



Outcome of Kidney Alone Transplantation in Patients with End Stage Kidney Disease with Compensated Cirrhosis

Abstract

Background: There is a lack of data regarding the need for liver transplantation in end-stage kidney disease (ESKD) patients with compensated cirrhosis. Overall outcomes of isolated kidney transplants in these patients in terms of renal graft outcome, hepatic decompensation, and survival are less clear. **Materials and Methods:** This is the retrospective analysis of patients treated at a single center. Patients with cirrhosis with evidence of portal hypertension who underwent kidney transplantation were compared with a matched control group without chronic liver disease (CLD) who underwent kidney transplantation during the same period. **Results:** Nineteen CLD patients with evidence of portal hypertension confirmed by endoscopy showing varices (8/19), hepatic venous pressure gradient (HVPG) >5 (12/19), or portosystemic collaterals on imaging (8/19) underwent kidney transplantation and were compared with 38 patients without liver disease transplanted during the same period. The discharge of creatinine was similar in both groups. The median follow-up was approximately 4 years in both groups, with the last mean serum creatinine of 1.3 and 1.37 mg/dl (unit for creatinine) in the patient and control groups ($P = 0.382$). Biopsy-proven acute rejections were similar [3 (15.8%) vs. 7 (18.4%), $p = 1$]. Two patients died in the CLD group, one due to hepatic decompensation with sepsis and the other due to cardiac cause. Four patients died in the control group (3 with sepsis and 1 with cardiac cause). Two patients had liver decompensation post-transplant (1-month post-transplant with ascites, 4 years post-transplant with ascites and hepatic encephalopathy). **Conclusion:** Kidney-alone transplantation in a carefully selected population with CLD and portal hypertension has comparable outcomes to those without liver disease.

Keywords: Chronic liver disease, Cirrhosis, Kidney alone transplant, Kidney transplantation

Introduction

The incidence of Hepatitis B (HBV) and Hepatitis C (HCV) is high in patients with chronic kidney disease (CKD) on maintenance hemodialysis and can lead to development of cirrhosis.^{1,2} Other etiologies of liver diseases like alcohol-related liver disease and non-alcoholic steatohepatitis (NASH) related liver disease add to this burden.

Cirrhosis is an independent risk factor for death in ESKD patients.³⁻⁵ with 35% higher mortality than those without cirrhosis.⁶ Optimal treatment options for the management of this sicker group of ESKD patients, like maintenance dialysis alone, combined or simultaneous liver-kidney transplant (SLKT), or kidney transplantation alone (KTA), are unclear.

Both kidney disease improving global outcomes (KDIGO) and the American Society of Transplantation (AST) recommend SLKT in patients with decompensated cirrhosis and ESKD.^{7,8} There is a lack of data regarding the need for liver transplantation in ESKD patients with asymptomatic advanced chronic liver disease or compensated cirrhosis. Previous recommendations have suggested that KTA should not be performed in a patient with a liver biopsy demonstrating advanced fibrosis.⁹⁻¹¹ Initial studies in viral hepatitis, especially HCV, suggested that there are more chances of liver decompensation and mortality if KTA alone is performed in patients with ESKD and advanced liver disease. However, these patients had better survival than those remaining on dialysis.¹²⁻¹⁴ Most recommendations are

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based on studies in viral hepatitis, especially HCV. The outcome of non-viral etiologies of liver diseases is unclear.

Model for end-stage liver disease (MELD) allocation system has been used to decide and waitlist the patients for liver as well as combined liver-kidney transplantation since 2002. However, ESKD patients on dialysis will have a MELD score of 20, even with normal bilirubin and international normalized ratio (INR). Thus, the MELD-based criteria are not suitable for deciding candidacy for liver transplantation in these patients. HVP (hepatic venous pressure gradient) can be used to assess the risk of liver decompensation and the need for a transplant. A study found that patients with compensated cirrhosis with HVP <10 mmHg are at less risk for decompensation.¹⁵ It has been suggested that these patients can be considered for KTA.

Overall outcomes of these patients regarding renal graft outcome, hepatic decompensation, and survival are less clear. The issue seems to be particularly important in countries where organ donations are mostly living donor-based, where long-term good-quality dialysis facilities are scarce, and where patients have to bear the cost of dialysis. We shared our single-center experience of KTA in patients with ESKD and advanced but compensated liver disease.

