TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

A review of the United States experience with combined heart-liver transplantation

Robert M. Cannon, Michael G. Hughes, Christopher M. Jones, Mary Eng and Michael R. Marvin

Division of Transplantation, Department of Surgery, University of Louisville, Louisville, KY, USA

Keywords
acute rejection, amyloidosis, multiorgan transplantation, UNOS.

Correspondence
Michael R. Marvin MD, 200 Abraham Flexner Way, Transplant Center, 3rd floor, Louisville, KY 40202.
Tel.: 502-587-4607;
fax: 502-587-4323;
e-mail: michael.marvin@jhsmh.org

Conflicts of Interest
The authors declared no conflicts of interests.

Received: 19 March 2012
Revised requested: 21 May 2012
Accepted: 20 July 2012
Published online: 2 September 2012

doi:10.1111/j.1432-2277.2012.01551.x

Abstract

Since first described by Starzl, combined heart and liver transplantation (CHLT) has been a relatively rare event, although utilization has increased in the past decade. This study was undertaken to review the United States experience with this procedure; UNOS data on CHLT was reviewed. CHLT was compared with liver transplantation alone and heart transplantation alone in terms of acute rejection within 12 months, graft survival, and patient survival. Survival was calculated according to Kaplan–Meier and Cox proportional hazards. Continuous variables were compared using Student's t-test and categorical variables with chi-squared. Between 1987 and 2010, there were 97 reported cases of CHLT in the United States. Amyloidosis was the most common indication for both heart (n = 26, 26.8%) and liver (n = 27, 27.8%) transplantation in this cohort. Liver graft survival in the CHLT cohort at 1, 5, and 10 years was 83.4%, 72.8%, and 71.0%, whereas survival of the cardiac allograft was 83.5%, 73.2%, and 71.5%. This was similar to graft survival in liver alone transplantation (79.4%, 71.0%, 65.1%; P = 0.894) and heart transplantation alone (82.6%, 71.9%, 63.2%; P = 0.341). CHLT is a safe and effective procedure, with graft survival rates similar to isolated heart and isolated liver transplantation.

Introduction

Since the original reports of Starzl [1] and Shaw [2], simultaneous transplantation of the heart and liver has been a relatively rare phenomenon in the United States. The majority of published data on this procedure consists of single-center case reports [3–8], with the experience of any single center being limited. The largest single-center experience reported to date is that of the Mayo Clinic, with 15 patients [9]. Te and colleagues have reported the United States experience based on UNOS data as of 2005, with 47 total cases reported at the time [10]. Such reports give credence to the feasibility of this formidable procedure, with outcomes that are similar to those of isolated heart transplantation [9,10].

Patients with combined failure of the heart and liver represent a relatively small percentage of the transplant waiting list [11]; however, the unique nature of dual vital organ failure means these patients are often critically ill and would benefit from an aggressive policy toward transplantation. The most common indication for simultaneous heart and liver transplantation appears to be systemic disease, such as amyloidosis, that involves both systems [10]. In the setting of familial amyloidosis, an otherwise normally functioning liver must be replaced to prevent recurrence of cardiac failure by the production of abnormal amounts of hepatic amyloid. There are a number of patients, however, with liver failure and concomitant severe cardiac disease who would not be candidates for liver transplantation unless they are able to undergo simultaneous cardiac transplantation. This review was undertaken to update the results of Te and colleagues [10] and provide a picture of the current status of simultaneous heart and liver transplantation in the United States.

Methods

Under an Institutional Review Board exemption, the UNOS database of liver and thoracic transplants as of

