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Referral patterns and waiting times for liver transplantation in Singapore

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ABSTRACT

Introduction: Referral patterns, waiting times, waiting list, and mortality provide information on how effectively a transplant programme deals with referred patients. This paper aims to review these parameters in the Singapore National Liver Transplant Programme.

Methods: Data of all patients referred to the Singapore National Liver Transplant Programme since its inception were captured and outcomes were retrieved and described.

Results: 562 patients were referred for liver transplant evaluation from 1990-2004, consisting of 457 adults and 105 children. The main indications for referral were hepatitis B liver disease and hepatocellular carcinoma in adults, and biliary atresia in children. Most patients were of United Network of Organ Sharing (UNOS) status 3 or 4 at the time of referral. 114 (20.28 percent) patients had transplants, consisting of 66 adults (14.44 percent) and 48 (45.71 percent) children. 138 adults and ten children were rejected for transplant, mainly for the reason of being "too early". The median waiting time for adults who had transplants was 3.3 months while adults still on the waiting list had been waiting for 16.2 months. The overall waiting list mortality was 44.3 percent, being 52.5 percent in adults and 23.2 percent in children.

Conclusion: The overall transplantation rate is low and the waiting list mortality is high as a result of low availability of organs, particularly in adults. Paediatric liver transplant appears to have been better at dealing with referred patients but this is probably due to availability of living-related liver transplant. Improvement in these may result from the Human Organ Transplant Act.

Keywords: liver transplantation, organ availability, patient referral patterns, waiting lists

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INTRODUCTION

Liver transplantation has revolutionised the care of patients with end-stage liver disease, and is now the standard of care for such patients⁽¹⁾. Before the era of liver transplantation, prognosis of patients with decompensated liver disease was poor and patients did not survive longer than months to years. This scenario has been transformed, and long-term survival is the norm⁽¹⁾. Similarly, in acute liver failure, liver transplantation is a life-saving procedure but in this situation, the rapid deterioration of patients and the narrow window of opportunity makes transplantation more urgent⁽²⁾. Despite the considerable progress in liver transplantation, many issues remain unresolved, including optimal timing of transplant for different indications, distribution of scarce donor organs and resources, and medical care of long-term post-transplant complications⁽²⁾. Some of these matters are discussed in the related articles in this issue of the journal.

Both the primary care physicians and specialists involved in the care of patients with both acute and chronic liver diseases need to understand and appreciate the criteria for referral for transplantation⁽²⁾. Many patients with chronic liver disease may remain stable for long periods and decompensation may occur abruptly secondary to an acute event such as variceal bleeding or spontaneous bacterial peritonitis^(3,4), or the prognosis may be altered due to development of hepatocellular carcinoma (HCC)⁽⁵⁾. Hence, timely referral is important for a successful outcome⁽⁶⁾. The ability to intervene, and to complete full evaluation as well as psychological preparation in potential transplant recipients for liver transplantation before any major deterioration is essential. On the other hand, donor liver availability is a critical issue particularly in Asia where organ donation rates are relatively low. The recent change in the Human Organ Transplant Act (HOTA) in Singapore may go

some way towards rectifying this problem⁽⁷⁾. However, the scope of the problem, the referral patterns, the status of the patient, waiting times, and mortality on the waiting list are important parameters for our transplant programme to be evaluated, particularly as a new liver transplant centre in the Singapore General Hospital is being set up.

METHODS

In Singapore, the Singapore National Liver Transplant Programme is located at the National University Hospital (NUH). The programme comprises a multi-disciplinary team including liver surgeons, hepatologists, gastroenterologists, intensivists, anaesthetists, paediatricians, psychiatrists, infectious diseases specialists, transplant coordinators, dietitians and social workers. Though the programme was physically located at NUH, the members are from all public restructured hospitals as well as the private sector. The transplant team meets twice a week to discuss its patients and transplant-related issues.

The programme runs on an "open" concept, i.e., any medical healthcare workers are welcome to participate. Decisions are made on a consensus basis. Patients are referred to the programme either by its regular members, doctors outside the programme, or rarely, are self-referred. Referred patients and their issues, including severity of liver diseases, indication for transplant, comorbidities, and social issues, are discussed at the regular weekly meetings and they are concluded as: (1) accepted to the waiting list; (2) accepted to the pending list; or (3) rejected. Initially this was based on a combination

of the Child-Pugh score and symptomatic end-stage liver disease. This remains essentially unchanged with the introduction of the MELD and PELD scores in the USA⁽⁸⁾, although these MELD and PELD scores are used to prioritise patients once they are listed.

