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Research Article

Analysis of 500 Referrals to a Liver Transplant Surgery Unit at a Tertiary Care Center in India: Are We Saving Enough Lives?

Ashish K Mishra[1]*, Ashish Bansal[2], S Soundappan[3], Raghuram Reddy[4] and P Kumaraswamy[4]

[1]*Consultant, Liver Transplant and HPB Apollomedics Hospital, Lucknow, India*

[2]*Assistan Professor, Surgical Gastro and Liver transplant, Nizam's Institute, Hyderabad, India*

[3]*Consultant, Liver transplant and HPB, GEM Hospitals, Chennai, India*

[4]*Consultant, Liver transplant, AIG Hospitals, Hyderabad, India*

***Corresponding Author:** Ashish K Mishra, Consultant, Liver Transplant and HPB Apollomedics Hospital, Lucknow, India.

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Abstract

Objective: Living donor liver transplant (LDLT) is the mainstay of liver transplants (LT) in India. Data on transplant referrals and their outcomes is lacking from the subcontinent. This study is aimed to elucidate the reasons for eligible LT candidates not being able to undergo liver transplant and impact on mortality for such patients.

Methods: We analyzed 500 referrals to the LT surgery team between November 2018 to July 2019. Patient particulars, diagnosis, MELD score and plan as advised by the team was noted. A questionnaire was answered individually by each patient or primary caretaker after a minimum waiting period of 4 weeks from the clinic or inpatient visit.

Results: LT was advised in 476 (95%) patients. 34 (7%) patients were lost to follow up.58 out of 442 (12%) eventually underwent LT. Of the 57 patients transplanted at our center there was no inpatient mortality. 306/442 (69.2%) patients did not agree for evaluation. 74 patients died during the period of study out of which 34/74 (45.9%) had no donors, 25/74 (33.7%) had no finances and 15/74 (20.2%) lacked both donor and finances. 30/442 (6.7%) patients improved on follow up and did not require LT.

Conclusion: We conclude that lack of finances and living/deceased donors are the major impediments for LT in the developing world.

Keywords: Organ-Shortage; Waitlist-Mortality; Liver Transplantation

Introduction

Liver transplant (LT) is still in a developing stage in India. Although many large centers have been established in India, the numbers remain low as compared to the requirement. As per government estimates, the required number of LTs in India is about 20/million population (20 - 25000) per year but only about 1200 - 1400 are being performed [1,2]. There has yet not been a study in the Indian subcontinent to analyze patients referred to a liver transplant surgery team and the reasons why patients did not reach liver transplantation. In this study we attempt to retrospectively analyze referrals made to the LT surgery team and reflect on the reasons for patients not undergoing this life saving surgery in India and the resulting impact on survival and mortality.

Material and Methods

This was a retrospective analysis of 500 referrals to the LT surgeryteam between November 2018 to July 2019 at AIG Hospitals, Hyderabad, India. Informed consent was taken from each participant and IRB (Institutional Review Board) clearance was obtained. Patient particulars, diagnosis, MELD (Model for End Stage Liver Disease) score, contact number, referring doctor and plan as advised by the team was noted. A questionnaire was answered individually by each patient or primary caretaker after a minimum waiting period of 4 weeks from the clinic or inpatient visit. This was done either by a telephonic interview or during clinic visit or during the hospital admission of the patient. All referrals were either outpatient or inpatient consults and were made by a dedicated team of senior hepatologists at our hospital. All referrals were assessed for need for LT. Reasons were noted for patients

who were not advised transplant. Patients who were advised transplant were counselled about risks, benefits and the cost involved in LT. The patients/relatives who did not agree for evaluation despite being LT candidates were grouped under "LT refused" while those who agreed for further evaluation were grouped under "LT agreed". Reasons were noted for those who did not agree for evaluation despite needing transplant while evaluation was initiated for those who agreed. Mortality, improvement or deterioration was enquired from the patients or the primary caretaker as part of the questionnaire. All patients were closely followed up until they got transplanted, dropped out due to various reasons, were lost to follow up, improved to an extent which did not merit transplant or died while being evaluated.

