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Liver Transplant in Singapore – Coming of Age

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ABSTRACT

Background/Aim of Study: Liver transplantation was first performed in 1967, and has become an accepted form of treatment worldwide for chronic liver diseases, acute liver failure and certain metabolic diseases. We document our experience in Singapore over the last 7 years since the first transplant was performed in 1990.

Method: Retrospective study at National University Hospital, Singapore.

Results: Twenty-two operations (10 paediatric and 12 adults) have been performed with the last 17 having been performed in the last 17 months. Currently, there are 15 survivors (68%) since 1990, and percentage survival is even better if one considers the cases from the last 17 months when the majority of cases (17 transplants – 77%) were performed (77% survival). The most common indication for transplant was biliary atresia for the paediatric group, while the adults were transplanted for hepatitis B and C cirrhosis, primary biliary cirrhosis, and fulminant liver failure. Tacrolimus is the main immunosuppression (10 patients), with the remaining 5 patients on cyclosporine. Various surgical techniques (living donor, graft reduction) have been employed successfully to provide a complete transplant service. Hospital and ICU stays are within normal limits and the hospital charges range from a low of S$30,000 to S$141,000.

Conclusion: Liver transplantation has become a reality in Singapore with outcomes comparable to other transplant centres. The shortage of donors remains the greatest stumbling block for further expansion.

Keywords: liver transplant, outcome, cost, indications, Singapore

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INTRODUCTION

The first successful orthotopic liver transplant was performed in 1963 by Starzl[1], and since then thousands of transplants have been performed worldwide. Five-year survival rates have been reported to be 70%[2] and the procedure has become an accepted mode of treatment for a variety of chronic liver diseases, metabolic diseases, and hepatomas. Certain subgroups like the patients with cholestatic liver diseases (primary biliary cirrhosis and primary sclerosing cholangitis) have an even better outcome (75% to 90% 1-year survival)[3]. The improvement in survival has occurred with the introduction of cyclosporine[4], and this is currently part of the standard triple therapy regimen (azathioprine, prednisolone and cyclosporine). More recently, tacrolimus has also been introduced[5] and forms the first choice with prednisolone as our immunosuppressive regimen. Various surgical techniques have also been pioneered to extend the range of possibilities: reduced grafts[6], split grafts[7], auxiliary transplants[8], and living-related transplants[9]. Anaesthetic practices as well as the care in the intensive care unit have improved. The practice of liver transplantation has become a multi-disciplinary team effort, and the number of transplant centres has grown rapidly over the last decade.

Singapore performed its first liver transplant in 1990, and that patient who had autoimmune hepatitis is currently still alive. She has also delivered a baby recently. The liver transplant programme is based at National University Hospital with a multi-disciplinary team. In addition, the programme receives valuable support from other doctors, in-line with it being a national programme. The programme is beginning to grow with an average of one transplant per month for the last 17 months, and it is thus timely to report our experience in Singapore (both cadaveric and living-related transplants) and also provide cost information for comparison with other countries.

PATIENTS AND METHOD

All liver transplant patients performed in National University Hospital (NUH), Singapore since 1990 up to 5 July 1997, were included in the study. Our current indications for transplant are listed in Table I. Their diagnosis, biodata and outcome are presented. Charges of the patient work-up and the transplant episode is presented. Data is presented as mean ± standard deviation.

RESULTS

There were 22 liver transplants (9 females, 13 males), with 12 adults and 10 paediatric cases. The majority of the cases (77%) was performed under the current Director over the last 17 months, with an average of one transplant per month (Fig 1).

