

Expanding the Donor Pool for Liver Transplantation in the Setting of an “Opt-out” Scheme – 3 years after New Legislation

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Abstract

Introduction: The revised Human Organ Transplant Act (HOTA) was implemented in Singapore in July 2004. We aim to evaluate expanding the potential donor pool for liver transplant in Singapore with the inclusion of marginal donors. **Materials and Methods:** All donor referrals between July 2004 and June 2007 were studied. All potential deceased liver donors were heart-beating. After being reviewed by the transplant coordinator, potential donors were assessed by a transplant hepatologist and a transplant surgeon for suitability of organ donation strictly based on the programme’s donor assessment protocol. Reasons for rejection as potential donors were documented. The clinical characteristics of all donor referrals were retrospectively reviewed, and an independent decision was made as to whether liver retrieval in each rejected case might have been possible. **Results:** Among the 128 potential donor referrals, 20 donors (15.6%) underwent liver retrieval. Of the 20 livers retrieved, 16 were implanted and 4 were not implanted (3 unfit recipients, and 1 donor liver with 40% steatosis). Another 10 donor livers were assessed intraoperatively and were rejected because of varying levels of steatosis. Of these livers assessed, 5 donor livers had steatosis <40% and 5 had steatosis >40%. Of the remaining potential donors, 45 were deemed not possible because of prolonged hypotension (9), on-going or unresolved sepsis (13), high-risk behaviour (4), non-actualisation (8), or pre-existing medical conditions (11). Another 53 donors may potentially have been suitable donors but were rejected because of possible sepsis (13), no suitable recipients (12), transient hypotension (10), transient abnormal liver function test (6), history of alcohol ingestion (5), non-actualisation because of consent (4) and other reasons (3). Overall, it was deemed that 61 donors (47.7%) might potentially have been suitable liver donors. **Conclusions:** Despite new legislation (HOTA) in Singapore, the utilisation of cadaveric donor livers showed no increase in the last 3 years. By expanding our donor criteria to include marginal donors, we could potentially increase the availability of deceased donor livers to meet our waiting list demands.

Ann Acad Med Singapore 2009;38:315-21

Key words: Liver transplant, Marginal livers, New legislation, Opt-out scheme

Introduction

Presently, liver transplantation has become routine management for an expanding group of patients with end-stage liver disease and hepatocellular carcinoma. However, organ availability limits the application of liver transplantation. As a result, there is a large increase in the liver transplant waiting list in the US and a significant increase in deaths while on the waiting list.¹ While the shortage of donor organs is a worldwide problem, the situation appears more critical in Asia where cadaveric organ donation remains below 5 per million population (pmp).² Several strategies employed in increasing the

availability of organs include using living-related liver donors,³⁻⁵ acceptance of marginal donors^{6,7} and legislation of deceased donor transplantation.^{8,9}

In Singapore, the number of cadaveric liver transplants performed remains small (5 to 10 per year), while the survival rates were comparable to well-established liver transplant centres.¹⁰ The small number of liver transplants performed was largely the result of the low cadaveric donation rate. In an attempt to increase organ availability, the Singapore government has revised its legislation on organ donation and made it an “opt-out” scheme for citizens and permanent residents between 21 and 60 years of age.

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The liver transplant unit at the National University Hospital, Singapore has previously applied relatively strict donor selection criteria, and did not include marginal donors. This policy is relevant for units in which small numbers of liver transplants are performed. In this study, we aim to evaluate expanding the potential donor pool for liver transplant in Singapore with the inclusion of marginal donors. Specifically, we explored the possibility of increasing the utilisation of currently available organs with the inclusion of marginal donors to meet our waiting list demands. We also examined the donor pool characteristics in the setting of the opt-out scheme 3 years after the implementation of the revised Human Organ Transplant Act (HOTA) in Singapore.

