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Outcome of liver transplantation in hereditary hemochromatosis

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Summary

Hereditary hemochromatosis (HH) is a genetic disorder of iron metabolism. It is an uncommon indication for liver transplantation (LT). It has been suggested that patients who undergo LT for cirrhosis related to HH have higher morbidity and mortality from cardiac, infectious and malignant complications. The purpose of this retrospective review was to determine whether these observations hold true in the current era. We analysed the data of 22 patients who had LT for HH from 1996 to 2007 at our center. Thirteen patients had LT for complications of end-stage liver disease, seven for hepatocellular carcinoma (HCC) and two for subacute liver failure. Cofactors promoting liver disease were identified in 15 patients. Ten patients had iron reduction with venesection before transplantation. Patient and graft survival at 1 and 5 years were 80.7%, and 74% respectively. There were seven deaths after a median follow up of 46 months either because of multiorgan failure, or caused by HCC recurrence. Bacterial infections were the commonest cause of morbidity. Patients with HH remain at a higher risk of developing HCC. Infectious complications are common. Iron reduction with preoperative venesection reduces the risk of cardiac and infection complications postoperatively. Improved survival post-LT reflects changes in selection, disease modification through venesection, and improvement in immunosuppression.

Introduction

Hereditary hemochromatosis (HH) is a genetic disorder of iron metabolism characterized by increased iron absorption and deposition in the liver, pancreas, heart, joints and pituitary gland. It is associated with clinically significant morbid and fatal complications related to iron deposition. Without treatment, death may occur from cirrhosis, primary liver cancer, diabetes or cardiomyopathy [1,2]. It is an autosomal recessive disorder, and the majority of cases are associated with a mutation of HFE gene on the short arm of chromosome 6, which results in a substitution of cysteine by tyrosine at position 282 of the gene product [3].

Liver transplantation (LT) is an effective treatment for patients with complications of end-stage liver disease and selected cases of hepatocellular carcinoma (HCC) with 1 and 5 year survival rates of 88% and 74% respectively [4]. However, it has been suggested that patients who undergo liver transplantation for cirrhosis related to HH have higher morbidity and mortality from cardiac, infectious and malignant complications [5,6]. Poor results with 1 and 5 year survival of 58% and 37% have been reported following LT for HH. There is also a debate about whether patients with HH are at a higher risk of developing liver cancer or not [7]. The purpose of this retrospective review was to determine if these observations hold true in the

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current era with improvement in pretransplant screening of co-morbidities and improved immunosuppression regimens.

Patients and methods

The medical records of all patients with genetic HH undergoing LT at King's College Hospital were retrospectively analysed. HFE gene was identified in 1996, since then till December 2007, 2266 patients have undergone liver transplantation at our institution. Of these, 22 (0.97%) were homozygous for the C282Y mutation on HFE mutation analysis, and were included in the study. Twenty patients were diagnosed with HH before LT. Two patients (aged 60 and 30 years) presented with seronegative subacute liver failure, and were diagnosed with HH after the identification of grade-II and grade-IV siderosis on explant histology and HFE mutation analysis are also included in the study. The serum ferritin in these two patients was 7800 and 5800 μg/l respectively. One patient diagnosed with hemochromatosis before the discovery of HFE gene who had venesection and subsequent liver transplantation and later tested positive on mutation analysis was also included in the study.

Recipient demographics

Patient demographics, clinical and laboratory details, coexisting morbidity and immediate and long-term post-operative complications were evaluated from the patient records (Table 1). The etiology of the cirrhosis and degree of siderosis were confirmed by explant histology. Of 22 patients, 17 were male and five were female subjects, with a median age of 55 years (range from 30 to 72 years). Laboratory investigations included (median) serum albumin of 28 g/l (range: 17–43), bilirubin 162 μmol/l (range: 14–406), ferritin 662 μg/l (range: 11–10 000) creatinine 97 μmol/l (range: 67–240) and INR 1.30 (range: 0.94–3.2). Of 20 patients having elective LT, the indications included 13 patients with complications of end-stage liver disease including encephalopathy, refractory ascites or variceal bleeding, and seven patients with HCC (Table 1).