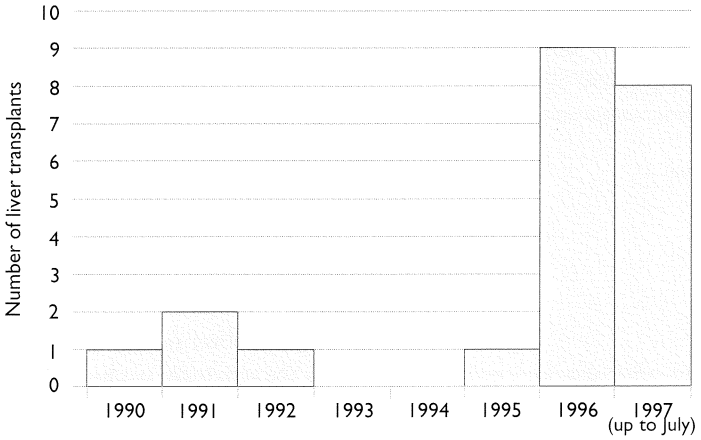

Fig 1 – Number of liver transplants performed by year

Table I – National University Hospital indications for liver transplantation

Ciirrhosis
- Cryptogenic
- Autoimmune
- Hepatitis B
- Hepatitis C

Biliary diseases
- Primary biliary cirrhosis
- Secondary biliary cirrhosis
- Sclerosing cholangitis
- Biliary atresia
- Hypoplastic ducts

Primary metabolic disease
- $Alpha_1$ – antitrypsin deficiency
- Wilson's disease
- Tyrosinaemia
- Glycogen storage diseases

Hepatocellular carcinoma (no metastases, and minimum size)

Fulminant liver failure

Table II – Indications for liver transplant

	Diagnosis	Number
Paediatric		
	Biliary atresia	7
	Cryptogenic liver cirrhosis	1
	Glycogen storage disease	1
	Hypoplastic bile duct	1
Adult		
	Hepatitis B cirrhosis*	3
	Primary biliary cirrhosis	3
	Fulminant liver failure	2
	Hepatitis C cirrhosis*	1
	Auto-immune	1
	Drug-induced	1
	Familial-amyloid	1

* One patient has associated hepatoma

The ages ranged from 15 months to 64 years (adults: mean 49 ± 12 (SD) years; paediatric: 4.5 ± 3.5 years). There were 16 Chinese recipients (73%), 3 Malays (13.6%) and 3 Indians. Currently, 68% are alive and well. Over the last 2 years, when the bulk of the transplants were performed (17 transplants – 77%), 76.5% are currently well and alive. There were 4 living-related liver transplants (3 paediatric, 1 adult) with no mortality for the living-donors. Three recipients (13.6%) were non-residents.

The indications for transplant are listed in Table II. There were no re-transplants. For the paediatric group, biliary atresia was the most common indication, while hepatitis cirrhosis was the most common indication for the adults. All hepatitis B patients were HBV DNA negative (Chiron) at transplant, and were treated with lamivudine prior to transplant and post-transplant. They are currently (post-transplant) all hepatitis B surface antigen negative except one. Patients for the last 2 years had to wait 12.7 ± 10 weeks (range 1 to 32 weeks) for their transplant, with 4 patients having waited for more than 6 months.

There were 7 deaths and the cause of death is listed in Table III. There were 2 paediatric deaths and 5 adult deaths. Most deaths (6/7) occurred within 3 months of the transplant where 4 of the adults died from the transplant episode itself.

The hospital length of stay for the adults that survived to discharge since 1996 was 28 ± 10 days (range from 17 to 42 days), while the paediatric patients had a longer hospital stay (41 ± 11 days (range 30 to 64 days)). Length of stay in the intensive care unit was 11.7 ± 6 days (range 4 to 25 days). Charges for transplant ranged from as low as S$30,000 to S$141,000 (excluding professional fees).

Since 1996, 7 livers were harvested under the Human Organ Transplant Act 1987 (HOTA), 6 under the Medical (Therapy, Education and Research) Act 1972, and 4 living-related donors. Three mothers donated to their child and one husband donated to his wife. There were no ABO mismatches.

DISCUSSION

The overall results are encouraging as the survival figures have improved recently and are comparable to those described in USA or Europe. Patient selection is a major determinant of outcome[10]. Those patient who were sufficiently ill to be in the ICU prior to the transplant had a uniformly dismal outcome (all 3 died post-transplant). However, without transplantation, it is unlikely for those with fulminant liver failure to survive[11]. Thus, it was decided to proceed despite the knowledge that poorer results may ensue by transplanting such a group of patients. The programme has increased its activity over the last 17 months (Fig 1), and the more recent survival figures (76.5%) bodes well for the programme. In addition, the introduction of living-related transplants and reduced grafts have expanded our capabilities to provide a comprehensive service in our setting of donor shortage.