Data of all referred patients are captured in a database, and are fully evaluated. Patient's status is classified according to the United Network of Organ Sharing (UNOS) (Table IIIB)⁽⁹⁾. Decisions on listing are made by the transplant team at its weekly meeting based on established criteria in the Liver Transplant Protocol. The verdicts are then conveyed to the patients and the referring doctors. Patients who are listed on the waiting or pending lists are followed-up at the transplant clinic at regular intervals, and their progress are updated regularly to the rest of the team members. Patients who are rejected for liver transplantation are usually discharged back to the referring doctors for further follow-up. Patients who are initially considered unsuitable for transplantation may be referred and discussed at a later date when their liver diseases progressed. All data are captured in the Liver Transplant Database.

For this study, all patients who were referred to the Liver Transplant Programme from January 1990 to December 2004 were analysed for the referral patterns as well as the outcome of the referred patients. Frequency and proportion of categorical data were presented descriptively and median (minimum-maximum) was used to describe continuous data.

RESULTS

Over the 15-year period, 562 patients were referred to the programme for consideration for liver transplantation. 105 (18.7%) were paediatric and 457 (81.3%) were adult patients. The number of referrals for transplants per year is shown in Table I. The average number of referrals per year since 1996 was 56. Indications for referrals are listed in Table II. Hepatitis B cirrhosis, HCC and cryptogenic cirrhosis were the commonest indications for adult referrals. On the other hand, biliary atresia was the most common indication for paediatric referrals.

The status of the patients is listed in Table IIIA. The majority of patients was at UNOS status 3 and 4 when referred (see Table IIIB for definitions of UNOS status). However, 21 (4.2%) of the total referred patients were at UNOS status 1, i.e. that they had grave prognosis without a transplant. Six of these 21 patients died before a full evaluation of transplantation could be performed, nine were listed on the waiting list, but only three eventually had transplants.

The outcome of referral is listed in Table IV. Overall, 177 adult and 69 paediatric patients were accepted on the waiting list. 148 patients were rejected

Table I. Number of referrals for liver transplant by year.

	Adult referrals	Paediatric referrals	Total
1990-91	12	4	16
1992	14	3	17
1993-94	11	3	14
1995	3	6	9
1996	31	10	41
1997	35	12	47
1998	46	11	57
1999	47	12	59
2000	70	8	78
2001	42	10	52
2002	54	4	58
2003	45	12	57
2004	47	10	57
Total	457	105	562

Table II. Indications of referrals for liver transplant.

Indication	All patients n (%)	Transplanted n (%)
Adult patients		
1. Hepatitis B cirrhosis/Hepatitis B-related	138 (30.2 %)	20 (30.3 %)
2. Hepatocellular carcinoma	94 (20.5 %)	20 (30.3 %)
3. Cryptogenic cirrhosis	51 (11.1 %)	6 (9.0 %)
4. Hepatitis C cirrhosis	32 (7.0 %)	5 (7.5 %)
5. Alcoholic liver diseases	29 (6.3 %)	1 (1.5 %)
6. Drug-induced liver failure	29 (6.3 %)	4 (6.0 %)
7. Primary biliary cirrhosis	20 (4.3 %)	3 (4.5 %)
8. Primary sclerosing cholangitis	11 (2.4 %)	2 (3.0 %)
9. Wilson's disease	9 (1.9 %)	1 (1.5 %)
10. Acute liver failure	10 (2.2 %)	0 (0.0 %)
11. Autoimmune hepatitis	11 (2.4 %)	1 (1.5 %)
12. Others	23 (5.0 %)	3 (4.5 %)
Paediatric patients		
1. Biliary atresia	77 (73.3 %)	38 (79.2 %)
2. Byler's disease	4 (3.8 %)	1 (2.1 %)
3. Alagille syndrome	5 (4.7 %)	3 (6.3 %)
4. Glycogen storage disease	3 (2.8 %)	2 (4.2 %)
5. Hypoplastic bile duct syndrome	2 (1.9 %)	1 (2.1 %)
6. Neonatal hepatitis	2 (1.9 %)	0 (0.0 %)
7. Others	12 (11.4 %)	3 (6.3 %)

Proportion of referred patients who were transplanted:

Adult (66/457) = 14.4%; Paediatric (48/105) = 45.7%; Total (114/562) = 20.3%

Table IIIA. UNOS status of all referred patients.