Materials and Methods

Donor Assessment and Referral Process

The Liver Transplant Programme at the National University Hospital was the sole national liver transplant programme until July 2005. All imminent deaths were initially identified by intensivists, who would then inform the liver transplant coordinator. All donor referrals between July 2004 and June 2007 were studied following the implementation of the revised HOTA. All potential deceased liver donors were heart-beating. After being reviewed by the transplant coordinator, potential donors were assessed by a transplant hepatologist and a transplant surgeon for suitability of organ donation based on the programme's donor assessment protocol. Once brain death certification was done, the transplant team would proceed with organ retrieval. The NUH donor exclusion criteria included presence of significant liver disease, presence of systemic infection or intra-abdominal sepsis, presence of malignancy (other than central nervous system malignancies), documented hypotension with systolic BP <60 mmHg for more than 4 hours, presence of DIVC, history of alcohol or substance abuse and donor liver biopsy with macrosteatosis >30%. The presence of Hepatitis B surface antigen, the presence of anti-Hepatitis C viral antibody and positive HIV antibody serology were also exclusion criteria.

Donor Characteristics

The number of referrals, liver retrievals and actualised liver transplants were documented. The clinical characteristics of all donor referrals were retrospectively reviewed. The cause of death, pre-existing medical history, presence of sepsis, episodes of hypotension, laboratory results and degree of steatosis were abstracted.

Definitions and Classifications of Reasons for Rejection

For the purpose of our study, we have defined and classified the reasons for rejection following a review of the potential donor's characteristics. We retrospectively

reviewed the reasons stated for rejection of each potential donor and carefully looked at factors such as steatosis, sepsis, prolonged hypotension, and alcohol ingestion which might have resulted in utilisation of the livers albeit marginal grafts. An independent decision was made as to whether liver retrieval in each rejected case might have been possible based on the donor characteristics.

Prolonged hypotension was defined as hypotension with systolic blood pressure (BP) <60 mmHg for more than 2 hours with need for inotropic drugs. Hypotension which lasted less than 2 hours and with systolic BP >60 mmHg was classified as transient hypotension.

On-going or unresolved sepsis was defined as positive blood cultures from potential donor, positive cultures from 2 or more sites (sputum/endotracheal tube, urine, wound), or persistent fever or elevated total white counts despite antibiotic therapy. Possible sepsis was defined as transient febrile episodes, elevated total white count with negative cultures, or positive cultures from single site with no evidence of bacteraemia.

Non-actualisation was when potential donors became unstable or asystolic before brain death certification, when potential donors cannot be certified brain dead, or when no consent was obtained from the family under the Medical (Therapy, Education and Research) Act (MTERA) or from the state coroner.

Marginal livers with steatosis <40% were deemed as possibly suitable for liver transplant. Routine donor liver biopsies were done during liver retrieval and liver with steatosis >30% were not retrieved.

Abnormal liver function test (LFT) was defined as persistently elevated aspartate aminotransferase (AST) >150 IU/L and/or total bilirubin >2 mg/dL.¹¹ Transient abnormal LFT was defined as an initial abnormal LFT with subsequent improvement, or no further LFT evaluation following initial abnormal LFT.

Statistics

Data were expressed in means \pm SEM unless otherwise stated.

Results

In total, 128 potential donor referrals were made over the 3-year period between July 2004 and June 2007. Characteristics of donor referrals are shown in Table 1. Donors were generally young and the majority were males. The commonest causes of death were cerebrovascular accidents (73%), including both intracranial haemorrhage and ischaemic infarcts, and trauma-related head injury (23%). Potential donor referrals came under HOTA in 112 (88%) cases and MTERA in 16 cases (12%).