It is encouraging to be able to perform transplants for hepatitis B cirrhosis, and it is hoped that with lamivudine the recurrence rate may be reduced[12]. At this moment, hepatitis B surface antigen are negative in all 3 recipients with hepatitis B cirrhosis. No hepatitis B immunoglobulins were given in these 3 patients who received lamivudine. Previously, we had employed hepatitis B immunoglobulin (HBIG) in one patient who was

Table III – Cause of death

Original diagnosis	Cause of death of death (time post-transplant)
Primary biliary cirrhosis	Rejection after discontinuation of immunosuppression by patient (26 months post-transplant)
Fulminant liver failure	Died from bleeding (post-operative)
Fulminant liver failure	invasive aspergillus (POD 9)
Familial-amyloid	Primary graft failure (POD 10)
Drug-induced	Ischemic graft (POD 21)
Biliary atresia	PTLD ($2^1/_2$ months)
Biliary atresia	CMV infection ($5^1/_2$ months)

PTLD – post-transplant lymphoproliferative disease, POD-post-operative day
CMV – cytomegalovirus

HBsAg positive, prior to the availability of lamivudine. Long-term HBIG[13] is reported to reduce the incidence of reinfection (36% vs 75% at 3 years), as well as improve patient survival (76% vs 45% at 3 years), but the cost is prohibitive and concerns exist about the mercurial preservative present (thimerosal) causing toxicity[14].

The medical cost of liver transplants in NUH does not include the doctor's professional fees or other capital or training costs. As such, it is an underestimation of the true cost. In USA[15] and the Netherlands[16], the reported cost of liver transplants are significantly higher (US$223,000 and US$125,000 respectively). In a Royal Free study from London[17], the cost of medical care is also higher for a chronic cirrhosis patient compared to a liver transplant patient in the first 6 months (£3,795 versus £1,964). Further to this, a cost-effective study from USA suggested that liver transplant is more cost-effective than the treatment of acute leukaemia[18]. Singapore's charges are therefore reasonable and lower than the West.

The hospital length of stay is higher in the paediatric group than the adults. Reduced grafts are commonly used in the paediatric group and the majority of the paediatric cases had prior operations (Kasai for the biliary atresia). As a result of these factors, there are more frequent re-operations and abdominal collections that require drainage post-transplant that increase hospital length of stay. In USA, they have reported an average hospital stay of 64 days[15]. However, this was a small group of patients (n=32) and the underlying diagnosis and severity of illness will have an important impact on subsequent outcome and resource consumption.

Living-related liver transplants have been performed extensively in Japan[8]. They provide a good graft with the possibility of less rejection. The operation is an elective procedure. It is important that the family members do not feel coerced into the donation. We send the potential donor for psychiatric assessment prior to donation to detect any such possibility and provide ample time for reconsideration before transplantation. It is also important to maintain the safety of the donor, who undergoes a hepatectomy. To date, none of our donors has died. They have been discharged within one week and are currently well.

Five patients are on cyclosporine while 10 patients are on tacrolimus. All the patients are still on prednisolone. Tacrolimus and prednisolone are the preferred immunosuppression as there appears to be a lesser incidence of acute rejection in the first year post-transplant[5]. Cyclosporine had to be employed instead of tacrolimus in 2 patients because of neurotoxicity that was expressed as disinhibited behaviour despite normal levels of tacrolimus.

In summary, liver transplant has become a viable option for the treatment of chronic liver diseases and metabolic liver diseases in Singapore. The results are good and the cost is reasonable. Transplanting sicker patients will lead to poorer outcomes, but as the programme matures and if there are suffcient organs, such patients should be given an opportunity. The main stumbling block at the moment is the lack of donors, with several patients dying while waiting for their transplants. This has led us to perform living-related transplants where there is a potential risk to the healthy donor. There is still much that can be done to improve the supply of cadaveric organs. These include the application of HOTA to livers instead of the current restriction to kidneys; the adoption of brain-death as legal death outside HOTA; and better education of the public about the process of transplantation[19]. As Singapore strives to be a medical hub of excellence in Southeast Asia, a successful liver transplant programme will go a long way in achieving this goal and demonstrate the coming of age of Singapore medicine. More importantly, Singapore patients with severe chronic liver cirrhosis and certain metabolic disease, now have an opportunity for a significant improvement in their outcome and quality of life by undergoing liver transplantation in their own country.