Results

88% patients were male and 61% were between the age group of 41-60 years (Range: 6 months to 70 years, Mean Age 47 years ± 13 years (Standard Deviation)). Etiology and regional distribution of patients from India and abroad are shown in table 1 and 2 respectively. 95.2% (476/500) were found eligible for LT and 6.8% patients were lost to follow up. Out of the 24 (4.4%) patients who were rejected for transplant, 12 (2.2%) had advanced cardiopulmonary disease, Hepatocellular cancer beyond criteria or were generally considered unfit for transplant. The other 12 (2.2%) patients were considered too early for transplant and were advised close follow up. 6% of all referrals were initially advised LT but improved subsequently without LT and are under close follow up (Figure 1). Out of the patients who refused evaluation and are still alive at the time of study, 25.8% have no donors (5 donors were rejected after complete evaluation: 3 with low graft recipient weight ratio and 2 with unfavorable anatomy). 42.6% patients who refused evaluation have no financial means for LT and 31.4% lack both finances and donors (Figure 2). 11 donors were rejected based on Body Mass Index of more than 30 or a CT scan showing Liver Attenuation Index close to 0 or negative. 21.2% (106/500) patients agreed for evaluation. 8.4% (9/106) of those who agreed died during evaluation, or if LT was not completed or post-transplant. 5/9 were under work-up. 3/9 patients reached LT but were not transplanted due to various reasons (1 had undiagnosed miliary tuberculosis, 1 had Hepatocellular carcinoma which had become metastatic and 1 had extensive venous thrombosis at the time of surgery). 1 patient underwent LT elsewhere and the reason for mortality is unknown. 57 patients were transplanted at our center with no mortality (mean follow-up 4 months, Range: 1 to 9 months) and 40 patients were under work up at the time of completion of the study. In the "LT refused" group, 74 patients died during the period of study. 34/74 (45.9%) had no donors, 25/74 (33.7%) had no finances and 15/74 (20.2%) lacked both donor and finances. MELD specific Kaplan Meier curves for mortality are shown in figure 3. The Log Rank test and Hazard Ratios for overall mortality based on MELD score are shown in table 3. Mean Survival in patients who refused evaluation is shown in table 4.

Diagnosis	Number of patients (n = 500)
Ethanol CLD	309 (62%)
NASH CLD	77 (16%)
Cryptogenic CLD	26 (5%)
HBV and HCV CLD	41 (8%)
Autoimmune CLD	11 (2%)
Acute Liver Failure	11 (2%)
Miscellaneous CLD	25 (5%)

Table 1: Etiology of referrals. (CLD: Chronic Liver Disease; NASH: Non-alcoholic Steato-Hepatitis; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus).

Regional distribution (India and Abroad)	Number (n = 500)
North and west India	80 (16%)
Andhra Pradesh and Telangana (Local states)	230 (46%)
Eastern India	154 (30.6%)
Other states (India)	22 (4.5%)
Foreign	14 (2.8%)

Table 2: Geographical distribution of patients: 2.8% of patients were from outside India.

Chi-squared	7.4771
DF	2
Significance	P = 0.0238

MELD Score	15 - 20	21 - 30	31 - 40
15 - 20	-	2.3581 1.1873 to 4.6833	3.5776 1.6797 to 7.6199
21 - 30	0.4241 0.2135 to 0.8423	-	1.5172 0.8964 to 2.5679
31 - 40	0.2795 0.1312 to 0.5953	0.6591 0.3894 to 1.1156	-

Table 3: Comparison of survival curves (Logrank test) and Hazard ratios for mortality based on MELD Score in patients who refused LT evaluation (N = 74).

(MELD: Model for End Stage Liver Disease; DF: Degrees of Freedom).

MELD Score	Mean	SE	95% CI for the mean
15 - 20	25.500	4.573	16.536 to 34.464
21 - 30	16.488	1.251	14.036 to 18.940
31 - 40	14.345	0.854	12.670 to 16.019
Overall	16.135	0.845	14.479 to 17.792

Table 4: Mean survival based on MELD score in patients who refused evaluation and died (N=74) (SE: Standard Error; CI: Confidence Interval; MELD: Model for End Stage Liver Disease).