Among the 128 potential donor referrals, 20 donors

Table 1. Characteristics Of Potential Donors (July 2004 To June 2007) after Revised Human Organ Transplant Act

Description	July 2004-July 2007 (3 years after HOTA)
Potential donor referrals	128
Age, years	44.8 ± 1.0
Male (%)	79 (62)
Ethnicity	
Chinese	114 (89)
Indian	7 (6)
Malay	3 (2)
Others	4 (3)
Hospitals	
Public hospitals (%)	123 (96)
Tan Tock Seng Hospital	51 (40)
National University Hospital	31 (24)
Singapore General Hospital	23 (18)
Changi General Hospital	17 (13)
KK Women and Children's Hospital	1 (1)
Private hospitals (%)	5 (4)
Cause of death (%)	
Cerebrovascular accidents	93 (73)
Trauma-related head injury	29 (23)
Others	6 (4)

(15.6%) underwent liver retrieval. Of the 20 livers retrieved, 16 were implanted (10 implanted at National University Hospital and 6 implanted at Singapore General Hospital). Four retrieved livers were not implanted as three recipients were deemed unfit for liver transplant, including one who collapsed intraoperatively during induction, and one retrieved liver had 40% steatosis. Another 10 donor livers were assessed intraoperatively and were not retrieved because of varying levels of steatosis. Of these livers assessed, 5 had steatosis <40% and 5 had steatosis >40%.

Of the remaining potential donors, 45 were deemed not possible because of prolonged hypotension (9), on-going or unresolved sepsis (13), high-risk behaviour (4), non-actualisation (8), or pre-existing medical conditions (11) (Table 2). There were 7 potential donors with prolonged hypotension with systolic BP <60 mmHg despite inotropic support for more than 2 hours, and 2 potential donors with asystole >20 minutes with elevated AST. Six potential donors had proven bacteraemia with positive blood cultures, 4 had uncontrolled sepsis despite antibiotics, 2 had evidence of dengue infection, and 1 had active herpes infection with facial rash. Non-actualisation occurred in 8 potential donors

as 3 had no consent under MTERA, 3 collapsed before brain death certification and 2 had no brain death certification. Eleven potential donors were excluded because of pre-existing medical conditions: aggressive brain tumours (2), Hepatitis B carriers (positive Hepatitis B antigen) (3), Hepatitis C infection (1), haemophilia (1), significant alcohol ingestion with previous variceal ligation (1), significant obesity (150 kg) (1), myeloproliferative disorder (1) and advanced age (68 years) with significant cardiac history (1).

Another 53 donors may potentially have been suitable donors but were rejected because of possible sepsis (13), no suitable recipients (12), transient hypotension (10), transient abnormal LFT (6), history of alcohol ingestion (5), non-actualisation because of consent (4) and other reasons (3). Thirteen potential donors were rejected because of possible sepsis – 8 with positive cultures from single site either endotracheal aspirates (7) or urine cultures (1), 5 with transient febrile episodes or elevated total white counts. Twelve potential donors were rejected because of no suitable recipients: size mismatch (5), no suitable blood group (5) and high-risk recipients (2). Ten potential donors were rejected because of transient hypotension – none of whom had hypotension longer than 2 hours (8 with normal AST, and 2 with AST <150). Six potential donors were rejected because of transient abnormal LFT – 4 had AST <150 IU/L, and 2 had single AST reading >150 IU/L. Five potential donors were rejected because of history of alcohol ingestion – 4 with normal LFT and 1 with AST 151 IU/L. None of these patients had a history of variceal bleeding or ascites. Four potential donors were not actualised because of lack of consent from the state coroner (3) and no consent from the family. The remaining 3 rejections were because of previous total hysterectomy with bilateral salpingo-oophorectomy for cervical intra-epithelial neoplasia (1), presumed steatosis for BMI 24 (1) and the surgeon declined the offer (1). In these 53 potential donors, it was deemed that liver transplant may have been possible from the donor characteristics.

Overall, it was deemed that 61 donors (47.7%) may potentially have been possible liver donors, including 3 retrieved livers that were not implanted and 5 assessed livers with steatosis <40%.