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REFERENCES

1. Starzl TE, Marchioro TL, Von Kaulla KN, Hermann G, Brittain RS, and Waddell WR. Homotransplantation of the liver in humans. Surg Gynaecol Obst 1963; 117:659-76.
2. Detre KM, Belle SH, Beringer KC, Bost JE, Daily P. Overall national results of liver transplantation between 1987 and 1991. In: Transplantation of the liver. Busuttil RW, Klintmalm GB (eds). Philadelphia: WB Saunders,1996: 824-34.
3. Gordon RD, Todo S, Tzakis AG, Fung JJ, Stieber A, Staschak SM (eds). Liver transplantation under cyclosporine: A decade of experience. Transplant Proc 1991; 23:1393-6.
4. Starzl TE, Klintmalm GBG, Porter KA, Iwatsuki S, Schroter GPJ. Liver transplantation with the use of cyclosporine A and prednisone. N Engl J Med 1981; 305:266-9.

5. The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 1994; 331:1110-5.
6. Strong R, Ong TH, Pillay P, Well D, Balderson G, Lynch S. A new method of segmental orthotopic liver transplantation in children. Surgery 1988; 104:104-7.
7. Otte JB, de Ville de Goyet J, Alberti D, Alberti D, Balladur P, de-Hemptinne B. The concept and technique of the split liver in clinical transplantation. Surgery 1990; 107:605-12.
8. Terpstra OT, Schalm SW, Weimar W, Willemse PJ, Baumgartner D, Groenland TH, et al. Auxiliary partial liver transplantation for end-stage chronic liver disease. N Engl J Med 1988; 319:1507-11.
9. Tokunaga Y, Tanaka K, Uemoto S, Tanaka A, Morimoto T, Yamaoka Y. Risk factors and complications in living related liver transplantation. Transplant Proc 1994; 30:140-4.
10. Shaw BM Jr, Wood RP, Gordon RD, Iwatsuki S, Gillquist WP, Starzt TE. Influence of selected patient variables and operative blood loss on six-month survival following liver transplantation. Semin Liver Dis 1995; 5:385-93.
11. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439-45.
12. Grellier L, Mutimer D, Ahmed M, Brown D, Burroughs AK, Rolles K, et al. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. Lancet. 1996; 348:1212-5.
13. Samuel D, Muller, Alexander G, Fassati L, Ducot B, Benhamou JP, Bismuth H. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993; 329:1842-7.
14. Terrault NA, Zhou S, Combs C, Hahn JA, Lake JR, Roberts JP, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. Hepatology 1996; 23:1327-33.
15. Kankaanpaa J. Cost-effectiveness of liver transplantations – how to apply the results in resource allocation. Preventive Medicine 1990; 19:700-4.
16. Bonsel GJ, Klompmaker IJ, Essink-Bot ML, Habbema JDF, Slooff MJH. Cost-effectiveness analysis of the Dutch liver transplantation programme. Transplant Proc 1990; 22:1481-4.
17. Burroughs AK, Blake J, Thorne S, Else M, Rolles K. Comparative hospital costs of liver transplantation and the treatment of complications of cirrhosis. A prospective study. Eur J Gastroenterol Hepatol 1992; 4:123-8.
18. Valazuela TD, Criss EA, Spaite D, Meislin HW, Wright AL, Clark L. Cost-effectiveness analysis of paramedic emergency medical services in the treatment of prehospital cardiopulmonary arrest. Ann Emerg Med 1990; 19:1407-11.
19. Lee KH. Right to die: Time for Singaporeans to discuss the issues openly. Straits Times 22 Feb 1993.