

Liver Transplantation in the Elderly: Indications and Outcomes

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Liver transplantation improves survival for selected patients with chronic liver disease, fulminant hepatic failure and hepatocellular carcinoma. There is no absolute upper age limit for liver transplantation and the proportion of patients undergoing liver transplantation who are older than 60 years is increasing. Although the indications for liver transplantation in elderly patients do not differ from those in younger patients, the prevalence of comorbidities that are contraindications to liver transplantation are higher among the elderly. Outcomes after transplantation for selected patients over 60 years of age with Child-Pugh class B cirrhosis who are well nourished and at home are comparable to those for younger patients.

Key words: liver transplantation, fulminant hepatic failure, hepatocellular carcinoma, indications.

Introduction

Liver transplantation improves the survival and quality of life of selected patients with fulminant hepatic failure (FHF), decompensated cirrhosis and hepatocellular carcinoma. Initially, an upper age limit for transplantation of 50–55 years was arbitrarily selected by most transplant programs.¹ More recently, with improvements in operative and perioperative care and the introduction of newer immunosuppressive medications, the age of transplant recipients has been extended. There has been a resultant increase in the proportion of liver transplant recipients who are older than 60 years in the U.S., from 10% in 1989 to 19% in 1998.² In Canada, liver transplant centres do not consider recipient age to be an extremely or very important criterion when listing a patient for transplantation.³ The costs of transplantation are greater for patients older than 60 years, which will have resulting resource implications as the proportion of elderly patients undergoing liver transplantation increases.⁴

We review the current status of liver transplantation in the elderly, and in particular, the selection of patients for liver transplantation and the available data regarding outcomes.

Liver Disease in the Elderly

Although there are no liver diseases specific to advanced age, the clinical course and management of liver disease in the elderly may differ significantly from those in a younger population. For the

purpose of this article, liver diseases will be grouped according to whether they present with FHF or chronic liver disease in an elderly population (Table 1). Hepatocellular carcinoma will be considered separately.

Fulminant Hepatic Failure

FHF is defined as the development of hepatic encephalopathy within eight weeks of the onset of jaundice in a patient without a prior history of liver disease, and is associated with a mortality rate of approximately 85% without transplantation.⁵ Because FHF is uncommon in elderly populations, reports are confined to small series of patients. In a recent prospective, multicentre study from the U.S., only 15 (4.9%) of 308 consecutive cases presenting with FHF were older than 65 years.⁶ The survival in this elderly cohort was significantly lower than

Table 1
Causes of Liver Disease in Elderly Patients

Fulminant Hepatic Failure	Chronic Liver Disease
Acute viral hepatitis: – hepatitis A virus – hepatitis B virus	Chronic viral hepatitis: – hepatitis C virus – hepatitis B virus
Autoimmune hepatitis	Primary biliary cirrhosis
Drug-induced: – overdose (e.g., acetaminophen) – idiosyncratic (e.g., ciprofloxacin)	Autoimmune hepatitis
Ischemic hepatitis	Ethanol-induced cirrhosis
Liver infiltration: – metastatic carcinoma – lymphoma	Primary sclerosing cholangitis
	Genetic: – hemochromatosis – α -1-antitrypsin deficiency
	Metabolic: – non-alcoholic steatohepatitis – cryptogenic cirrhosis

that observed in younger populations (33% vs. 63–77%, respectively).

Acute viral hepatitis and drug-induced liver disease are the two most common causes of FHF in the elderly population. The differing clinical course of liver disease in the elderly can be illustrated by acute hepatitis A, which, although uncommon, is associated with a dramatic increase in the incidence of FHF and death in elderly patients.⁷ Polypharmacy and increased drug consumption, coupled with alterations in pharmacodynamics and pharmacokinetics, contribute to the increased frequency and severity of drug-induced liver disease among the elderly.

Chronic Liver Disease

The management of chronic liver disease and complications of portal hypertension (ascites, gastrointestinal bleeding, hepatic encephalopathy) continues to improve, and so the proportion of patients with chronic liver disease who reach the seventh and eighth decade is increasing. In addition, the peak prevalence of hepatitis C virus (HCV) in the U.S. population is observed in persons aged 30–49 years (3.9%), with a prevalence of 0.9% and 1.0% seen in persons 60–69 years and older than 70 years, respectively.⁸ It is anticipated that as this middle-aged population ages over the next two to three decades, the prevalence and duration of HCV infection in the elderly population will rise, resulting in greater liver-related morbidity and mortality from HCV among the elderly.

The diagnostic criteria for the autoimmune liver diseases—primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH) and primary sclerosing cholangitis—remain the same regardless of age. Although these conditions usually present earlier in life, published series report that one-fifth to one-quarter of patients with PBC and AIH present over the age of 65 years. These elderly patients appear to experience similar liver-related morbidity to younger patients.