All patients underwent cardiac assessment which included electrocardiogram, echocardiogram, and stress echocardiogram. Five patients were identified with cardiac problems and were further investigated with coronary angiography and/or cardiopulmonary exercise testing. These problems included, atrial fibrillation in one, ischemic heart disease requiring coronary angioplasty and stenting in one, mild left ventricular hypertrophy in one

Table 1. Pretransplantation clinical data.

Patient Id	Age (yrs)/ sex	Co-etiology	Ferritin (μg/l)	Bilirubin (μ mol/l)	Albumin (g/l)	Creatinine (μmol/l)	Cardiac disease	Diabetes	Venesection
1	44/M	ALD	10000	34	28	240	No	Yes	Yes
2	39/F	ALD	2280	17	26	79	AF	Yes	No
3	55/M	ALD,	662	70	32	102	No	Yes	No
4	50/M	ALD	1325	26	32	75	No	Yes	No
5	41/M	HCV	894	38	29	90	No	No	No
6	45/M	HCC	2505	22	37	98	No	Yes	Yes
7	65/M	–	403	151	22	128	Mild DCM	No	No
8	67/M	HCC	61	18	42	126	IHD	Yes	Yes
9	47/M	ALD	478	44	26	97	No	Yes	Yes
10	53/M	HCC, ALD	282	63	28	67	No	Yes	Yes
11	51/M	ALD	992	23	27	82	Moderate DCM	Yes	Yes
12	60/F	SALF	7841	406	17	226	No	No	No
13	72/M	HCC	4001	18	43	95	No	Yes	No
14	51/F	HBV, HCV	69	54	24	71	No	Yes	No
15	58/M	ALD	334	14	37	166	No	Yes	No
16	63/M	ALD	2285	14	32	105	No	No	No
17	67/F	PBC	94	76	27	115	No	Yes	Yes
18	59/M	HCV, HCC	247	19	24	148	No	Yes	No
19	68/M	HCC	107	18	41	93	No	Yes	Yes
20	57/M	ALD, HCC	11	33	31	93	No	No	Yes
21	30/M	SALF	5882	376	26	78	LVH	No	No
22	52/F	ALD	181	42	28	104	No	No	Yes

ALD, alcohol liver disease; HCV, hepatitis C; HCC, hepatocellular carcinoma; SALF, sub-acute liver failure; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; AF, atrial fibrillation; IHD, ischemic heart disease; DCM, dilated cardiac myopathy; LVH, left ventricular hypertrophy.

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and mild dilated cardiomyopathy in two patients. None of these problems were considered a contraindication to transplantation.

Co-etiology and venesection

Cofactors promoting liver disease were identified in 15 patients and included alcohol ($n = 11$), hepatitis C ($n = 2$), hepatitis B and hepatitis C co-infection ($n = 1$) and primary biliary cirrhosis ($n = 1$). Of the 22 patients, 15 were diabetic and nine were maintained on insulin. Iron reduction by venesection had been performed in 10 patients before LT (Table 1). Of these 10, eight had no iron deposition, one had grade I and one had grade IV siderosis on explant histology. Patients who had not undergone venesection before LT had grade-III ($n = 4$) and grade-IV ($n = 7$) siderosis on explant histology.

Donor and operative details

The median donor age was 50 years (range = 12–67) with a median ICU stay of 2 days (1–6). Median cold and warm ischemia times were 622 min (range = 390–1020) and 40 min (range = 30–60) respectively. The overall quality of the donor organ was good. Seven patients received mildly steatotic grafts (<30% steatosis).

All patients received deceased donor whole organ grafts except one patient who was transplanted with split right lobe graft. Thirteen patients were transplanted by piggy-back technique and nine patients by caval replacement with the use of veno-venous bypass. There were no adverse events recorded in any of the patients during transplant operation.

Immunosuppression protocol

Induction immunosuppression was achieved with steroids and tacrolimus or cyclosporin (only two patients were on cyclosporin). Maintenance immunosuppression consisted of a calcineurin inhibitor with low-dose steroids or as monotherapy. Rejection episodes were treated with intravenous methylprednisolone. The dose of calcineurin inhibitors was adjusted to maintain plasma 12-h trough levels for cyclosporin of 100–150 μg/l and tacrolimus of 5–10 μg/l. Dose adjustments were performed according to the trough levels, renal function, systemic complications of calcineurin inhibitors and post-transplant time interval at the point of dose adjustment.