UNOS status	Adult patients n (%)	Paediatric patients n (%)
1	18 (5.9)	3 (3.8)
2	50 (16.3)	6 (7.7)
3	117 (38.1)	37 (47.4)
4	80 (26.1)	17 (21.8)
7	42 (13.7)	15 (19.2)

for liver transplant. The reasons for rejection are listed in Table V. "Too early" was the commonest reason for rejection, followed by too extensive HCC. At our centre, the Milan criteria for transplantation for HCC were used⁽⁶⁾. Briefly, patients with HCC were considered for transplant if they have one nodule less than 5 cm in diameter, or a maximum three nodules with maximum size of 3 cm each, and with no evidence of regional or systemic spread.

The median waiting time for liver transplantation in those who already had transplants was 3.3 months but those still waiting for transplantation have waited

Table IIIB. United Network of Organ Sharing (UNOS) score definition.

Status	Definition
7	Temporarily inactive. A patient listed as Status 7 is temporarily inactive.
4	At home and functions normally. Patients in Status 4 are considered to be elective patients.
3	Continuous medical care. A patient listed as Status 3 requires continuous medical care and has a Child-Turcotte-Pugh (CTP) score ≥ 7 . Status 3 patients may be followed up at home or near the transplant centre. Short hospitalisations for intercurrent problems are not considered justifications for a change in status.
2	Continuously hospitalised. These patients are in such a medical condition that they cannot leave the hospital; therefore continuous hospitalisation of at least five days on a hospital floor, or in the ICU, but not qualifying as a Status 1.
1	ICU. A patient has fulminant liver failure with a life expectancy without a liver transplant of less than 7 days.

Table IV. Outcome of patients referred for transplant.

Outcome	n
Adult patients	
1. Transplanted and well	49
2. Rejected	138
3. Refused/absconded	25
4. Recovered	23
5. Transferred	22
6. Died after transplant	17
7. Died before evaluation	56
8. Died while waiting	93
9. Still waiting	18
10. Pending	16
Total	457
Paediatric patients	
1. Transplanted and well	39
2. Rejected	10
3. Refused/absconded	5
4. Recovered	3
5. Transferred	8
6. Died after transplant	9
7. Died before evaluation	2
8. Died while waiting	16
9. Still waiting	5
10. Pending	8
Total	105

Table V. Reasons for rejection from transplant.

	n
Adult patients	
1. Still early for transplant	31
2. Extensive tumour/ big tumour size/secondaries	32
3. Old age/medical problems/ unfit	17
4. DNA +/-active infection	3
5. For resection of HCC	3
6. No family/social support after transplant	2
7. Others/reason not recorded	50
Total	138
Paediatric patients	
1. Still early for transplant	8
2. No funds for LRLT	1
3. Severe pulmonary stenosis	1
Total	10

Table VI. Duration of different outcomes.

Outcome	Median time (min-max) (in months)
Waiting time for liver transplant 3.26 (0.07-19.67)	
In adult patients	3.03 (0.07-18.03)
In paediatric patients	3.61 (0.10-19.67)
Died while waiting 0.93 (0.07-31.57)	
In adult patients	0.76 (0.07-30.83)
In paediatric patients	5.60 (0.13-31.57)
Patients still waiting 16.15 (4.83-57.33)	
In adult patients	16.15 (4.83-52.67)
In paediatric patients	16.61 (9.27-57.33)

Table IIIC. UNOS status of patients who were transplanted.

UNOS status	Adult patients n (%)	Paediatric patients n (%)
1	2 (4.1)	1 (2.6)
2	6 (12.2)	1 (2.6)
3	31 (63.3)	26 (66.7)
4	10 (20.4)	10 (25.6)
7	0 (0.0)	1 (2.6)

Table IIID. UNOS status of patients who died while waiting.

