

Graft Outcomes in Kidney Transplantation Alone with Concomitant Cirrhosis

Patel Anish, Harrison Stephen, Rudraraju Madhavi

Patel A, Gastroenterology and Hepatology, Carl R. Darnall Army Medical Center, Ft. Hood, TX, the United States

Harrison S, Gastroenterology and Hepatology, San Antonio Military Medical Consortium, San Antonio, TX, the United States

Rudraraju M, Methodist Specialty and Transplant Hospital, San Antonio, TX, the United States

Correspondence to: Anish Patel, 36000 Carl R. Darnall Army Medical Center, Ft. Hood, TX 76544, the United States

Email: anishpa81@gmail.com

Telephone: +254-553-1804

Fax: 254-288-2306

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and Methodist Hospital overall (89%). Study also demonstrates the benefit of a liver biopsy with or without portal pressure measurement prior to transplantation in patients with viral hepatitis and/or other hepatic disease to accurately stage fibrosis.

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Key Words: Kidney transplantation; ESRD; Hepatitis C; Hepatitis B; Cirrhosis; Kidney graft

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ABSTRACT

AIM: The influence of cirrhosis on kidney graft survival post-transplantation has not been well defined. As previously demonstrated, lower rates of patient overall survival (31%) were in conjunction with lower rates of 5-year graft survival (31%) in cirrhotic patients who received a kidney transplant alone. Unfortunately, there is scarce data on the graft survival in patients who receive a kidney transplant alone with concomitant cirrhosis.

METHODS: Among 131 patients with kidney transplantations at Methodist Specialty Hospital in San Antonio, TX between January 1999 and December 2011 with hepatitis B or C or cryptogenic cirrhosis, 12 patients were found to have concomitant cirrhosis at time of transplantation. Rates of survival at 3-years were compared to the national average and overall for Methodist Specialty Hospital.

RESULTS: In the 12 patients, cirrhosis etiologies included hepatitis B ($n = 2$), hepatitis C ($n = 7$) and cryptogenic ($n = 3$). All were confirmed by histology at or within 6 months prior to kidney transplantation. The median graft survival was 8.1 years and graft survival at 3- and 5-years were 75% and 58%, respectively.

CONCLUSION: Preliminary data suggests that cirrhotic patients might be considered for combined liver and kidney transplantation. Graft survival at 3 years is far below the national average (82%)

INTRODUCTION

The incidence of chronic kidney disease (CKD), in particular end-stage renal disease (ESRD), is rising at an alarming rate. The Centers for Disease Control and Prevention estimate that 1 in 10 American adults, more than 20 million, have some level of CKD^[1]. The incidence of ESRD is about 350 per million population with up to 400 000 patients on hemodialysis (HD) as the primary mode of therapy^[2]. Kidney transplantation is a viable long-term solution to ESRD with 3-year national graft survival rates (combined deceased and liver donor) of up to 82%^[3]. The impact of advanced liver disease on the impact of kidney graft survival is not well defined.

The prevalence of chronic liver disease (CLD) in the general population has risen over the past 10 years and is estimated to affect up to 15% of the United States population. The predominant etiologies include hepatitis C (HCV), alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD), a disease that is rapidly rising in both incidence and prevalence^[4]. In patients with CLD and ESRD, the incidence of cirrhosis is estimated to be as high as 22%^[5]. The concern in patients with kidney transplantation is that of further decompensation of liver disease and long-term graft survival.

Cirrhosis is an essential independent predictor of death in renal transplant patients and current recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) group considers cirrhosis secondary to HCV a contraindication to kidney transplantation alone (KTA)^[6]. These patients could potentially have better outcomes with combined liver-kidney transplantation (CLKT). However, the use of CLKT remains controversial and portends significant implications on the allocation of available livers, *i.e.*, will further deplete the availability of limited numbers of livers.

The purpose of this study was to review a single center experience in cirrhotic patients with ESRD who underwent KTA and determine overall patient and graft survival.