Discussion

Marginal donors were previously not included for potential liver retrievals as the liver transplant unit applied strict donor selection criteria with routine intraoperative biopsies for assessment of steatosis. However, with the increasing acceptance of marginal donors,^{6,7} we embarked on a review of our policy on potential liver donors. This was especially important as we had significant drop-outs and

Table 2. Reasons For Rejection

Stated reasons for rejection	Actual rejection	Potential utilisation of marginal livers
Steatotic livers (10)	Steatosis >40% (5)	Steatosis <40% (5)
Hypotension (19)	Prolonged hypotension (9)	Transient hypotension (10)
Sepsis (26)	Ongoing sepsis (13)	Possible sepsis (13)
Alcohol ingestion (5)	Nil	Alcohol ingestion (5)
Abnormal LFT (6)	Nil	Transient abnormal LFT (6)
High-risk behaviour (4)	High-risk behaviour (4)	Nil
Pre-existing medical condition (13)	Pre-existing medical condition (11)	Pre-existing medical condition (2) - presumed steatosis (BMI 24) - THBSO for CIN
Non-actualisation (12)	Non-actualisation (8)	Possible actualisation (4)
No recipients (12)	Nil	No recipients (12)

Another 3 retrieved livers may have been utilised and 1 liver offer was declined.

deaths on the waiting list (63%). There were 13 patients on the waiting list on the 1 July 2004, and another 28 patients were put on the waiting list over the 3-year period. Of these 41 patients, 10 patients were transplanted. Twenty-six patients died or dropped out while on the waiting list – 11 died on the waiting list, 9 dropped out because of disease progression and 6 were unfit for transplant. Two patients were no longer keen for transplant while 3 patients remained on the waiting list. Hence, expanding our donor pool by including marginal donors may have reduced our drop-out rates and deaths on the waiting list.

Singapore has implemented an “opt-out” scheme with regard to deceased donor transplantation. This important legislation was made in an attempt to increase the potential donor pool, hence benefiting patients who were waiting for suitable organs. There are 2 laws governing organ donation in Singapore: HOTA 1987 and MTERA 1972. Presently, the majority of organs retrieved fall under the HOTA scheme. The HOTA is an opt-out system, where the organs of those who died can be used for transplantation, unless the person had earlier opted out of the system. On the other hand, MTERA is an opt-in scheme, where people pledge their organs to be used for transplants, education or research after they die. Relatives may also donate organs of a brain dead patient who has not made this pledge.

The original HOTA in Singapore was passed in 1987, and allowed retrieval of kidneys from brain-dead, non-Muslim citizens and permanent residents aged 21 to 60 years old and who are of sound mind for the purpose of transplantation, unless there was documented objection from the deceased prior to their deaths.¹² Under the original HOTA, informed consent from the deceased family was needed for liver retrieval. The Singapore government passed

a revised legislation, the revised HOTA, in January 2004, which added liver, heart, and cornea in the organ recovery list, in the event of all causes of death.¹² The revised HOTA was implemented in Singapore in July 2004, and in essence the revised act is an “opt-out” scheme. For religious reasons, Muslims were excluded under the revised HOTA. On 21 January 2008, the Human Organ Transplant (Amendment) Bill was passed by the Singapore Parliament to include Muslims into HOTA. Muslims have been included under HOTA since 1 August 2008.

The unit has had previously performed routine intraoperative biopsies for the assessment of steatosis, and rejected donor livers with steatosis >30%. Following recent data,^{13,14} we are prepared to accept marginal livers with mild-to-moderate steatosis, and we have audited our potential donors according to our current criteria. In a recent study, it was found that severely steatotic grafts (>60%) can be used with no significant difference in 60-day mortality (5% vs 5%) and 3-year survival rate (83% vs 84%) between the control and severe steatosis group.¹⁴ We will apply the clinical judgement of experienced liver surgeons during liver retrievals in the assessment of steatosis similar to the experience of United Kingdom Transplant units. While it can be argued that the clinical judgement of these surgeons about the organ quality can differ substantially from the histological analysis,¹⁵ we note that, to date, there is no publication on the accuracy of intraoperative clinical assessment of liver steatosis. Hence, we will perform routine exploration of the liver of every donor proposed, and only where the liver is deemed steatotic, then needle biopsies for frozen section will be obtained.