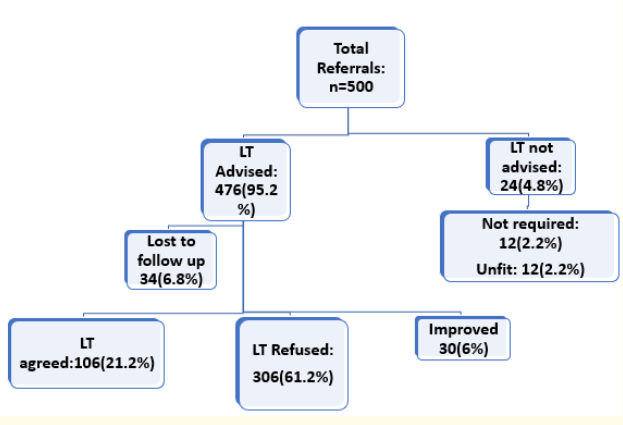

Figure 1: Flow chart for all referrals. (LT: Liver Transplant, "LT agreed" means Patient and/or relatives agreed for transplant evaluation, "LT refused" means patients and/or relatives refused for transplant evaluation despite being LT candidates).

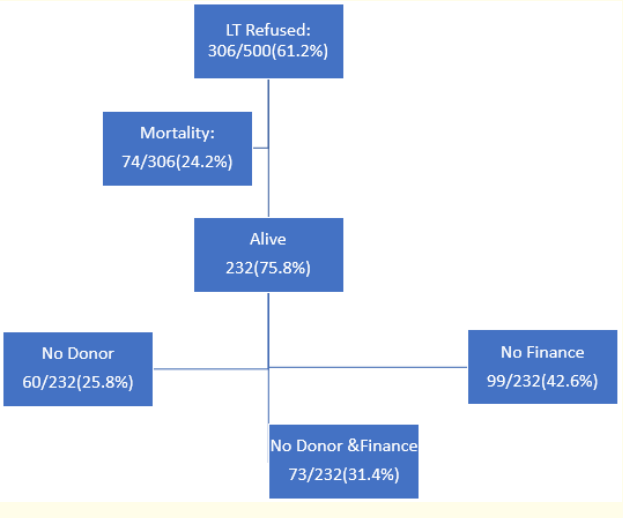

Figure 2: Reasons for refusing transplant evaluation. (LT: Liver Transplantation, LT refused means patient and/or relatives refused evaluation for liver transplant, Alive refer to patients who are eligible for LT and were alive at the time of study).

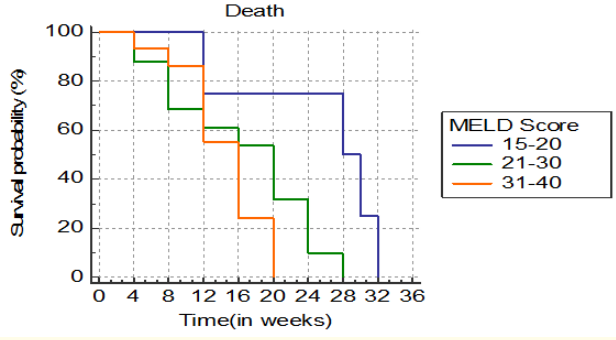

Figure 3: Kaplan Meier Survival Analysis based on MELD score from time of referral to death in patients who refused transplant evaluation (N = 74) (MELD: Model for End Stage Liver Disease).

Discussion

From the Indian subcontinent, Jayshri., *et al*. studied referrals from physicians and the impact of early referrals on mortality [3]. We could not find any study from the Indian subcontinent which looks at reasons for not reaching LT amongst those who refuse transplant. A study from Singapore found that they were able to transplant 20.2% of their total referrals which was mainly attributed to the unavailability of deceased donors [4]. The overall mortality amongst referrals in this study was 44.3% over a span of 15 years.

The Indian scenario is much different from the west or some of the developed Asian countries. Low deceased donation rate is a contributor [5] to the low transplant rates but that has been partially countered to some extent predominantly by LDLT programs [6]. This counters waitlist mortality and offers transplants to patients when they are relatively fitter. However, in the Indian context the problem is not the availability of LDLT programs, but the availability of two main factors required for the LDLT, i.e. willing related liver donor and finances. Since almost all LT programs in India are private set ups and mostly do LDLTs [7], finances and donors become the limiting factor for LTs.