Survival analysis

Patient and graft survival was calculated at 30 days, 1 and 5 years post-transplantation. For the analysis of post-transplantation survival, patients were censored at the time when they were last traced alive. Graft failure was defined as liver failure requiring retransplantation or patient death from any cause. Time was measured from the date of liver transplantation to the date of death or last follow-up.

Results

Hospital stay

Post-LT median ICU stay was 3 days (range 1–75 days) and median stay in hospital was 18 days (range 12–90 days) and this was not different from patients transplanted at our center for other causes during the study time. Post-LT clinical data and complications are shown in Table 2 and discussed below.

Morbidity

Infections

Infection rate in our cohort was 45.5% (10/22). Two patients developed bacterial systemic sepsis. One was positive for *Staphylococcus aureus* infection (MRSA-positive blood cultures) and the other had a positive blood culture for *Klebsiella* (both died within 3 months of LT as discussed in the mortality section). One patient developed MRSA chest infection and two patients had *Staphylococcus aureus* wound infections. One patient developed herpes simplex skin eruptions and another developed Epstein–Barr virus (EBV)-related and Cytomegalovirus (CMV)-related viremia. There were no fungal infections identified. Of note, eight of 10 patients who developed post-LT infections did not receive venesection prior to LT.

Cardiac complications

Five patients developed cardiac complications. Four patients developed atrial fibrillation in the immediate postoperative period and responded to amiodarone therapy. One patient developed angina postoperatively, which was managed initially with medical treatment (nitrates and beta-blockers) and underwent a combined coronary artery bypass graft surgery and Roux-en-Y hepatico-jejunostomy for biliary stricture at 11 months post-LT and is alive 5 years post-LT. There were no deaths secondary to cardiac complications.

Other complications

Three patients had a single episode of acute cellular rejection, which resolved with methylprednisolone. Three patients underwent postoperative hemofiltration for renal impairment. Three patients developed vascular complications. One patient developed hepatic artery thrombosis

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Table 2. Early post-liver transplantation (LT) clinical data.

ICU stay	3 days (range = 1–75)	
AST (48 h post-LT)	227 IU/l (range = 56–1394)	
Creatinine (48 h post-LT)	119 μmol/l (78–231)	
Bilirubin (48 h post-LT)	29 μmol/l (9–246)	
INR	1.09 (1.1–2.46)	
Cardiac	AF: (*n* = 4)	5 (22%)
	Angina: (*n* = 1)	
Renal failure	Requiring CVVH: (*n* = 3)	3 (13%)
Vascular	HAT: (*n* = 1)	3 (13%)
	RHV thrombosis: (*n* = 1)	
	DVT: (*n* = 1)	
Infections		10 (45.45%)
Bacterial	MRSA in blood: (*n* = 1)	
	MRSA chest: (*n* = 1)	
	Staphylococcus aureus in blood and ascities: (*n* = 1)	
	Staphylococcus aureus wound infection: (*n* = 2)	
	Klebsiella in blood: (*n* = 2)	
Viral	HSV skin infection: (*n* = 1)	
	EBV and CMV viremia:(*n* = 1)	
Fungal	Nil	
Biliary	Bile leak: (*n* = 1)	2 (9%)
	Bile duct stricture: (*n* = 1)	
Rejection	ACR: (*n* = 3)	3 (13%)
Neurologic	Intracerebral hemorrhage: (*n* = 2)	2 (9%)

Important early post-LT data for 22 patients included in our study is shown here. Biochemical data is expressed as median and range is shown. Each incident of post-LT complication is mentioned here along side percentages.
ICU, intensive care unit; AST, aspartate aminotransferase; INR, international normalization ratio; MRSA, Methicillin-resistant *staphylococcus aureus*; HSV, herpes simplex virus; EBV, Epstein–Barr virus; CMV, cytomegalovirus; AF, atrial fibrillation; HAT, hepatic artery thrombosis; RHV, right hepatic vein; DVT, deep vein thrombosis; ACR, acute cellular rejection; CVVH, continuous veno-venous hemofiltration.

following severe bacterial sepsis and died (discussed in mortality section). Another patient developed early right hepatic vein thrombosis with mild graft dysfunction following 'piggyback' LT, which was managed successfully with intravenous heparin. A third patient was treated with warfarin for early deep vein thrombosis. There were two biliary complications; a bile leak requiring early post-LT laparotomy [this patient later died because of sepsis and multi-organ failure (MOF)]. Another patient developed anastomotic stricture, which was reconstructed by Roux-en-Y hepatico-jejunostomy at 11 months post-LT. Two patients developed neurologic complications including a small intracerebral hemorrhage, which settled without residual disability and one had grand mal seizures and fatal intracerebral hemorrhage 7 months post-LT.