Bacterial and fungal infections have previously been contraindicated in cadaveric organ donation due to the risk

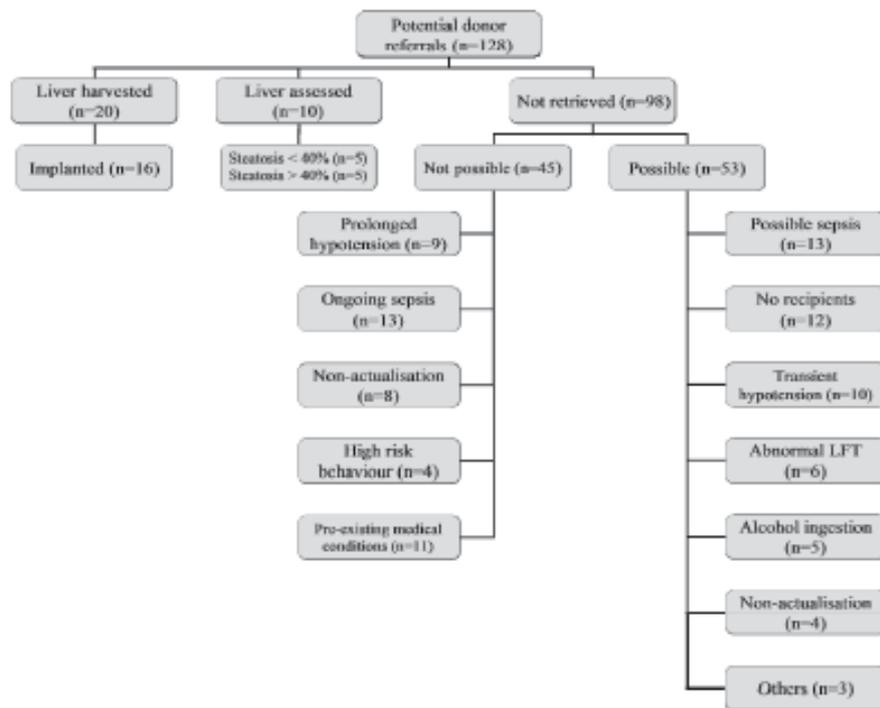


Fig. 1. Outcome of potential donor referrals.

of transmitting these pathogens to immunologically suppressed recipients. Besides the direct transmission of infection, the release of endotoxins or other bacterial products has been proposed to contribute to primary non-function of the graft.¹⁶ However, it has also been shown in 2 large series^{17,18} that despite the presence of bacteraemia in 5% of donors at the time of procurement, no transmission of the isolated pathogen was documented from the donor to the recipient. Furthermore, bacteraemia in the donor did not lead to a negative outcome in the recipients. There were 13 potential donors in our series that were rejected because of possible sepsis based on positive non-haematogenous cultures from a single site without a corresponding positive result on blood culture, transient febrile episodes or an elevated total white count. These allografts could have been accepted for transplantation with minimal or no impact on the clinical outcome. In spite of positive blood cultures, as seen with 6 of our potential donors, these grafts could potentially have been used with the continuation of antibiotics as guided by culture sensitivities with documented therapeutic response in the donor and the same antibiotic should be instituted in the recipient. There is no controlled trial indicating the optimal duration of therapy, but 5 to 7 days of appropriate therapy appears to be the most frequently cited regime.¹⁹ However, it remains prudent to reject donors with uncontrolled sepsis and multi-organ failure at the time of procurement, or where the causative micro-organism is multi-drug resistant.²⁰

Previous United Network for Organ Sharing (UNOS) data have shown that donor organs subjected to prolonged hypotension have no significant increase in post-transplantation graft loss.²¹ However, other studies have shown increased graft dysfunction when donors received norepinephrine or higher doses of dopamine.^{22,23} In a recent study examining donor risk factors from 20,023 transplants as the basis for deriving a donor risk index that may facilitate organ acceptance decisions, hypotension or increased pressor use were not associated with increased graft failure.²⁴ On balance, the evidence is in favour of using grafts from donors with short periods of hypotension (less than 2 hours) with or without vasopressor use. Hence, the 10 donors in our study that were rejected based on transient hypotension could potentially have been grafted. More contentious would be the consideration for transplantation in the 7 patients with systolic BP <60 mmHg despite inotropic support. Parallels can be drawn from the evidence concerning the use of livers from non-heart beating donors (NHBD). Controlled non-heart beating donation with a warm ischaemia time of less than 30 minutes is generally considered to be feasible.²⁵ Even though the results of controlled NHBD approach those of heart-beating donation, vascular and biliary complications might still be higher for a recipient of a NHBD graft.²⁶⁻²⁸ At present, NHBD grafts are not part of the donor liver organ pool in Singapore.