In the 500 referrals to us within the span of just 9 months, transplant evaluation itself was refused by 306 out of the 476 in whom it was advised initially. Strict organ donation laws in India [8] allow for donation only from nearest family member (wife, parents, siblings and children, grandparents, grandchildren). For all other donors, government permission has to be obtained which is often a cumbersome process. 60/306 patients are still alive and require transplants but have no available fit donors. There were 5

donors in this group who were rejected: 3 because of low Graft recipient weight ratio and 2 because of unfavorable anatomy. Weight loss was encouraged in donors who were rejected for fatty liver or high BMI for re-evaluation. This highlights the importance of organ donation and the allocation system for deceased donors, especially because waiting for donors to become fit can lead to mortality or complications on the waitlist. In the absence of a UNOS (United Network for Organ Sharing) like system, currently organ allocation from deceased donors is state-wise, transplant center-based system where the sickest patient may not be able to get the desired organ. The problem is compounded by a low organ donation rate in most of India.

Almost 99/306 patients do not have the finances to undergo transplant despite having a family member willing to donate part of their liver. This highlights two important points. One, because LT is currently offered in mostly in private hospitals and is expensive as per Indian standards with a range from 2 to 2.5 million Indian rupees ($27,000 to $34,000 approximately) at most centers [1] (Average per capita income in India is 5350$ [9]), a majority of patients are not able to afford LT. Many of those who afford it do so after selling their properties and assets which often lead to increased financial burden and often bankruptcy for many families. Secondly, current government schemes offer too little and because LT is low on priority, majority of health spending in the country is on communicable and preventive medicine [10]. Even in the patients that we transplanted, 8 patients received financial support from Non-Governmental Organizations and/or crowd funding. The long-term clinical impact on these patients is still unknown as immunosuppressive drugs, management of complications and continuity of care will still require finances.

We concentrated on MELD based mortality in our study to highlight the urgency for liver transplant. We did not consider ALF (Acute Liver Failure) as that is a distinct group of patients. The overall mean survival amongst patients who died with MELD above 30 and refused transplant evaluation was about 14 weeks but in those who had MELD lower than 21 was about 25 weeks. This was significant on cumulative Log Rank test ($P < 0.05$). This data, although small, and the hazard ratios (Table 3) highlight that high initial MELD score at referral is a significant indicator for early death and should prompt urgent LT unless contraindicated.

There are many limitations to this study. First, we were unable to ascertain the validity of the responses of the patients or their primary caretaker. Initially, the patient/caretaker may be over whelmed after knowing the financial, legal and medical aspects of a LT. Secondly, reasons for mortality are not clearly elucidated for all patients as being related to liver disease or otherwise as this was a retrospective study and follow up is usually not at the same center except for a few patients who visit our center regularly. The overall median survival amongst patients who refused transplant evaluation and died was 16 weeks but in those who had MELD lower than 21 was about 28 weeks. This data seems skewed towards higher MELD as lower MELD patients who died were fewer and patients referred to us had high MELD. Thirdly, we do not have the data about the patients who got transplanted elsewhere and cannot predict the outcomes at other centers even though only one caretaker reported a mortality in these patients. Fourth, long term outcomes of patients and financial burden on the families is undetermined, especially because most of the patients are between the financially productive age group of 40 - 60 years and are often the breadwinners of the family. Also, the indirect costs to the families may not have been fully elucidated and hence the financial burden may be even more grave. Fifth, for those patients who improved and did not require transplant, data for reasons of their initial refusal is lacking. Last, but not the least, we have not assessed social and educational status of the patients and we accept that some patients even after detailed counselling may refuse transplant despite having resources or may not put their potential donor at risk.

Despite these shortcomings, this is the first study from the Indian subcontinent which focusses exclusively on referrals to a LT surgical team. It highlights the fact that deceased donation and financial support are the key to prevent deaths in patients eligible for transplantation in the Indian subcontinent. We recommend strengthening of transplant programs at government institutions, increase in government aid to poor patients eligible for transplant, better organ allocation system which is patient centric and extensive promotion of deceased donation to counter organ deficiency to save more lives.

Conclusion

We conclude that lack of finances and living/deceased donors are the major impediments for LT in the developing world.

Author's Contribution

Ashish Mishra: Consultant, Liver Transplant and HPB, Apollomedics Hospital, Lucknow, India.

Ashish Bansal: Assistant Professor, Surgical Gastroenterology and Liver Transplant, Nizams Institute, Hyderabad, India.

S Soundappan: Consultant, HPB and Liver Transplant, GEMS Hospital Coimbatore, India.

Raghuram Reddy: Consultant, Liver Transplant and HPB, AIG Hospitals, Hyderabad, India.

Kumaraswamy P: Consultant, Liver Transplant and HPB, AIG Hospitals, Hyderabad, India.

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