Materials and Methods

This is the retrospective analysis of a prospectively maintained database where we screened all renal transplant patients at our center from Jan 2011 to Dec 2021, a large multi-specialty private sector hospital. Patients with cirrhosis either on elastography or on cross-sectional imaging with evidence of portal hypertension (based on upper GI endoscopy or hepatic venous portal gradient (HVP) evaluation or evidence of collaterals on cross-sectional imaging) were included. Patients with no signs of clinical decompensation in the form of jaundice/encephalopathy/ascites were considered “compensated.” Patients with ascites but HVP <10 mm were also considered “compensated.”

Acoustic radiation force impulse elastography (ARFI) or fibroscan was done in a 4 h fasting state, after or the day after in case of evening dialysis. Fibroscan LSM >13.6 kPa and ARFI value >2.1 m/s were considered to suggest cirrhosis.^{16,17}

Their baseline demographic data, cause of CLD, and status of CLD at the time of transplant, including liver function test (LFT), international normalized ratio (INR), platelets, and albumin, were collected. Post-transplant outcomes, including graft outcomes (creatinine, graft survival, biopsy-proven acute rejection), patient survival, and decompensation of liver disease, were analyzed.

These patients were compared with a matched (matched for age, sex, diabetes, induction agent) control group

without CLD, who underwent kidney transplantation during the same period.

Statistical analysis for this study was performed using SAS software version 2021 (SAS Institute Inc., Cary, NC, USA). Data are reported as mean \pm standard deviation. Continuous variables were compared using the unpaired *t*-test and ANOVA, while categorical values were compared using the Mann-Whitney U test, Chi-square test, or Fisher's exact test. Multivariable regression analysis was performed to detect independent predictors of outcomes. *P*-value <0.05 was considered significant. The study was completed by the 1964 Helsinki Declaration and its later amendments and patient consent was obtained.

Results

Between 2011 and 2021, a total of 2240 patients underwent kidney-alone transplantation at our center. Out of these, 35 patients had evidence of liver disease (coarse echotexture) on imaging, but only 19 were classified as having advanced liver disease, i.e., cirrhosis with portal hypertension. Patients with advanced fibrosis F4 on ARFI/fibroscan or with evidence of portal hypertension on imaging or endoscopy in the form of portosystemic collaterals, varices, or raised HVP of more than 5 mmHg were included. Ascitic tapping was not done in all the patients; hence not included in the analysis. Table 1 explains the liver-related parameters of the patients. These patients were compared with a matched control group of 38 patients (1:2) without CLD who underwent kidney transplantation during the same period [Table 2].

NASH-related CLD was the most common cause of cirrhosis (*n* = 7) followed by viral etiologies (HBV = 5, HCV = 3, HBV + HCV = 2).

All 19 patients had evidence of portal hypertension in our study by various methods like Upper GI endoscopy, HVP, and imaging [Table 1]. 12/19 patients had ARFI scan done, 8 having F4 fibrosis, 4 having F3 fibrosis. But all had evidence of portal hypertension confirmed by either endoscopy showing varices (8/19), HVP >5 (12/19), or portosystemic collaterals on imaging (8/19). 7/19 had platelet count <100,000. Splenomegaly was present in 15 patients, 10 had ascites.

There was no difference in baseline characteristics, including age, sex, diabetes, basic diseases, use of induction, etc., between patients and matched controls. The estimated glomerular filtration rate (eGFR) at discharge was similar in both groups (90.93 ml/min/1.73² in CLD vs 82.17 ml/min/1.73² in no CLD group, *p* = 0.179).

The median follow-up was approximately 4 years in both the groups, with the last mean eGFR of 77.07 (SD 23.91) ml/min/1.732 and 69.78 (SD 23.37) ml/min/1.732, respectively, in CLD and control groups (*p* = 0.275). Biopsy-proven acute rejections were similar [3 (15.8%) vs 7 (18.4%), *p* = 1].