3/31/11 was reviewed retrospectively. The time period under study was from October, 1987 through December, 2009. All patients undergoing simultaneous orthotopic heart and liver transplantation were reviewed. Patients undergoing isolated heart and isolated liver transplantation during the same time period were analyzed for comparisons of acute rejection within 1 year, as well as graft and patient survival. Graft survival was defined in months from the date of transplantation to the date of graft failure, death, or last follow-up. Patients who died with a functioning graft were not censored. Patient survival was defined in months from transplantation to death or last follow-up. Graft and patient survival was calculated according to Kaplan–Meier and compared in a univariable fashion using the log-rank test. Multivariable analysis of patient and graft survival was performed using Cox-proportional hazards regression. Continuous variables were summarized as means, whereas categorical variables were summarized as counts/percentages. A *P*-value of <0.05 was considered significant. All statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Between 1987 and 2010, there were 97 cases of simultaneous orthotopic cardiac and hepatic transplantation performed in the United States. During this same period, there were 96 033 liver alone transplants and 67 852 heart alone transplants. A simultaneous kidney transplant was performed in nine patients, whereas lungs were transplanted in 10 cases. The mean age of recipients was 43.7 years, with the oldest patient being 67 years old and the youngest less than 1 year. The majority of recipients (68, 78.1%) were males. Remaining baseline characteristics in the simultaneous cardiac-liver transplantation patients are presented in Table 1. In the post Model for Endstage Liver Disease (MELD) era, there were 65 patients undergoing simultaneous transplantation with an average laboratory MELD score of 13.8. Seventeen patients (26.2%) had an active MELD exception at the time of simultaneous transplantation. Fourteen exceptions were for familial amyloidosis, one was for portopulmonary hypertension, and the final was for reasons not specified in the dataset. In terms of cardiac listing status, 43 (44.3%) of simultaneous heart-liver recipients were listed as cardiac status 1a/1b versus 20 520 (33.3%; $P = 0.021$) of those undergoing isolated cardiac transplantation. The frequency with which simultaneous heart-liver transplantation has been performed has been on the rise in recent years. From a sporadic event in the early 1990s, there has been at least one simultaneous transplant per year since 1995, with greater than 10 performed per year since 2007. The most performed in a single year has been 13 in 2009 (Fig. 1).

Table 1. Baseline characteristics of patients undergoing simultaneous cardiac-liver transplantation. Continuous variables are presented as mean (standard deviation) while categorical variables are presented as count (percentage).

Age	43.7 (16.0)
Gender	
Male	68 (70.1%)
Female	29 (29.9%)
Body mass index (kg/m^2) at registration	24.3 (5.1)
MELD Score at transplant (2002 and after)	13.8 (5.4)
Hemodynamics at registration	
Cardiac output (l/min)	4.5 (1.6)
Pulmonary arterial systolic pressure (mmHg)	42.8 (18.9)
Pulmonary arterial diastolic pressure (mmHg)	21.8 (9.9)
Pulmonary arterial mean pressure (mmHg)	30.2 (11.6)
Pulmonary capillary wedge pressure (mmHg)	19.5 (7.8)
VAD support at registration	4 (4.1%)
IABP support at registration	0 (0.0%)
Ventilator support at registration	4 (4.1%)
Inotropic support at registration	24 (24.7%)
Creatinine at transplant (mg/dl)	1.42 (0.96)

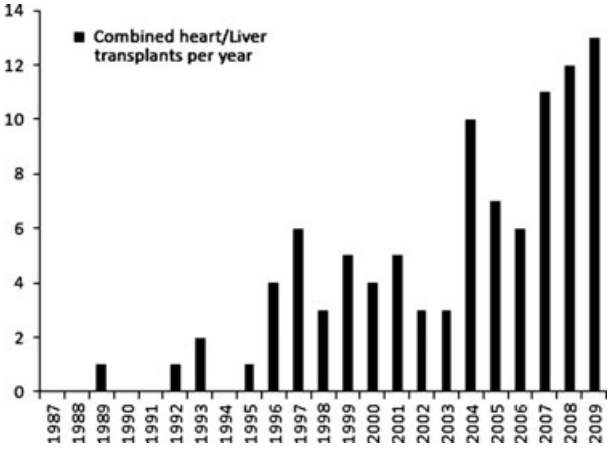

Figure 1 Combined heart/liver transplants performed by year in the United States.

The most common indication for cardiac transplantation was amyloidosis in 26 (26.8%) patients, followed by 17 (17.5%) with congenital cardiac disease and 14 (14.4%) patients with idiopathic dilated cardiomyopathy. The most common indication for liver transplantation was amyloidosis in 27 (27.8%) patients, followed by cardiac cirrhosis in 17 (17.5%) patients. Remaining indications for transplantation are listed in Table 2. There were 12 liver graft failures and 1 cardiac graft failure. The sole case of heart graft failure was because of primary graft nonfunction. The most common contributor to liver graft failure was infectious in four cases, followed by primary graft nonfunction in three cases. There were two graft

Table 2. Indications for simultaneous cardiac-liver transplantation.