MATERIALS AND METHODS

We performed a retrospective study approved by the institutional review board at Methodist Specialty and Transplant Hospital (MSTH) in San Antonio, Texas.

Patient Protocol

Charts from patients who underwent kidney transplantation (both living and deceased donors) between January 1999 and December 2011 with serological evidence of hepatitis B or C were reviewed. Serological evidence was defined as positive hepatitis B surface antigen and hepatitis B DNA and/or positive hepatitis C RNA. Data was obtained from a combination of a computerized database and paper charts. Patients with compensated and decompensated cirrhosis were included and exclusions included patients who underwent CLKT and those that did not have a confirmed diagnosis of cirrhosis prior to KTA.

Patients with KTA were divided into two groups, a cirrhotic group and a non-cirrhotic group. The non-cirrhotic group was composed of age-matched patients with history of chronic liver disease but no evidence of advanced fibrosis and/or cirrhosis (histologically or radiographically), who underwent KTA during the same time interval. The cirrhotic group was composed of age-matched patients with history of CLD with biopsy evidence of cirrhosis. We evaluated patient demographics, kidney disease parameters, and hepatic disease parameters. Post-KTA outcomes include patient survival, and 3- and 5-year graft survival rates.

Statistical Methods

Continuous variables were analyzed with an independent sample *t* test. Kaplan-Meier survival analysis was used for patient and graft survival. Graft survival was calculated from the time of transplant to return to hemodialysis, death or last follow-up. Three- and five-year graft survival was not censored for death with functioning graft. All analysis was performed using SPSS software and *P* < 0.05 was considered significant. Only ten age-matched patients in the non-cirrhotic group were used as a larger patient volume did not affect the power of the study.

RESULTS

One hundred and thirty-one patient charts were reviewed over a 12-year time span. Of the initial 131 patients who underwent KTA, only 12 patients were diagnosed with biopsy-proven cirrhosis at the time of kidney transplantation (cirrhotic group). Ten randomly selected age-matched patients were selected from the remaining 119 patients who underwent KTA within the similar time interval as those without cirrhosis (non-cirrhotic group). The mean age

Table 1 Recipient Demographics at Time of KTA.

	Cirrhotic Group (n = 12)	Non-Cirrhotic Group (n = 10)
Age, yrs	60.3 (6.2)	57.4 (6.2)
Ethnicity		
Hispanic	7 (58)	4 (40)
Caucasian	3 (25)	3 (30)
African-American	2 (17)	3 (30)
Cause of Liver Disease		
Hepatitis C	7 (58)	5 (50)
Hepatitis B	2 (17)	0
NAFLD/NASH	2 (17)	0
Other	1 (8)	0
No Disease	0	5 (50)
Cause of ESRD		
Hypertension	0	4 (40)
Diabetes	2 (17)	3 (30)
PCKD	1 (8)	1 (10)
IgA nephropathy	1 (8)	0
Unknown	8 (67)	2 (20)
Ascites Present	3 (25)	0
Hepatic Encephalopathy Present	1 (8)	0
MELD (average)	21	n/a
Childs-Pugh		
A	10 (83)	n/a
B	2 (17)	n/a

Continuous variables are described as mean (SD), and categorical variables are described as *n* (%). NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ESRD, end-stage renal disease; PCKD, polycystic kidney disease.

was 60.3 (± 1.79) years for the cirrhotic group vs 57.4 (± 1.97) for the non-cirrhotic group (Table 1). Hispanics made up the largest ethnic proportion of transplant patients among both groups (58% in cirrhotic group vs 40% in the non-cirrhotic group). There were no statistically significant differences in the demographic variables between the two groups.

The most common cause of ESRD was largely unknown (10 patients, 46%) followed by diabetes mellitus (5 patients, 23%). In regards to the cause of cirrhosis in the cirrhotic group, HCV was the primary etiology (7 patients, 58%) followed by hepatitis B and NASH (2 patients, respectively, 17%). Within the non-cirrhotic group and those with CLD (but no advanced disease on biopsy), the predominant etiology was also HCV (5 patients, 50%). Only 2 patients within the cirrhotic group showed clinical evidence of decompensation with ascites and hepatic encephalopathy. Laboratory values reported were from the day of KTA (Table 2). There were no significant differences in etiology and laboratory parameters between the two groups.