In Singapore, a significant number of patients on the waiting list have hepatitis B viral (HBV) liver disease or

have hepatocellular carcinoma in the background of HBV viral infection. The unit has previously excluded donors who are hepatitis B antigen positive with the specific concern of transmitting HBV infection to the recipient. In addition, de novo HBV infection has been documented in recipients of livers from HBsAg-negative, HBcAb-positive donors.²⁹⁻³¹ Whilst lamivudine mono-prophylaxis may be adequate for the prevention of HBV infection from a HBcAg-positive donor to a naive recipient,³² the use of hepatitis B immune globulin (HBIG) alone or in combination with anti-viral appears to be more effective but also much more expensive.³³ In short, any liver donor positive for HBsAg or HBcAb has a high likelihood of transmitting HBV infection to the naive recipient. Hence, these organs are ideally used for candidates already exposed to HBV who are the majority in our waiting list, and we have revised our donor criteria to reflect this policy. In addition, it may also be appropriate to consider HBcAb-positive donor livers for HBV-negative candidates who are at extremely high risk of dying without transplant as there is effective preventive therapy for HBV infection.

Hepatitis C virus (HCV)-associated chronic liver disease is becoming a major cause for liver transplantation worldwide. HCV recurrence after liver transplantation is nearly universal and may lead to graft failure.^{34,35} There appears to be no difference in graft and patient survival when recipients with HCV-related liver diseases are transplanted with liver grafts from anti-HCV positive donors as compared to those receiving grafts from HCV-negative donors.^{36,37} Unlike HBV where effective prophylactic regimens exist, livers from HCV-positive donors are best used for recipients with HCV infection. However, it will be important to assess HCV activity in the donor liver with liver biopsies because livers with active hepatitis or fibrosis are likely to have poorer results. In addition, as HIV-infected individuals also often have HCV infection, this may result in the consideration of liver transplantation from an HIV-infected donor pool.

History of alcohol abuse in potential donors was a cause for exclusion for liver retrieval. Unless excessive, it may be difficult to quantify the number of units of alcohol consumed by someone who gives a history of regular alcohol consumption. As such, we have proposed that unless biochemical, radiological or histological evidence of liver dysfunction and damage is evident, potential donors should not be rejected based on a history of alcohol consumption per se. At the very least, such donors should be given the benefit of an operative assessment by the procurement team, and if need be, a biopsy performed to further determine whether to use the liver allograft.

In this study, we acknowledge certain limitations as it is retrospective in nature. Specifically, some clinical data

may not have been captured but may have been relevant to the decision to reject potential donors. We have also coded the stated reason of no appropriate recipients as potential utilisation of donor organs. This is because these donor organs may potentially have been utilised if suitable recipients were available. Some of these donors were rejected on the basis that the potential recipients on the waiting list constituted high-risk recipients and that marginal grafts in these recipients may result in a poorer outcome. We were unable to account for the number of such decisions in our study.

This study is the first study critically evaluating our donor pool in Singapore 3 years after the implementation of HOTA. It appears that donor referrals remain at 40 to 45 per year which shows no increase despite the implementation of HOTA compared to an earlier study.⁸ Hence, our policy review to expand our donor pool to include marginal donors is especially important to reduce deaths and drop-out rates on the waiting list. A greater awareness of our policy to include marginal donors amongst our anaesthetists and intensivists colleagues may also potentially result in a greater number of donor referrals.

In conclusion, there is scope to expand the donor pool by including marginal donors in Singapore. This may potentially result in an increased utilisation of donor referrals from the HOTA scheme.

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