Primary cardiac diagnosis, *n* (%)	
Amyloidosis	26 (26.8)
Idiopathic dilated cardiomyopathy	14 (14.4)
Ischemic dilated cardiomyopathy/coronary artery disease	7 (7.2)
Alcoholic dilated cardiomyopathy	3 (3.1)
Other dilated cardiomyopathy	6 (6.2)
Restrictive cardiomyopathy (not because of amyloid)	5 (5.2)
Congenital cardiac disease	17 (17.5)
Hypertrophic cardiomyopathy	3 (3.1)
Valvular disease	3 (3.1)
Primary pulmonary hypertension	2 (2.1)
Hemochromatosis	4 (4.1)
Glycogen storage disease	1 (1.0)
Cystic fibrosis	1 (1.0)
Sarcoidosis	1 (1.0)
Unknown/not specified	4 (4.1)
Primary liver diagnosis, *n* (%)	
Amyloidosis	27 (27.8)
Cardiac cirrhosis	17 (17.5)
Chronic hepatitis C	12 (12.4)
Cryptogenic cirrhosis	10 (10.3)
Alcoholic cirrhosis	4 (4.1)
Chronic hepatitis type not specified	2 (2.1)
Acute hepatic failure	2 (2.1)
Primary biliary cirrhosis	3 (3.1)
Primary sclerosing cholangitis	2 (2.1)
Biliary atresia/hypoplasia	2 (2.1)
Hemochromatosis	6 (6.2)
Other metabolic disease	2 (2.1)
Cirrhosis not otherwise specified	3 (3.1)
Carcinoid	1 (1.0)
Cystic fibrosis	2 (2.1)
Budd-chiari syndrome	1 (1.0)
Unknown/not specified	1 (1.0)

losses from acute rejection, and another two graft losses from vascular thrombosis.

The incidence of acute liver rejection within 1 year for patients with liver graft survival greater than 1 year was 5.2% ($n = 4$) for those undergoing simultaneous transplantation versus 12.2% ($n = 8929$) for those undergoing liver transplantation alone ($P = 0.060$). The incidence of acute cardiac rejection within 1 year for patients with cardiac graft survival greater than 1 year was 8.9% ($n = 7$) for those undergoing simultaneous transplantation compared with 23.9% ($n = 13017$) for those undergoing heart transplantation alone ($P = 0.002$).

The mean age of recipients of simultaneous transplants was 43.7 years, compared with 45.4 years for liver alone recipients and 46.4 years for heart alone recipients ($P < 0.001$). Pairwise comparison between the three groups revealed only the difference between liver alone and heart alone recipients to be statistically significant ($P < 0.001$). Simultaneous transplant recipients were significantly more likely to be male (70.1%) than recipients of liver alone (61.5%) or heart alone (67.9%) recipients ($P < 0.001$). Donors were significantly younger for recipients of simultaneous transplants (28.7 years) than for recipients of liver alone transplants (35.5 years; $P < 0.001$). There was no significant difference in donor age for recipients of simultaneous transplants and recipients of heart alone transplants (28.7 years; $P = 1.0$).

Liver graft survival at 1, 5, and 10 years for patients undergoing simultaneous heart and liver transplantation was 83.4%, 72.8%, and 71.0% compared with 79.4%, 71.0%, and 65.1% ($P = 0.894$) for those undergoing liver transplantation alone during the same time period (Fig. 2).

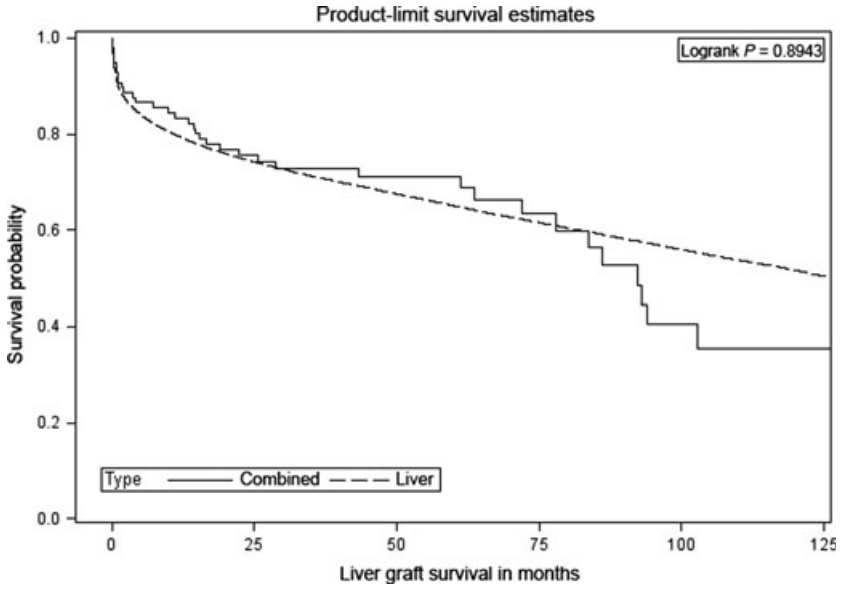

Figure 2 Liver graft survival of patients undergoing combined heart/liver transplantation versus isolated liver transplantation.