HCC patients

Patients who underwent LT for HCC were screened with contrast-enhanced CT scan and MRI. All patients were within Milan criteria on preoperative imaging. Four patients had single tumors with a median size of 20 mm (range: 12–30 mm). Two patients had two tumors each, with the larger one measuring 30 mm. One patient had three tumors with the largest being 25 mm. Three patients with multiple tumors received transarterial chemoembolization while waiting for LT. One patient with a single lesion of 22 mm diameter received pre-LT radio-frequency ablation. Explant histology showed that two patients were beyond Milan criteria. One of these patients had five tumors on explant with the largest tumor measuring 45 mm (imaging 7 weeks before transplant showed solitary tumor of 20 mm), and the other patient had 12 tumor nodules on explant with the largest tumor of 25 mm (the imaging in this patient 5 weeks before transplant showed two tumors with the larger one measuring 30 mm). Both patients had significant microvascular invasion. The observed difference between the imaging and histologic findings in term of tumor number and size may be explained by the intrinsic inability of the imaging modalities to pick up smaller lesions and also by tumor biology and the effect of local treatment. Four out of seven patients with HCC had microvascular invasion on histology. Complete tumor necrosis was present in two patients after receiving transarterial chemoembolization in one and radiofrequency ablation in the other.

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Recurrent HCC/secondary tumors

Four patients developed malignancy following LT for HH. Two patients developed metastatic HCC in bones, skin, adrenals and lungs. Two patients developed extra-hepatic malignancies; one developed metastatic prostate cancer and died 82 months post-LT and the other patient developed pancreatic cancer 70 months post-LT, which was irresectable but remains alive 75 months post-LT.

The patients with recurrent HCC did not receive chemotherapy. The prostate cancer patient was started on anti-androgenic therapy and the pancreatic cancer patient received chemotherapy. Immunosuppression was reduced in all these patients.

Outcome

Patient and graft survival at 3 months, 1 and 5 years were 90%, 80.7%, and 74% respectively (Fig. 1). There were no re-transplants for graft loss in surviving patients. No patient required venesection post-LT (Table 3). The 3-month, 1- and 5-year survival for all other transplant recipients during the same period was 92%, 86.83% and 78.3% respectively. Comparison of 5-year survival of the two groups is shown in Fig. 1. There were seven deaths

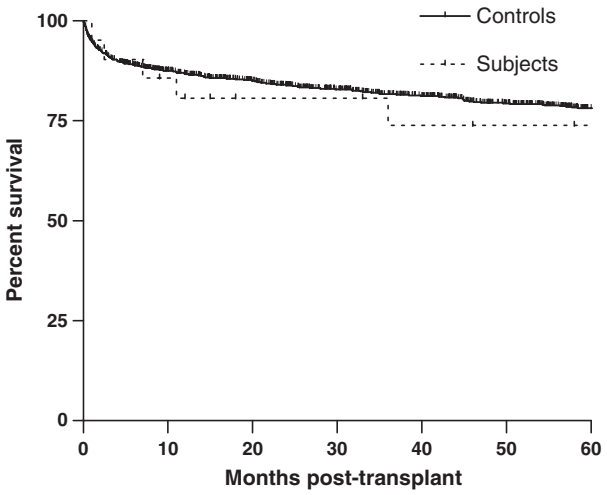

Figure 1 Outcome of liver transplantation for hereditary hemochromatosis. Twenty-two patients undergoing LT for HH were followed up for a median of 46 months (range: 12–213). There were a total of seven deaths in the HH group and 15 are alive at last follow-up. They were compared with a control group that had a total of 297 deaths and 1166 patients are alive at last follow-up. The Kaplan–Meyer survival data (with 95% confidence intervals) for the controls at 1 year and 5 years was 86.83% (85.0–88.6) and 78.3% (76.0–80.6) respectively. The mean survival for the HH group at 1 and 5 years was 80.7% and 74.0% respectively. Comparing the survival between the controls and subjects using a log rank test there is no difference in survival ($P = 0.44$) between the controls and those transplanted for HH up to 5 years post-LT.