UNOS status	Adult patients n (%)	Paediatric patients n (%)
1	6 (8.3)	1 (8.3)
2	21 (29.2)	4 (33.3)
3	39 (54.2)	5 (41.7)
4	6 (8.3)	2 (16.7)

an average of 16.2 months. For patients who died on the waiting list, they had waited for a median of only one month before their demise (Table VI). The overall waiting list mortality was 44.3%, mainly contributed by the adult waiting mortality rate of 52.5% compared to the much lower paediatric waiting list mortality of 23.2%. Among those adults who died on the waiting list, a higher proportion of patients had more severe liver disease, 8.3% and 29.2% who died were UNOS 1 and 2, respectively, compared to 4.1% and 12.2%, respectively, of patients who had transplants. Similar results were seen in paediatric patients (Tables IIIC & IIID).

DISCUSSION

Liver transplantation is the treatment of choice for patients with end-stage liver diseases⁽¹⁰⁾. This is now an

established treatment in Singapore with excellent results since 1995, as shown in the other articles in this issue of the journal. As such, the numbers of referrals have increased. However, the transplantation rate is low; only 20.2% of all referred patients had transplants. This is largely a result of the low cadaveric organ donation rate, and consequently our waiting list mortality is much higher than larger transplant centres, such as in the USA, which was 106 per 1,000 patients year in the year 2002⁽¹¹⁾. For those lucky enough to receive a liver transplant, the median waiting time was only three months, but for those still on the waiting list, the median waiting time has now risen to a high of 16 months. However, this seems to compare favourably with the USA, where UNOS status 3 waiting time increased from 22.6 months to 53.5 months from the year 1997 to 2000⁽¹¹⁾.

It remains to be seen whether the changes in the HOTA are able to address our poor donation rate. Other methods have been used to attempt to increase the pool of liver donors, such as public education on the benefits of liver transplantation, refined surgical techniques such as split liver grafts for paediatric patients and left lobe living donors for paediatric patients⁽¹²⁾. Recently, right lobe living-related transplants have also been performed on adult patients⁽¹³⁾. Such measures could improve the overall availability of donor livers and address the shortfall in transplant requirements.

Survival of patients at UNOS status 1 is poor without liver transplantation⁽¹⁴⁾. Unfortunately, these patients were often referred late. Of the 21 patients referred, six (28.6%) died even before a full evaluation of liver transplantation could be performed, while another six (28.6%) were rejected mainly due to significant pre-morbidity and presence of sepsis. Of the nine who were listed on the waiting list for transplant, only three eventually received a liver transplant and the other six patients died before a liver graft was available. For these patients, early referral is critical as the window of opportunity is narrow, and measures to optimise liver function, prevent sepsis and complications may be life-saving. Nonetheless, patients in UNOS status 1 are often those with acute or fulminant hepatic failure and are unlikely to obtain a cadaveric donor at short notice. This is the main problem with a small liver donor pool as we have in Singapore, and urgent cases can only resort to adult living-related donor transplantation. While changes in HOTA may increase availability of liver donors, it is uncertain whether this will meet the narrow time-lines required for fulminant hepatic failure.

Timing of referral has been a subject of discussion. Guidelines from the American Association of Study of Liver Diseases (AASLD) suggest that patients should be referred to a transplant centre if they develop evidence

of synthetic dysfunction, experience their first major complication (e.g. ascites, variceal bleeding, or hepatic encephalopathy), or develop malnutrition; and they should be listed for transplantation once the CTP ≥ 7 ⁽¹⁰⁾. Guidelines from the United Kingdom recommend early referral of potential candidates to transplant programmes to facilitate the timing and outcome of transplantation and that referral, and hence transplantation, should preferably occur before the development of malnutrition, hepatorenal failure, and an advanced UNOS score⁽¹⁵⁾. It is noteworthy that 26% of transplant rejections were due to the patient being too early for transplantation. Although these patients may not warrant transplantation at the time of referral, they should be followed up closely as they are likely to meet transplant criteria in due course.

In summary, while the numbers of referrals for liver transplantation have increased over the years, the overall rate of transplantation remains low, and waiting list mortality high. The median time for those still waiting for transplantation is a very high 16 months. It remains to be seen whether the changes in HOTA will have a significant impact on these figures. The use of adult right lobe living-related transplantation and split liver transplants can go some way towards improving this problem.

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