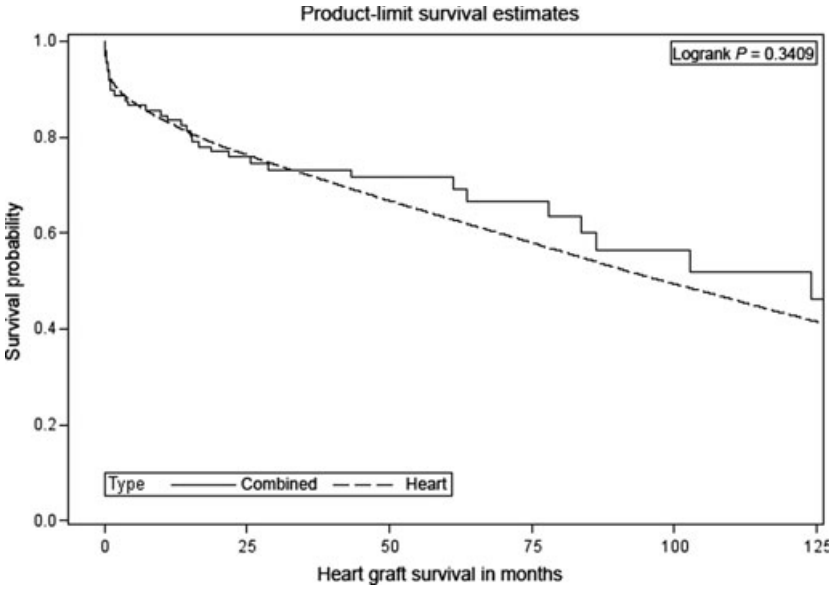

Figure 3 Heart graft survival of patients undergoing combined heart/liver transplantation versus isolated heart transplantation.

Table 3. 1, 3, and 5-year patient survival for patients undergoing isolated liver transplant, combined liver and heart transplant, and isolated heart transplant.

	1-year	3-year	5-year
Liver alone	85.4%	78.0%	72.4%
Combined	84.4%	73.9%	72.3%
Heart alone	83.3%	73.2%	64.8%

$P < 0.001$.

Heart graft survival at 1, 5, and 10 years for patients undergoing simultaneous transplantation was 83.5%, 73.2%, and 71.5% compared with 82.6%, 71.9%, and 63.2% ($P = 0.341$) for those undergoing heart transplantation alone during the same time period (Fig. 3). Patient survival for simultaneous cardiac and liver transplantation was between that for isolated liver transplantation and isolated heart transplantation (Table 3). There was no statistically significant difference in patient and graft survival in simultaneous transplant patients with amyloidosis versus other indications, although there appears to be a trend toward better outcomes with amyloidosis (Table 4).

Multivariable analysis of patient survival controlling for recipient age, recipient gender, and donor age revealed no significant increase in the risk for patient death (HR 1.30; 95% CI 0.93–1.84; $P = 0.127$) or graft failure (HR 1.09, 95% CI 0.79–1.52; $P = 0.589$) with simultaneous versus liver transplantation alone. Similar multivariable analysis of simultaneous versus heart alone transplantation also did not reveal differences in patient survival (HR 0.90, 95% CI 0.64–1.26; $P = 0.538$) or graft survival (HR 0.86, 95% CI 0.62–1.21; $P = 0.386$).

Table 4. Patient and graft survival for patients undergoing simultaneous cardiac-liver transplantation for amyloidosis versus other indications.