Hepatocellular Carcinoma

Unlike areas of the world with a high prevalence of chronic hepatitis B virus

infection, in the West hepatocellular carcinoma (HCC) is predominantly a disease of elderly cirrhotic patients. In a retrospective review from the U.K., 47% of patients presenting with HCC were aged 65 years and older.⁹ With the anticipated increase in prevalence of HCV-induced cirrhosis over the forthcoming decades, the incidence of HCC in Western countries is expected to rise. Unfortunately, in most cases HCC is advanced at the time of presentation and transplantation is infrequently an option.

Indications for Liver Transplantation

The indications and contraindications for liver transplantation in elderly patients are identical to those for younger patients with FHF or chronic liver disease (Tables 2 and 3). However, among the elderly there is a higher prevalence of comorbidities that are contraindications to transplantation. Thorough pre-transplant evaluation of all patients, especially the elderly, is therefore essential, including objective assessments of cardiac and pulmonary function and bone mineral density. Elderly patients that have successfully completed this pre-transplantation work-up are an extremely fit subgroup of the elderly population. The published outcomes for transplantation in this population reflect this cautious patient selection and cannot be generalized to all elderly patients with liver disease.

The minimal criteria that have to be satisfied in order to be placed on an active liver transplant waiting list are outlined in Table 2 and have been adopted with little variation across North America. The Child-Pugh scoring system (Table 4) is a nondisease-specific objective assessment of the severity of liver dysfunction in cirrhosis.¹⁰ A score of ≥ 7 in cirrhosis is associated with an expected one-year survival of less than 90%. As liver transplantation is associated with a $> 90\%$ one-year survival in most centres, this score is considered a sufficient indication to be placed on a list for liver transplantation if no contraindications are identified.

Table 2
Minimal Listing Criteria for Liver Transplantation

Fulminant Hepatic Failure*
I. Acetaminophen toxicity
A. Arterial pH < 7.3 , or
B. INR > 6.5 and serum creatinine $> 300\mu\text{mol/L}$ with Grade III or IV encephalopathy
II. All other patients
A. INR > 6.5 , or
B. Any three of the following variables:
1. Age < 10 years or > 40 years
2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reaction
3. > 7 day interval between jaundice and encephalopathy
4. INR > 3.5
5. Serum bilirubin $> 300\mu\text{mol/L}$
Chronic Liver Disease**
Child-Pugh score ≥ 7 (Child-Pugh class B or C).
Portal hypertensive bleeding or a single episode of spontaneous bacterial peritonitis, irrespective of Child-Pugh score.
Estimated one-year survival $< 90\%$.
Cirrhosis with significantly impaired quality of life.

* Kings College Criteria. Adapted from O'Grady JG, *et al.*, 1989.

** Adapted from Lucey MR, *et al.*, 1997.

Disease-specific criteria have been developed for certain conditions, such as cholestatic liver disease and HCC, in which survival may be represented inadequately by the Child-Pugh score. Validated mathematical models, which more accurately predict survival in patients with primary biliary cirrhosis and primary sclerosing cholangitis, have been developed to assist in the timing of transplanta-

Table 3
Contraindications to Liver Transplantation

Relative Contraindications	Absolute Contraindications
Cardiac disease:	Advanced cardiopulmonary disease
– coronary artery disease	
– pulmonary hypertension	
– valvular heart disease	
– cardiomyopathy	
Pulmonary disease:	Extrahepatic malignancy
– pulmonary hypertension	Metastatic liver disease
– incompletely treated tuberculosis	Active untreated sepsis
Intrinsic renal failure	Active alcoholism or substance abuse
Malignancy within two years; a longer interval is required for:	Cholangiocarcinoma
– breast carcinoma	Anatomic abnormality precluding transplant
– colonic carcinoma	Human Immunodeficiency Virus (HIV) seropositivity
– malignant melanoma	History of non-compliance with medical care
Chronic serious sepsis:	
– chronic osteomyelitis	
– bronchiectasis / empyema	
– abscesses / endocarditis	
– chronic fungal disease	
Morbid obesity (BMI > 39)	
Severe osteoporosis with previous fractures	
Prior abdominal or hepatic surgery	

tion.^{11,12} As the Child-Pugh score does not take into consideration the presence of HCC, separate guidelines for HCC have evolved. Only the minority of patients with HCC, that is, those with cirrhosis and small lesions (a single lesion < 5cm or three lesions < 3cm) without evidence of vascular invasion or lymphatic metastases, should be considered for transplantation.¹³ Other disease-specific criteria include abstinence from alcohol for at least six months and successful completion of a formal alcoholic rehabilitation program in patients with alcohol-related liver disease, as well as absence of detectable viral DNA in the serum of patients with chronic hepatitis B virus infection.

Liver Transplantation Outcomes

Several retrospective series have been published comparing the short- and long-term outcomes of liver transplantation in elderly patients compared with younger patients from the same centre (Table 5). Recipients older than 60 years have been selected in most of these case control studies¹⁴⁻²² and few, if any, patients older than 70 or transplanted for FHF have been included. Initial reports observed comparable patient survival in the older patient group for up to three years post-transplant.