Table 3. Outcome of 22 liver transplantation (LT) patients with hereditary hemochromatosis.

Median follow up	46 months (12–213)
Graft loss	Nil
Venesection post-LT	Nil
Number of deaths	7 (31%)
Cause of Death	
Infections	2
Hepatocellular carcinoma	2
Prostate cancer	1
Intracranial hemorrhage	1
Unknown	1

(Table 3) after a median follow up of 46 months (range 12–213 months). Four deaths occurred within the first year post-transplant. Of these, two patients died within 3 months of transplantation from sepsis and MOF. One of these patients died with a functioning graft, had a laparotomy for intra-abdominal bleeding on day 7 post-LT and had active sepsis involving *Staphylococcus aureus* in ascitic fluid and *Klebsiella* in blood cultures. The other patient developed a bile leak and underwent laparotomy. Subsequently, he developed CMV and EBV viremia and hemophagocytic lymphohistiocytosis and also had late hepatic artery thrombosis at the time of death. A third patient died from intracranial hemorrhage at 7 months post-LT. A fourth patient died at 11 months post-LT from recurrent HCC. This patient had five tumor nodules with the largest being 45 mm and extensive microvascular invasion on explant histology. Three deaths occurred after the first year of transplantation. One patient died at 36 months post-LT because of recurrent HCC. This patient had two tumors with the largest tumor diameter of 34 mm and extensive microvascular invasion on explant histology. The second patient died of metastatic prostate cancer at 82 months post-LT. The last patient in our cohort died at 213 months post-LT because of unknown cause with a functioning graft.

Graft function

At the time of last follow-up (median 46 months, range: 12–213 months) graft function was good in all surviving patients, except for two. These patients have biopsy-proven HCV recurrence, but only one has elevated ferritin levels and grade II siderosis on biopsy. Both patients are receiving antiviral treatment. None of the patients has required venesection or retransplantation.

Discussion

Hereditary hemochromatosis is an uncommon indication for LT accounting for 1% of the 2266 liver transplants performed over a period of 12 years in our program. Of

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22 patients with HH, 11 had a significant alcohol history; four had other associated liver diseases including hepatitis C, hepatitis B, primary biliary cirrhosis and two presented with subacute liver failure. There were only five patients in whom iron appeared to be the sole hepatotoxin and similar observations have been made by others. It was difficult in some patients to distinguish the relative contributions of co-factors such as alcohol or hepatitis C and hemochromatosis in the development of cirrhosis. Alcohol and hepatitis C act synergistically to accelerate liver disease in patients with HH and the risk of cirrhosis seems to be increased in HH patients who consume excessive alcohol [6,8,9].

The 1- and 5-year survival of 80.7% and 74% respectively is similar to that reported by Yu *et al.* [10] using The United Network of Organ Sharing (UNOS) database with 1-, 3- and 5-year survival of 86.1%, 80.8% and 77.3% respectively. The patients with HH were considered to have poor survival following LT [6] after an early report by Klipe *et al.* with 1- and 5-year survival between 1982 and 1991 in 37 US centers of 54% and 43% respectively in contrast to 80% for other liver diseases [11]. Kowdley *et al.* [12] in 1995 reported 1-year post-LT survival of 58% in 37 patients undergoing LT at five US centers. More recently in a multicenter, retrospective analysis involving data from 12 US centers Kowdley *et al.* [13] reported 1-, 3- and 5-year survival of 64%, 48%, and 34% respectively in 260 patients with hepatic iron overload. The HFE genotyping was available in 75% of patients. Post-LT mortality was primarily related to infection (23%), cardiac causes (20%), or a combination of both (8%). Infections, as a cause of death, were described as bacterial in 5.5%, fungal in 6.4%, viral in 4.6% and unspecified in 12.7%. In the study of Yu *et al.* [10] post-transplant deaths were because of cardiovascular complications in 27%, infection in 21% and malignancy in 13% of patients. The improved survival noted more recently may be because of changes in patient selection and particularly to screening prospective candidates for cardiac morbidity, which would exclude them from transplantation [6,13]. Crawford *et al.* [8] reported five deaths out of 11 because of recurrent HCC and four deaths secondary to cardiac complications. Kowdley *et al.* [13] had a 20% mortality related to cardiac complications.