	Amyloid indication	Other indications	*P*-value
Liver graft survival			0.585
1 year	92.2%	80.2%	
3 years	86.4%	67.8%	
5 years	79.7%	67.8%	
Heart graft survival			0.328
1 year	92.3%	80.3%	
3 years	86.5%	68.1%	
5 years	79.9%	68.1%	
Patient survival			0.375
1 year	92.3%	81.5%	
3 years	86.5%	69.1%	
5 years	79.9%	69.1%	

Discussion

Since the initial review of the United States experience with simultaneous heart-liver transplantation performed by Te [10], there has been substantial growth in the field. As of 2005, there have been 55 cases performed, with more than 10 per year since 2007. As previously noted, amyloidosis remains the most common indication for simultaneous transplantation. Amyloidosis describes a relatively diverse group of disease processes with the end result being amyloid protein deposits building up primarily in the peripheral nervous system as well as in end organs, such as the heart and liver [12]. Despite frequent involvement of the liver, the frequency of significant hepatic failure appears to be relatively rare [13]. Cardiac

involvement, on the other hand, frequently results in congestive heart failure and a poor prognosis [14].

The form of amyloidosis most relevant to heart and liver transplantation is familial amyloidosis, which results in deposition of the mutant protein transthyretin, most commonly in the peripheral nervous system [10]. As the majority of transthyretin is produced in the liver, hepatic transplantation has become accepted treatment for this devastating disease [15,16]. There are over 80 variants of familial amyloidosis [17], of which the most common is the Portuguese variant, which does not typically affect the heart [9]. For patients with other variations of familial amyloidosis, however, amyloid deposition in the heart continues to occur after liver transplantation with progression of cardiac failure. Because of this, simultaneous heart and liver transplantation is the preferred treatment[18]. In a review of their single center experience at the Mayo clinic, Raichlin and colleagues found that the specific form of familial amyloidosis did not affect the success of simultaneous heart and liver transplantation [9].

Despite the formidable nature of simultaneous cardiac and hepatic transplantation, outcomes following the procedure are quite good. We have found in this review that graft survival following the simultaneous procedure is equivalent to that following isolated heart or isolated liver transplantation. An interesting finding is that patients receiving simultaneous transplantation appear to exhibit lower rates of acute rejection than those patients undergoing heart transplantation alone. In an analysis of the UNOS database, Rana *et al.* found that rejection rates in patients cotransplanted with a heart, liver, or kidney from the same donor are significantly lower than when those organs are transplanted in isolation [19]. The liver in particular appears to provide a protective effect to other organs. A proposed mechanism for this protective effect is the shedding of soluble human leukocyte antigens [20,21]. This protective effect has led some to propose that patients undergoing simultaneous liver and heart transplantation may tolerate a reduced level of chronic immunosuppressive therapy compared with patients undergoing isolated cardiac transplantation [9].

Given the severe metabolic and physiologic derangements caused by combined cardiac and hepatic failure, modifications to the organ allocation policy may be justified for patients with combined disease. The allocation systems for isolated heart and liver transplantation were designed for their specific organ, and thus do not take into account derangements caused by the failure of the other organ system. For example, patients may be listed as cardiac status 2 if the decrease in systemic vascular resistance caused by hepatic dysfunction allows sparing of inotropic support, even though their cardiac function alone is poor enough to otherwise justify status 1A or 1B [11]. Although this phenomenon may occur in patients with very severe hepatic failure, we have found that recipients undergoing simultaneous cardiac-liver transplantation were actually more likely to be listed as cardiac status 1a/1b than their counterparts undergoing isolated heart transplantation. The second and third most common diagnoses for combined transplantation were dilated and ischemic cardiomyopathy, with liver transplantation performed for cardiac cirrhosis. In this setting, cardiac function would be severely impaired, which would account for the greater proportion of patients undergoing simultaneous cardiac-liver transplantation with status 1A or 1B than in the cardiac transplant alone population.

Our data shows that the average laboratory MELD at the time of simultaneous cardiac and transplantation is relatively low; however waitlist mortality for these patients would undoubtedly be higher than patients with isolated hepatic failure at a similar MELD score. Porrett and colleagues have examined the effect of allocation policies on patients with combined cardiac and hepatic failure, and found that current policy tends particularly to disadvantage patients with MELD scores in the range of 20–29 and cardiac status 2. In their review, they found that national wait list mortality for patients listed for both heart and liver transplant was 42%. In light of this effect, they proposed granting of exception MELD points and cardiac status 1 for patients with combined cardiac/liver failure [11]. Our current review indicates that only a minority of such patients receive MELD exception points.

This study is limited by nature of being a retrospective review of registry data. All such studies are prone to variability in data entry, and the lack of data on post-transplant immunosuppressive regimes is a major weakness that limits the strength of conclusions that can be drawn regarding acute rejection and graft survival. Our current review indicates that simultaneous transplantation of the heart and liver is on the rise within the United States, with outcomes that are similar to what is seen with isolated transplantation of the heart and liver alone.