Table 1: Liver related parameters of cirrhosis group

Age/Sex	Etiology	Serum Albumin	ARFI M/s	Evidence of portal hypertension					HVPg
				Platelet	Spleno-megaly	Collaterals on imaging	Ascites	UGI endoscopy	
40/M	Ethanol	4	2.7	91	Yes	Yes	No	Erosive gastropathy	14
56/M	NASH	3	2.4	201	Yes	No	No	No varices	7
48/M	NASH	2.3	2.3	163	Yes	No	Yes	No varices	7
44/M	HBV	2.9	1.8	190	No	No	Yes	No varices	8
48/M	NASH	3.2	–	80	Yes	Yes	Yes	No varices	8
59/M	HCV/HIV	4.2	–	116	yes	no	no	Small esophageal varices	7
49/M	NASH	2.7	–	80	Yes	Yes	Yes	PHG	8
50/M	NASH	3.6	–	167	Yes	Yes	Yes	No varices	7
45/M	HCV	3.6	2.7	155	No	No	No	Small esophageal varices	8
34/M	HBV+HCV	2.8	2.1	214	Yes	No	Yes	No varices	8
61/M	NASH	2.5	2.1	75	Yes	yes	No	GAVE	Not done
60/M	NASH	3.7	–	70	Yes	Yes	No	Grade 1 varices	Not done
38/M	HBV	3.5	2.6	134	No	No	Yes	No varices	9
48/M	HCV	3.8	2.5	150	Yes	No	Yes	Small esophageal varices	Not done
25/M	HBV+HCV	2.9	–	89	No	No	Yes	Small grade 1 varices	Not done
32/M	HBV	2.8	2.1	202	Yes	Yes	No	PHG	Not done
34/M	HBV	3.7	–	70	Yes	Yes	Yes	Small esophageal varices	11
26/M	Crypto	4.2	2.5	204	Yes	No	No	Grade I varices	Not done
59/M	HBV	3.9	2.2	101	Yes	No	No	Small esophageal varices	not done

NASH: Nonalcoholic steatotic hepatitis, HBV: Hepatitis B virus, HCV: Hepatitis C virus, Crypto: Cryptogenic, Ethanol:1, UGI endoscopy: Upper gastrointestinal endoscopy, HVPg: Hepatic venous pressure gradient, GAVE: Gastric antral vascular ectasia, PHG: Portal hypertensive gastropathy, ARFI: Acoustic radiation force impulse elastography

The number of patients requiring hospital admission for infections was similar in both the groups (21.05% in the CLD group vs. 39.4% in the control group, $p=0.23$).

Two patients died in the CLD group. One died due to hepatic decompensation with sepsis; the other died of cardiac cause. Four patients died in the control group (3 with sepsis and 1 with cardiac cause).

Two patients had post-transplant decompensation. One had decompensation in the form of ascites 1 month post-transplant, another had decompensation 4 years post-transplant with ascites and hepatic encephalopathy.

Discussion

This study predominantly looked at the outcome of kidney transplant alone in patients with CLD with portal hypertension with ESKD. Most studies conducted in patients with CLD with ESKD were done in HCV or HBV-related liver disease.¹⁸⁻²¹ Our study includes patients with different etiologies of CLD, i.e., NASH being the most common, followed by viral etiologies. Considering the newer era of directly acting antivirals (DAAs) in HCV, the burden of HCV-related CLD has gone down. It is important to study the outcome of other etiologies of CLD.

In our study, both groups had similar death-censored graft survival and patient survival. Paramesh *et al.*¹⁸ compared the outcome of patient and graft survival in 9 cirrhotic patients to 28 noncirrhotic patients. They demonstrated

equivalent 1- and 3-year patient and graft survival rates with an average follow-up of 32 months. This study's strength was that all patients underwent trans-jugular liver biopsy with HVPg assessment. HVPg was less than 10 mmHg for all the patients. In our study, 12/19 patients underwent HVPg assessment, and 2 had HVPg more than 10 mmHg. However, none underwent liver biopsy. Parsikia *et al.*¹⁹ compared 18 HCV-related cirrhotic with 103 HCV-positive non-cirrhotic; 11 had histological evidence of cirrhosis, 4 had both histological and radiological evidence, and 3 had only radiological assessment. One- and three-year cumulative patient survival rates were 91% and 82% for non-cirrhotic and 100% and 83% for cirrhotic patients, respectively ($P = NS$). One- and three-year cumulative death-censored graft survival rates were 94%, 81%, 95%, and 82% for the non-cirrhotic and cirrhosis groups, respectively ($P = NS$). Both of these mentioned studies are in HCV-positive recipients.

Patel *et al.*²¹ compared 12 biopsy-proven cirrhotics with different etiologies with 10 age-matched non-cirrhotics and found inferior graft and patient survival in cirrhotics. This study doesn't mention the details of radiological assessment or endoscopy in terms of assessment of portal hypertension or decompensation.

