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Liver Transplant Outcome: Case Selection and Timing of Referral are the Keys

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ABSTRACT

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Incidence of Liver cirrhosis is exponentially increasing in Kerala due to genetic factors, sedentary lifestyle, dietary factors and alcoholism. Since metabolic syndrome is a common background for cirrhotic transformation, the role of internists and general practitioners in diagnosing and following up cirrhosis cases cannot be underestimated. Among many factors which result in poor post-transplant outcome, delayed referral has been identified as a major cause in India. There seems to be an unmet need in making these healthcare professionals aware of the "standard of care" practices and guidelines regarding when to refer a patient for transplant evaluation. This review attempts to highlight the central role of referral network in optimal timing of referral and consequent good post-transplant outcome.

Keywords: Compensated and decompensated liver failure, Liver transplantation outcome, Delayed referral, Followup

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INTRODUCTION

Cirrhosis of liver in India has seen a progressive increase in incidence over the past few decades.[1] Principal contributors to this incremental incidence are an unmasking of the genetic predilection for Metabolic Syndrome (MetS) coupled with widely prevalent unhealthy dietary and lifestyle factors including alcoholism. It would be pertinent to point out that both these factors are the result of socio-economic progress in the country. Asians have an inherent genetic predilection for metabolic syndrome which includes visceral obesity, dyslipidemia, hypertension and diabetes. A sedentary lifestyle along with the diet which is rich in refined carbohydrates and fats has fuelled the rise of metabolic syndrome and Non Alcoholic Steatohepatitis (NASH) in India, 8-10 % of which progress to cirrhosis.

The healthcare sector in Kerala has developed in parallel to the economic development resulting in a larger pool and hence, easier access to qualified specialist health care practitioners which increases the likelihood of a cirrhotic getting channelized towards the transplant track at the right time. However, the exponential rise of Diabetes and metabolic syndrome in the country, both which playing causal role in cirrhosis of liver, will only lead to a more central role for internists and even the primary care physicians, in the diagnosis and management of chronic liver disease. There exists a tangible and unmet need to equip these healthcare professionals with the "standard of care" practices and guidelines of when to refer a patient for transplant evaluation.[2]

Long Term Management of Cirrhosis & Timing of Transplant Refferal

Every patient with chronic liver disease (alcoholic, non alcoholic, viral or autoimmune) eventually progresses to cirrhosis with the passage of time. However, this progression is largely asymptomatic and hence, physicians must actively keep a watch on subtle early features of cirrhosis with regular blood work and periodic imaging.

Once cirrhosis sets in, it is a progressive disease usually culminating in death unless, transplantation is performed. The median survival of compensated cirrhosis is 12 years and decompensated cirrhosis is 2-4 years. The transition from a compensated to decompensated phase occurs at approximately 5-7% per year and can be divided into stages:

Stage 1- Absence of esophageal varices or ascites

Stage 2- Varices have formed but ascites is yet to develop

Stage 3- Onset of ascites

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Stage 4- Variceal bleed with or without ascites

Stage 1 & 2 are compensated phases while stages 3 & 4 are decompensated phases. Ascites is the most common first presentation of decompensation. The division of these stages has prognostic significance as reflected by the mortality rates which range from 1% for stage 1 to 57% for stage 4. The rate of progression of cirrhosis is variable and can roughly be estimated to 10% per year.[3] Nearly half the deaths in stage 4 occur within 6 weeks of portal hypertensive bleeding. In addition to this eventual decompensation, Hepatocellular Carcinoma (HCC) can complicate the course of illness at 3% per year and can occur in any stage. Though HCC is not defined as a decompensating event, detection of the same necessitates referral to a hepatologist for transplant evaluation and/or loco regional ablation therapies like Radio Frequency Ablation (RFA), Trans arterial Chemo Embolisation (TACE) and Transarterial Radioembolisation (TARE).