Authorship

RMC: study idea and design. RMC, MGH, CMJ, ME and MRM: analysis and interpretation of data. RMC and MRM: drafting of the manuscript. RMC, MGH, CMJ, ME and MRM: critical revision for intellectual content. RMC, MGH, CMJ, ME and MRM: final approval.

Funding

The authors have no financial disclosures to make and the study received no outside funding.

Acknowledgements

This study was supported in part by Health Resources and Services Administration contract 234–2005–370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

References

1. Starzl TE, Bilheimer DW, Bahnson HT, *et al.* Heart-liver transplantation in a patient with familial hypercholesterolaemia. *Lancet* 1984; **1**: 1382.
2. Shaw BW, Jr., Bahnson HT, Hardesty RL, Griffith BP, Starzl TE. Combined transplantation of the heart and liver. *Ann Surg* 1985; **202**: 667.
3. Alkofer BJ, Chiche L, Khayat A, *et al.* Liver transplant combined with heart transplant in severe heterozygous hypercholesterolemia: report of the first case and review of the literature. *Transplant Proc* 2005; **37**: 2250.
4. Arpesella G, Chiappini B, Marinelli G, *et al.* Combined heart and liver transplantation for familial amyloidotic polyneuropathy. *J Thorac Cardiovasc Surg* 2003; **125**: 1165.
5. Grazi GL, Cescon M, Salvi F, *et al.* Combined heart and liver transplantation for familial amyloidotic neuropathy: considerations from the hepatic point of view. *Liver Transpl* 2003; **9**: 986.
6. Nardo B, Beltempo P, Bertelli R, *et al.* Combined heart and liver transplantation in four adults with familial amyloidosis: experience of a single center. *Transplant Proc* 2004; **36**: 645.
7. Praseedom RK, McNeil KD, Watson CJ, *et al.* Combined transplantation of the heart, lung, and liver. *Lancet* 2001; **358**: 812.
8. Ruygrok PN, Gane EJ, McCall JL, Chen XZ, Haydock DA, Munn SR. Combined heart and liver transplantation for familial amyloidosis. *Intern Med J* 2001; **31**: 66.
9. Raichlin E, Daly RC, Rosen CB, *et al.* Combined heart and liver transplantation: a single-center experience. *Transplantation* 2009; **88**: 219.
10. Te HS, Anderson AS, Millis JM, Jeevanandam V, Jensen DM. Current state of combined heart-liver transplantation in the United States. *J Heart Lung Transplant* 2008; **27**: 753.
11. Porrett PM, Desai SS, Timmins KJ, Twomey CR, Sonnad SS, Olthoff KM. Combined orthotopic heart and liver transplantation: the need for exception status listing. *Liver Transpl* 2004; **10**: 1539.
12. Cohen AS. Amyloidosis. *N Engl J Med* 1967; **277**: 522.
13. Gillmore JD, Lovat LB, Hawkins PN. Amyloidosis and the liver. *J Hepatol* 1999; **30**(Suppl 1): 17.
14. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. *Arch Intern Med* 2006; **166**: 1805.
15. Holmgren G, Ericzon BG, Groth CG, *et al.* Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. *Lancet* 1993; **341**: 1113.
16. Suhr OB, Herlenius G, Friman S, Ericzon BG. Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; **6**: 263.
17. Benson MD, Yazaki M, Magy N. Laboratory assessment of transthyretin amyloidosis. *Clin Chem Lab Med* 2002; **40**: 1262.
18. Pomfret EA, Lewis WD, Jenkins RL, *et al.* Effect of orthotopic liver transplantation on the progression of familial amyloidotic polyneuropathy. *Transplantation* 1998; **65**: 918.
19. Rana A, Robles S, Russo MJ, *et al.* The combined organ effect: protection against rejection?. *Ann Surg* 2008; **248**: 871.
20. Davies HS, Pollard SG, Calne RY. Soluble HLA antigens in the circulation of liver graft recipients. *Transplantation* 1989; **47**: 524.
21. McMillan RW, Gelder FB, Zibari GB, Aultman DF, Adamashvili I, McDonald JC. Soluble fraction of class I human histocompatibility leukocyte antigens in the serum of liver transplant recipients. *Clin Transplant* 1997; **11**: 98.