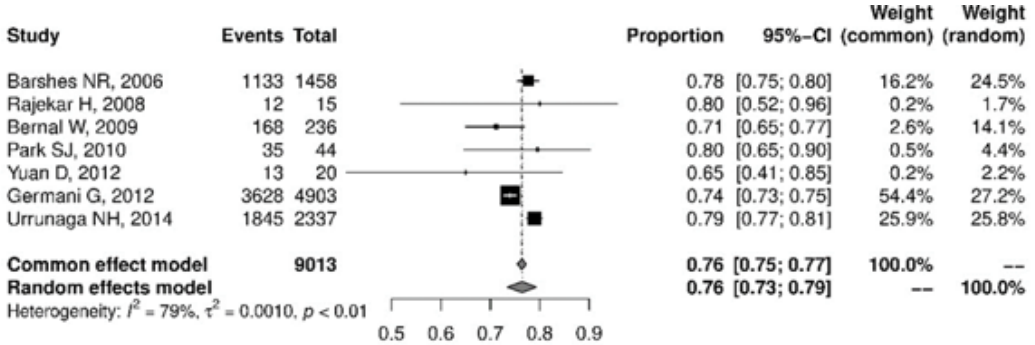

Figure 2 Overall survival analysis at 1year

CI: Confidence interval

Overall survival at 3, 5, and 10years

The 3-year overall SRwas 71% with about 3,457 out of 4,938 patients surviving post-LT. The heterogeneity between studies was high (I^2 = 0%, t^2 = 0, P=0.65) (Figure 3).

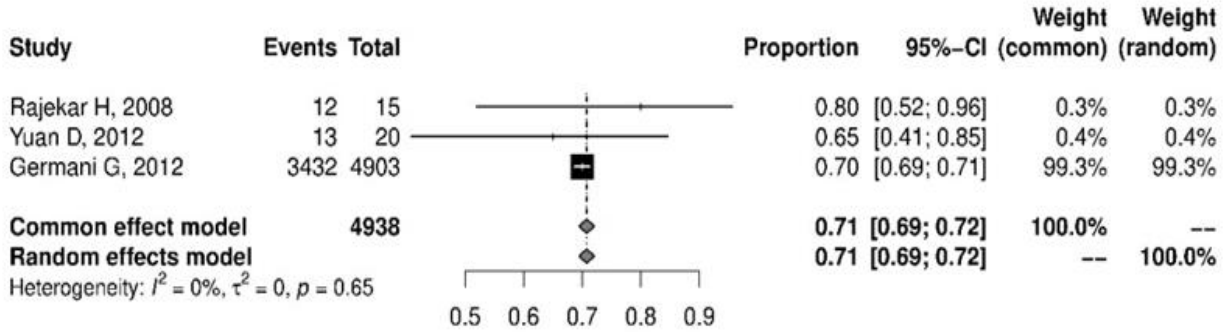

Figure 3: Overall survival analysis at 3years

CI: Confidence interval

The 5-year overall SR was 69%, with 5,986 out of 8,713 patients surviving post-LT. The heterogeneity between studies was high (I^2 = 67%, t^2 = 0.0003, p = 0.03) (Figure 4).

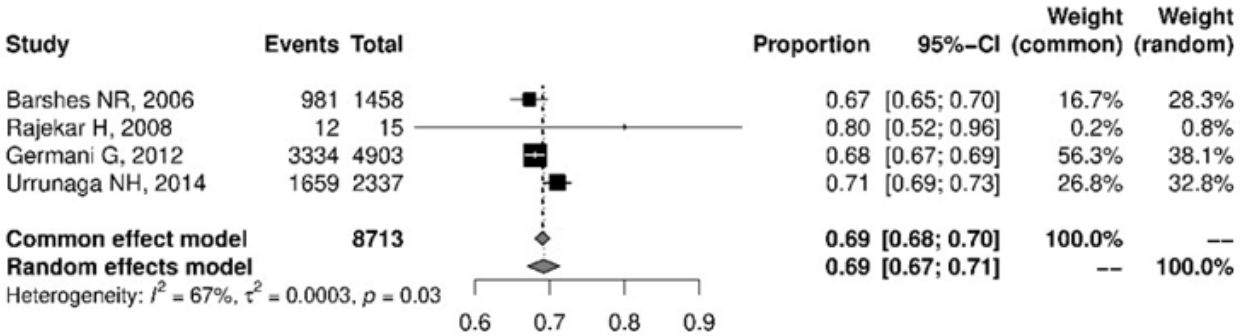

Figure 4: Overall survival analysis at 5years

CI: Confidence interval

Continuing the down wardtrend from years 1 to 5, the 10-year overall SR showed that3,958 out of 6,361 patients, (62%) patients survived. The heterogeneity between studies was high (I^2 = 82%, t^2 = 0.0005, P=0.02) (Figure 5).