Transplantation for malignancy is a common indication in HH and accounts for 31% of our series. There is a reported 20-fold increase in the risk of liver cancer in HH patients [14] and thus has been reported in association with increased iron deposition in liver [8,15,16]. In a prospective study, the risk of patients with well defined HH (mostly C282Y homozygotes) developing HCC was 1.8 times higher than that of patients with non-iron-related chronic liver disease [7].

It appears that patients with cirrhosis older than 55 years of age with a history of heavy alcohol use or viral hepatitis have a significantly increased risk of developing HCC. However, Boige *et al.* [17] reported that the HFE mutation did not appear to be associated with an increased risk of HCC in patients with cirrhosis.

Two patients in our study developed extra-hepatic malignancy. One patient died with metastatic prostate cancer and the other patient is currently alive with pancreatic cancer. Both patients had grade-IV siderosis on histology and did not have venesection treatment before LT. Francanzani *et al.* have reported an increased risk of extra-hepatic malignancies including colorectal, pancreatic, pulmonary and prostatic cancer in patients with HH (confidence interval: 95, relative risk 1.8), as reported by Nelson *et al.* [7,18]. There is conflicting evidence concerning the role of iron in extra-hepatic malignancies [19,20]. Whether iron removal therapy reduces the risk of subsequent liver and extra-hepatic malignancy remains to be tested in larger studies.

Mortality within the first year post-transplantation was primarily related to infection. Multiple bacterial infections with organisms such as *Staphylococcus aureus* and *Klebsiella* were associated with MOF. Brandhagen *et al.* [5] reported fungal infections as the leading cause of mortality in 24% of their patients. We did not identify fungal sepsis in our patients, although routine fluconazole prophylaxis was given. Bacterial and fungal infections have been reported to be important cause of death in several studies [5,6,13]. Excess iron has been shown to exert effects on the immune system by altering proliferation and function in a variety of cells involved in the host immune response. These include an abnormal CD4:CD8 ratio, decreased cutaneous hypersensitivity and abnormal proliferative responses by peripheral blood mononuclear cells to mitogenic stimuli [13,21]. Macedo *et al.* [22] reported low CD8 lymphocyte numbers and low serum transferrin levels associated with a more severe expression of iron overload in HH patients. From our limited data it appeared that infectious complications were more common in patients who did not have venesection therapy before LT. It may be that iron depletion before LT reduces the risk of infections and cardiac complications. Farrell *et al.* [6] suggested that early initiation of venesection with or without chelation therapy may decrease endomyocardial iron stores and impact favorably on cardiac function. Kowdley *et al.* observed similar survival rates in patients who had undergone iron depletion prior to LT compared with study population. However the proportion of patients (4.6%) treated with iron depletion was too small to provide a definitive answer [13].

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Hemochromatosis rarely presents as acute liver failure although cases of neonatal hemochromatosis and subclinical hemochromatosis with superimposed sepsis have been described [23,24]. Perez Roldán *et al.* [25] reported a case of acute liver failure that was caused by supplemental iron intake in the presence of unrecognized HH. No etiology was identified for our two patients with subacute liver failure and had grade-II and -IV siderosis on explant histology. It is possible that a second unknown hit to the liver may have precipitated liver failure.

This is the largest single-center experience of LT for patients with HH, however, the study is limited by being retrospective and the numbers being small. Patients with HH remain at a higher risk of developing HCC and extra-hepatic malignancies. Infectious complications are common and serious. Thorough cardiac evaluation prior to transplantation may reduce the mortality and morbidity of surgery. Iron reduction reduces the risk of cardiac and infectious complications post-LT. Improved survival of patients undergoing LT for HH probably reflects a change in selection, disease modification through venesection and improvement in immunosuppression.

Authorship

NH, AB and MR designed research and study. FSD and WF performed research and study. NAD contributed important reagents. FSD, WF, AB and AO'S collected data. FSD, AB and MZ analyzed data. FSD, WF, JO'G, MH and NH wrote the paper.

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