The median patient survival within in each group was 7.6 years (95% CI: 5.4 to 9.8) in the cirrhotic group versus 12.9 (95% CI: 11.0 to 14.9) years in the non-cirrhotic group. Figure 1 shows the Kaplan-Meier curves for patient survival rates between the groups (*P* = 0.026). Two patients in the cirrhotic group vs no patients in the non-cirrhotic group died; 1 patient died with a functioning graft in the cirrhotic group. The reasons for death were metastatic hepatocellular carcinoma and severe sepsis. No patients developed liver failure after transplantation.

Graft survival rate at 3- and 5-year for the cirrhotic group were 75% and 58%, respectively, and for the non-cirrhotic group 100% and 92%, respectively. Figure 2 shows the Kaplan-Meier curves for graft survival between the two groups with mean graft survival of 8.1 years (95% CI: 5.9 to 10.3) in the cirrhotic group and 12.9 years (95% CI: 11.0 to 14.9) for the non-cirrhotic group (*P* = 0.052). The

Table 2 Recipient Laboratory Parameters at time of KTA.		
	Cirrhotic Group (n = 12)	Non-Cirrhotic Group (n = 10)
WBC (× 10 ³)	6.6 (2.0)	7.2 (2.0)
Hemoglobin (g/dL)	12.6 (1.7)	12.5 (1.6)
Hematocrit (%)	37.3 (4.5)	37.9 (4.2)
Platelets (× 10 ³)	182.1 (64.6)	212.7 (61.4)
Sodium (mEq/L)	136.8 (2.8)	138.4 (2.7)
BUN (mg/dL)	43.9 (34.3)	45.1 (21.6)
Creatinine (mg/dL)	8.4 (4.4)	8.3 (2.6)
Albumin (g/dL)	3.7 (0.5)	3.7 (0.3)
Protein (g/dL)	7.7 (1.3)	7.9 (0.7)
Alkaline Phosphatase (U/L)	126.1 (38.4)	141.8 (69.0)
Total Bilirubin (mg/dL)	0.7 (0.3)	0.5 (0.1)
AST (U/L)	33.9 (29.7)	27.4 (16.4)
ALT (U/L)	63.4 (57.2)	42.1 (21.4)
PT (sec)	13.5 (0.7)	13.6 (1.7)
INR	1.1 (0.1)	1.1 (0.3)

Continuous variables are described as mean (SD). WBC: White blood cell count; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; INR: International ratio.

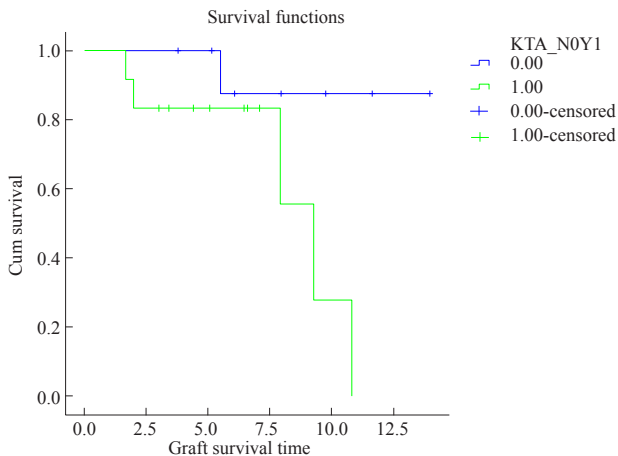


Figure 1 Kaplan-Meier curves comparing patient survival after transplantation between patients with cirrhosis (green) and without cirrhosis (blue).

reasons for graft failure were recurrent kidney disease (3 in cirrhotic group, 1 in non-cirrhotic group), chronic allograft nephropathy (1 in cirrhotic group) and death with functioning graft (1 in cirrhotic group).