More recent, larger studies¹⁸ with longer follow-up¹⁹ report that older patients have significantly lower survival rates after transplantation. However, as liver transplantation resulted in a comparable improvement in quality of life in the older patient group, it was concluded that transplantation should be considered for carefully selected patients over the age of 60.¹⁸ This enthusiasm should be tempered by other recent reports that have analysed patient survival not only by age but also by liver disease severity^{20,21} and patient status at the time of transplantation (nutritional status, managed at home, in hospital or requiring ICU care).²¹ These studies report that older, malnourished patients with higher Child-Pugh scores (> 10) and those hospitalized or in an ICU at the time of transplantation, have significantly higher mortality rates compared with older, well nourished patients with lower Child-

Table 4
Child-Pugh Grading of Liver Disease Severity

	1	2	3
Encephalopathy	None	Mild / Moderate	Severe
Ascites	None	Mild / Moderate	Severe
Serum albumin (μmol/L)	> 35	28–35	< 28
Serum bilirubin (μmol/L)	< 35	35–50	> 50
INR	< 1.7	1.7–2.2	> 2.2

For each patient, a point value reflecting disease severity is assigned for each of the five parameters of liver function. The sum of the five parameters allows categorization into Child-Pugh grade A (score 5–6), Child-Pugh grade B (score 7–9) and Child-Pugh grade C (score 10–15).

Adapted from Pugh *et al.*, 1983.

Table 5

Studies Reporting Outcomes in Elderly Patients After Liver Transplantation

Author, Year	Centre	Number of patients (age in years)	Follow-up	Patient survival (%)
Stieber, <i>et al.</i> 1991	Pittsburgh, PA.	965 (18–60)	3 years	71
		156 (61–76)		65
Pirsch, <i>et al.</i> 1991	Wisconsin	84 (18–59)	2 years	76
		23 (60–72)		83
Emre, <i>et al.</i> 1993	Mt Sinai, New York	Patients at home	1 year	
		107 (18–59)		87
		19 (60–69)		84
		Patients in hospital	66	
		56 (18–59)		66
Bromley, <i>et al.</i> 1994	King's College, U.K.	20 (60–69)	2 years	75
		289 (18–59)		73
Zetterman, <i>et al.</i> 1998	National Institute of Diabetes & Digestive & Kidney Diseases	42 (60–69)	1 year	72
		600 (16–59)		90
Rudich, <i>et al.</i> 1999	University of California	135 (60–77)	3 years	81*
		33 (<70)		76
Collins, <i>et al.</i> 2000	Wisconsin	33 (>70)	10 years	61
		387 (18–59)		60
Garcia, <i>et al.</i> 2001	Birmingham, U.K.	91 (60–72)	5 years	35*
		701 (< 60)		76
Levy, <i>et al.</i> 2001	Dallas, TX.	174 (> 60)	3 years	69
		1205 (< 60)		75
Filipponi, <i>et al.</i> 2001	Pisa, Italy	241 (> 60)	3 years	57*
		173 (18–59)		73
24 (60–65)				

* p < 0.05

Pugh scores who did not require hospital care prior to their transplants. Age did not influence survival if the patients were waiting at home prior to transplantation.

Outcomes of liver transplantation among those older than 70 years have been reported in a single study. Thirty-three patients (mean age 72) who had undergone liver transplantation were paired with younger controls (mean age 47), matched for all other demographic and preoperative parameters.²³ Although the prevalence of preoperative comorbidities was not reported in either group, this is likely to have been a physiologically perfect subset of

patients over 70 years of age. After a median of three years post-transplantation, no significant differences in patient survival or complications were noted, except for increased postoperative cardiac arrhythmias (43% vs. 6%, p<0.01) and encephalopathy (37% vs. 20%, p<0.04) in the older patients. Overall, similar rates of postoperative complications have been reported in patients older than 60 years at the time of transplantation; however, older patients require longer ICU^{14,18,22} and hospital stays.^{14,17,18} This finding accounts for the increased costs of liver transplantation in patients older than 60 years.⁴

Conclusions

Liver transplantation improves the survival and quality of life of selected patients with FHF, decompensated cirrhosis and hepatocellular carcinoma. Fortunately, FHF in the elderly population is rare, but the prevalence of chronic liver disease in the elderly population is increasing and is anticipated to rise further over the forthcoming decades. Although indications for liver transplantation in elderly patients do not differ from those in younger patients, the prevalence of comorbidities that are contraindications to liver transplantation is higher among the elderly. Outcomes after transplantation for patients older

than 60 years with Child-Pugh class B cirrhosis and who are well nourished and at home are comparable to outcomes for younger patients. Malnourished patients with Child-Pugh class C cirrhosis and who are hospitalized fare poorly, and serious consideration has to be given to the merits of liver transplantation in this population. ◆

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