In short, long term management of Cirrhosis includes regular assessment of the stage of the disease and appropriate timing for transplant referral. Patients and the care-giving physician must recognize the fact that survival rapidly dwindles for patients once they enter the decompensation phase. More importantly, they need to understand that beyond a certain point while following up a decompensated disease, the outcomes of transplantation will also be adversely affected, progressively towards futility. This tipping over point or optimal time of referral does matter a lot. Akin to late referral, a too early transplant is equally not justifiable. Referral should not be done if the patient has sufficient functional parenchymal reserve and low portal pressures so that his one year mortality is less than 10%, which happens to be peroperative mortality during transplant surgery in the best of world centers. If projected one year mortality as pointed out by Child and MELD scores is more than 10 percent, then it is justified to embark on transplant surgery which has 10 % mortality. One needs to understand that even after recovery from transplant surgery, the patient will not have the same life span as his or her age and sex matched counterparts in general population. Instead, the transplanted patient is put in a time bound survival track of 90-95% at 1 year, 85-90% at 5 years and 60-70% at 10 years. These survival figures are related to adverse effects of immunosuppression, namely, accelerated metabolic syndrome (Post Transplant Metabolic Syndrome; PTMS), more predilection for malignancies and immunosuppressive medication induced chronic kidney disease (CNI Nephropathy).[4]

To put in nut shell, the decision to refer a cirrhosis case for transplant at the optimal time, weighing the survival benefit versus peroperative mortality, short term and long-term morbidity, poor outcomes of late referrals and disadvantageous situation of curtailed lifespan in case of too early referral, indeed is a delicate balancing act.

SUCCESS OF LIVER TRANSPLANTATION

Over the last two decades, liver transplantation has evolved from an experimental procedure to the standard of care for end stage liver disease. The survival rates for these patients are excellent with most studies showing a 90-95% survival at 1 year, 85% at 5 years and 60-70% at 10 years. However, these figures are subject to optimal timing of transplantation, precise protocol driven selection of patients looking at absolute and relative contraindications and meticulous long term post-transplant care centered round tailor made immunosuppression, management of post-transplant metabolic syndrome and cancer surveillance, delivered by a trained liver transplant physician.[5]

There has been a remarkable increase in the number of transplants across the major cities in India, but this rise has not been in proportion to the drastic increase in the incidence of cirrhosis thereby creating a wide disparity. The important bottlenecks are an absence of a robust dead donor program, unavailability of a suitable living donor and financial constraints especially in the absence of a third party benefactor or government funding. In addition, late referral beyond the point where transplantation cannot yield any meaningful outcome results in increased post-transplant morbidity and poor post-transplant survival. However, late referral is a modifiable factor easily offset by creating awareness in the referral network with regard to optimal timing for pre-liver transplant evaluation.

IMPORTANCE OF TIMING OF REFERAL FOR TRANSPLANT EVALUATION

Referral to a liver transplant physician is just the first step in an exhaustive long drawn pre transplant evaluation process. Numerous modifiable factors would be detected during the evaluation process, including cardiopulmonary factors like porto-pulmonary hypertension. If the patient is malnourished and "sarcopenic", nutritional therapy to optimize the patient for transplant surgery is another situation which leads to delay in transplantation. If the potential living related donor

has significant steatosis, diet and lifestyle modification to optimize the graft will prove to be time consuming.

Therefore the initial referral must happen when the patient is well enough to undergo evaluation and listing but at the same time decompensated enough to consider transplant intervention. In other words, referral must take place sufficiently early to incorporate adequate time for an exhaustive evaluation and to institute subsequent optimization strategies in order to achieve best possible post-transplant outcomes.[7]

OBJECTIVE GUIDELINE FOR REFFERING BASED ON SEVERITY OF DISEASE

Severity of cirrhosis as assessed by Child-Turcotte-Pugh score (CTP) or Model for Evaluation of End stage Liver Disease (MELD) score are objective ways for early referral. This CTP score employs five clinical measures of liver disease **(Table 1 & 2)**. Each measure is scored 1-3, with 3 indicating the most severe derangement.[6]

Table 1. Showing clinical and laboratory parameters used In CTP Scoring for assessing severity of liver disease

Measure	1 point	2 points	3 points
Total bilirubin, (mg/dl)	(<2)	(2-3)	(>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Table 2. Showing grading of severity of Chronic liver disease based on CTP Classes