In our patients, 10/19 patients had HVPg <10 mmHg, so they are considered to be compensated, and their ascites can be attributed to ESKD status. Two patients had HVPg >10 mmHg, out of which one had ascites. In patients in

Table 2: Comparison between the cirrhosis and noncirrhosis group

	With CLD N (%) =19	Without CLD (n=38)	P value
Demographics		(1HBsAg,4 HCV)	
Age	45.05 years (SD 11.3)	45.4 (10.5)	0.908
Sex (M:F)	19:0	35:3	0.54
Comorbidities			
Diabetes	15 (78.9)	26 (68.4)	0.53
Hypertension	19 (100)	37 (97.3)	1
Obesity	3 (15.8)	8 (21)	0.73
CAD	1 (0.05)	7 (18.4)	0.25
Cause of ESKD			
Diabetic nephropathy	15 (78.9)	25 (65.8)	
Chronic interstitial nephritis	2 (10.5)	6 (15.8)	
Chronic glomerulonephritis	1 (5.2)	4 (10.5)	
Unknown	1 (5.3)	3 (7.9)	
Type of induction			0.957
Simulect	11 (57.9)	21 (55.2)	
ATG	2 (10.5)	5 (13.1)	
No induction	6 (31.6)	12 (31.6%)	
ABO-incompatible transplant	2 (10.5)	5(13.1)	1
Outcome			
Mean creatinine at discharge	1.19 (SD 0.95)	1.17 (SD 0.36)	0.085
Mean eGFR at discharge ml/min/1.73 m ²	90.93 (SD 24.43)	82.17 (SD 22.2)	0.179
Median follow up	48 months (range 9-130)	49 months (13-130)	0.917
Creatinine at follow-up	1.3 (SD 0.43)	1.37 (SD 0.4)	0.382
Mean eGFR at follow-up ml/min/1.73 m ²	77.07 (SD 23.91)	69.78 (SD 23.37)	0.275
Biopsy-proven acute rejection	3 (15.8)	7 (18.4)	1
No. of patients requiring hospital admission for infections	4 (21.05)	15 (39.4)	0.23
Lost to follow up	2 (10.5)	6 (15.8)	0.705
Death-censored graft loss	0	2 (5.26)	0.548
Death	2 (10.5) (1 Sepsis hepatic decompensation, 1 cardiac)	4 (10.5) (3 sepsis, 1 cardiac)	1

CLD: Chronic liver disease, CAD: Coronary artery disease, ESKD: End stage kidney disease, ATG: Anti thymocyte globulin (rabbit), eGFR: estimated glomerular filtration rate

whom HVPg was not done, 2 had ascites. The cause of ascites in these three patients is either ESKD status or hepatic decompensation, and in the absence of ascitic fluid analysis, it is difficult to comment.

In our study, two patients had hepatic decompensation post-transplantation, one after a month of transplantation with new onset ascites and the other after four years of transplantation with jaundice and ascites getting complicated by sepsis eventually death. In a study by Paramesh *et al.*,¹⁸ no patient had decompensation post-transplant. In a study by Parsikia *et al.*,¹⁹ 3 patients in non-cirrhotic HCV and 1 in cirrhotic HCV died due to decompensation of liver disease. This study was done in the DAA era (2001-2010) when HCV treatment was complex with poor SVR rates, especially in patients with ESKD and post-transplant settings, which might be the reason for this high decompensation rate.

In the study by Paramesh *et al.*¹⁸ the negative prognosticators included recipient age and albumin level. The mean age of patients in the current study is 45.05 years, which is comparatively younger than most of the studies (57 years).^{18,21} Mean albumin was 3.33 g/dl in the current study, which was lower than other studies (3.4 g/dl in Paramesh *et al.*, 3.7 g/dl in Patel *et al.*, 3.5 g/dl in Parsikia A. *et al.*).^{18,21,19} None of the patients developed hepatocellular carcinoma till the last follow-up.

This is the first study from India comparing the outcome of kidney transplantation in CLD patients with advanced fibrosis or compensated cirrhosis with those without liver disease. This study has a few limitations. First, it is a retrospective study with a small number of patients. Information on quality of life before or after surgery, frequency and type of infections, and rehabilitation status is missing. In 10.5% of CLD and 15.8 % of non-CLD [Table

2] patients, follow-up data on graft and liver outcome data is unavailable. Second, the pretransplant workup was heterogeneous. However, all patients in our study were adequately evaluated for CLD with portal hypertension.

Kidney-alone transplantation in compensated CLD with portal hypertension has comparable outcomes in terms of graft function and episodes of liver decompensation to those without significant liver disease in a carefully selected population. More studies, especially with liver biopsies and HVPg assessment, are needed to understand these patients' disease course better.

Conflicts of interest: There are no conflicts of interest.

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