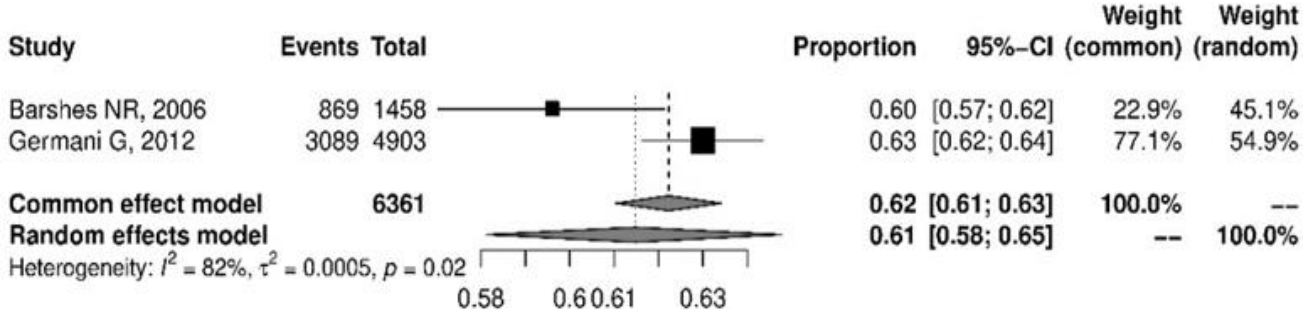

Figure 5 Overall survival analysis at 10years

CI: Confidence interval

Discussion

We believe the present SRMA is the first of its kind in analysing the long-term overall survivalin adults across various countries, who underwent LT for ALF, revealing key findings. The overall post-LT patient survival was 76% at1 year, decreasing to 71%, 69%, and 62% at 3, 5, and 10years, respectively, consistent with the studies included in the SRMA.[21-27]The overall mortality rates begin to riseafter 1-year post-LT.

In 2022, Ghelichi-Ghojogh et al. published a meta-analysis showing pooled SR at 1, 2, 3, 5, and 10 years, with 85% at 1 year and 71% at 10 years, highlighting a significant decline.[52] This is in line with our findings. In a2019

study, Pamecha V et al. examined outcomes for 61 patients who underwent LDLTfor ALF. They reported a 5-year post-LT SR of 65.57%, aligning closely with the 69% in our meta-analysis.[30]

On the contrary, in a 2008 study by Campsen J et al., of the 13 patients who underwent LT for ALF, 3 out of 10 LDLT recipients and 1 out of 3 deceased donor LT (DDLT) recipients did not survive. They concluded that while LDLT is rarely performed for ALF, it may be associated with acceptable donor morbidity and recipient mortality in select patients.[8]

Urrunaga et al. found no significant difference in SR between adults with ALF who underwent LDLT versus DDLT (P =764). The SR for LDLT recipients was 71% at both 1 and 5 years, while for DDLT recipients, it was79% and 71% at 1 year and 71% at 5 years. The study concluded that LDLT is a viable option when cadaveric donor liver is not available.[27]

Larger studies are needed to assess the effect of LDLT and DDLT on recipient survival.

A key take away from this SRMA was that none of the studies identified any ALF aetiology as an independent risk factor or prognostic indicator of survival post-LT.

Study limitations: Data were available for less than 38% of study population at 3-years, 66% at5-years, and 44% at 10-years post-LT. Other limitations included varying sample size, exclusion of non-English studies, and lack of assessment of parameters like health-related quality of life, post-LT work life, and post-LT recipient complications. A separate SRMA can be conducted to evaluate these parameters.

4. Conclusion

Overall post-LT SRin patients with ALF decreases over time, with higher SR in year 1 compared to 3, 5, and 10years.However, there is no significant reduction in SRafter the firstyear,indicating that LT remains an effective treatment for adults with ALF.

Conflict of Interest (CoI) statements:

The authors, Chetan Ramesh Kalal, Harshad Joshi, Shankar Zanwar, Anil Singh, Ankush Golhare, Gaurav Patel, Vibhor Vinayak Borkar, and Anurag Shrimal, declare no conflict of interest.

Declaration of funding source

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