Points	Class	One year Survival	Two year Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Criteria for optimal timed referral for best outcomes

1. Child- Pugh score (CTP) > 7
2. Model for Evaluation of End stage Liver disease (MELD) > 15
3. First decompensation event (Ascites, variceal bleed, hepatic encephalopathy)
4. Any space occupying lesion/Hepatoma in Imaging (USG / CT)

MELD is a mathematical score determined by using the following laboratory measures: Serum creatinine, Prothrombin time – INR (International normalized ratio) and serum bilirubin. Online calculators or smart phone applications are an easy avenue for the calculation of MELD score. MELD ranges from 6 – 40 and an individual score equates to 3 month mortality as shown in **Table 3.**

Table 3. Showing Prediction of 3 months mortality based on MELD scores

MELD	3 Months mortality
> 40	71.3
30-39	52.6
20-29	19.6
10—19	6
<9	1.9

INDICATIONS FOR LIVER TRANSPLANT[8]

Cirrhosis liver with first episode of decompensation (stage 3 & 4) warrants evaluation by a liver transplant physician. Apart from decompensation of liver function, another indication for transplant referral is Hepatocellular cancer (as diagnosed on imaging as a space occupying lesion on USG Abdomen or typical CT findings).

ABSOLUTE CONTRA INDICATIONS

1. Cardio-pulmonary diseases

A meticulous evaluation to look for significant coronary artery disease with dobutamine stress echocardiography in all and coronary angiogram in selected cases is a standard protocol followed in most transplant centers. A 2 D echocardiogram to look for features of Porto-pulmonary hypertension (PPH) is usually a good screening tool. PPH in its severe form is diagnosed by right heart catheterization and pressure measurements, is an absolute contraindication for liver transplantation. Hepatopulmonary syndrome (HPS) as diagnosed by agitated saline contrast echocardiography is an indication for transplantation owing to post-transplant reversibility. However, severe HPS is associated with high peri-operative mortality.

2. Sepsis / Active infection

Since immunosuppressive medications are given immediately after transplant, active infection if present at the time of transplant will progress to severe and often fulminant infections. Clinical situations like spontaneous bacterial peritonitis (SBP), cholangitis in case of chronic cholestatic liver diseases like primary

sclerosing cholangitis & recurrent pyogenic cholangitis should be carefully evaluated after adequately treating the infection with broad-spectrum or an appropriate culture sensitive antibiotic

3. Extra hepatic malignancy

An untreated extra hepatic malignancy is an absolute contraindication. Those with a past history of malignancy may be considered for transplantation if the malignancy was treated 2-5 years before the transplant evaluation. (Variability exists between various malignancies)

4. Active Substance abuse

Alcohol or any other ongoing recreational drug use is an absolute contraindication. In alcoholic liver disease, a 6 month period of abstinence is mandatory in most transplant centers world over.

RELATIVE CONTRAINDICATIONS

1. Advanced age:

As age advances, there is an increased possibility of complications owing to a progressive decline in cardiopulmonary reserve. Most centers keep an age cut-off of 65-70 years. However, a significant degree of flexibility is exercised, particularly if the patient is physiologically younger than his/her chronological age.

2. Obesity:

Obesity causes technical problems during surgery and an increased rate of post surgical complications. Most transplant centers keep a BMI of 40 as cut-off.

3. History of poor adherence to medications, Poor social support and major psychiatric illness

4. Malnutrition and frailty:

Advanced cirrhosis is associated with loss of muscle mass (sacropenia). Sacropenic patients tend to have prolonged stay in the ICU and poor post operative outcome. Hepatic sacropenia worsens due to late referrals and strict adherence to prevalent traditional beliefs regarding dietary restriction in liver diseases.

Hepatoma Surveillance

Given the fact that 80- 90 % of hepatomas, occur in the setting of cirrhosis, internists and primary care physicians should understand the importance of 4-6 monthly ultrasonography surveillance to look for Hepatocellular carcinoma. Loco regional ablation therapies like Radiofrequency Ablation (RFA) & Trans arterial Chemo Embolization (TACE) are available in select centers in India. Lesions identified at a smaller size (2-3 cm) have better results with these therapies. Also, contrary to popular misconception, hepatocellular cancer is an indication for liver transplant as long as it fits into the Milan criteria (A single lesion between 2-5 cm or up to 3 lesions largest measuring 3 cm with no lymphatic or vascular invasion).[9,10]

Inevitable delays during Evaluation and Optimisation of Liver Transplant Recipients and Donors Necessitate early Referral[7]

Liver transplantation indeed is an elixir of life for prolonging survival in cirrhosis, long considered a chronic disease with no cure. The first step before referral to a transplant center is to diligently dissect the indication for transplantation and weigh the mortality and morbidity associated with declining hepatic reserve to that incurred during surgery and the attendant post-surgical complications.[8,11,12] The liver transplant surgery itself carries a mortality of 10% with significant morbidity-post operative as well as long term medical complications (infections, malignancy, accelerated metabolic syndrome and macro vascular complications, immunosuppression associated renal damage) which culminates in financial and emotional burden. After approval of the indication, the second step would be to identify absolute contradictions. The final step is to identify modifiable factors in recipient and potential living donors, which may influence post-transplant outcomes and employ optimization strategies.

Examples of Evaluation & Optimization delays

1. Alcoholic liver disease: Ensure 6 month of abstinence. Facilitate referral to a de-addiction unit and self help groups like Alcoholics Anonymous (AA). Resurgence of alcoholism post-transplant is wasteful of resources.
2. Obesity: If BMI > 40, weight reduction should be advised. Obese recipients have poor postoperative outcomes.
3. Malnutrition, Sarcopenia – Dietary and physiotherapy inputs.
4. Cardio-pulmonary issues need to be addressed like CAD needing an angiogram; Porto-pulmonary hypertension should be evaluated with reversibility assessment and adequate management of Hepatopulmonary syndrome including home oxygen therapy if indicated.

5. Stop Smoking: Smoking enhances risk of malignancies post-transplantation due to immunosuppression which provides an environment conducive for neoplastic transformation.
6. In Cirrhosis due to HCV/HBV – Antiviral therapies have to be initiated and optimized before transplant to prevent post-transplant recurrence.
7. HCC should be subjected to loco regional ablation therapies like RFA / TACE as a bridge to transplant in cases which are listed for DDLT.
8. Living donor steatosis > 20 % as assessed by imaging +/- liver biopsy, demands a period of intense dietary and lifestyle modifications and re-evaluation to look for improvement.

CONCLUSION

The opportunity to prolong the life span of cirrhotics with liver transplantation is a potent intervention in our efforts to combat this chronic disease with devastating consequences. It is impossible to over emphasize the importance of early referral, optimal evaluation and therapy of transplant recipients and donors. The therapeutic window for liver transplantation with good results may be lost if the referral is omitted or delayed. Evaluation & optimization of the transplant recipients and donors can cause unforeseen delays in transplantation thereby highlighting the need for early referral of these patients. Every physician following up cases of cirrhotic patients including general practitioners, internists and gastroenterologists in non-transplant centers should keep a close watch for signs of decompensation with regular blood work & surveillance imaging for hepatoma. The first episode of decompensation should prompt referral to a liver transplant physician for pre-transplant evaluation. In those without overt decompensation, a MELD score > 15 may serve as an objective cut off for referral.[7]

END NOTE

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Abbreviations

MetS - Metabolic syndrome
NASH - Non Alcoholic Steatohepatitis
HCC - Hepatocellular carcinoma
RFA - Radiofrequency Ablation
TACE - Transarterial Chemo embolization
TARE - Transarterial Radio embolization
MELD - Model for Evaluation of End stage Liver Disease
CTP - Child-Turcotte-Pugh
USG - Ultrasonogram
CT - Computerised Tomogram
PPH - Portopulmonary Hypertension
HPS - Hepatopulmonary Syndrome
SBP - Spontaneous Bacterial Peritonitis
AA - Alcoholic Anonymous
HBV - Hepatitis B virus
HCV - Hepatitis C virus
DDLT - Deceased Donor Liver Transplantation
CAD - Coronary Artery Disease

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