DISCUSSION

Cirrhotic patients with ESRD remain a challenge in consideration for KTA versus CLKT. In addition to organ allocation, the liver disease needs to be taken into consideration with respect to kidney graft survival. There continues to remain controversy with respect to the appropriate management of this patient population. Previous recommendations have suggested that KTA should not be considered in patients with cirrhosis, irrespective of their condition (compensated versus decompensated)^[7,8]. Newer recommendations from KDIGO and the Consensus Conference on Simultaneous Liver-Kidney (SLK) suggest that a compensated cirrhotic could benefit from KTA; whereas a decompensated cirrhotic should be considered for CLKT^[9-10]. Unfortunately, these studies are limited on the number of patients studied and we believe that ours is the largest single-center study to date looking at KTA in biopsy-proven cirrhotic patients.

We were able to demonstrate that patient and graft survival were

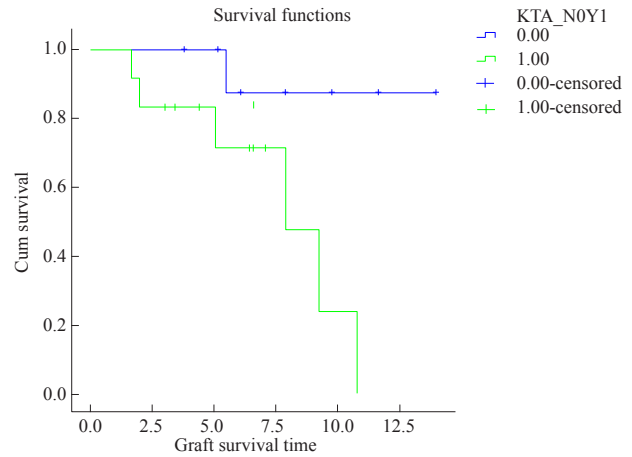


Figure 2 Kaplan-Meier curves comparing graft survival after transplantation between patients with cirrhosis (green) and without cirrhosis (blue).

both improved in patients without cirrhosis as opposed to those with cirrhosis. In comparison to previous studies, our 5-year graft survival in cirrhotic patients of 58% correlated with previously reported lower graft survival rates in such a population of patients.¹¹ With respect to patient survival, we demonstrated a statistically significant benefit in survival in non-cirrhotic age-matched patients. One of the primary issues with KTA in a cirrhotic patient is the major outcome measure: patient and graft survival. Mouquet *et al* demonstrated in one of the earliest documented studies that patient and graft survival after KTA in a cirrhotic was significantly lower than those without cirrhosis (31% vs 92% at 5 years)^[11]. This study was limited as they included patients that developed cirrhosis after KTA. A more recent study showed improved overall patient survival (3 year 86%) and graft survival (3 year 79%) but only a small number of these patients had cirrhosis during KTA^[12]. We were able to demonstrate a significant patient survival benefit and longer graft survival in non-cirrhotic KTA patients.

Patients at risk for chronic liver disease, such as hepatitis B or C, should be considered for liver biopsy prior to a KTA to assess the extent of fibrosis as this can have important implications in the post-operative management plan for the patient. Many studies have recommended the use of liver biopsy for staging purposes in order to consider the patient for KTA versus CLKT^[7,13].

The evaluation for the extent of portal hypertension is slowly becoming a common practice to categorize cirrhotic patients for possible KTA. Clinical evaluation in those with ESRD would be difficult as complications to include ascites occur in both. The most accurate measure of portal pressure is through the transjugular approach with a hepatic portal venous gradient (HVPG) > 10 mm Hg indicating decompensation^[13]. The Consensus Conference on SLK further discussed that cirrhotic patients with an HVPG < 10 mm Hg without other co-morbidities should be considered for KTA^[10]. Paramesh *et al*^[12] further demonstrated a survival benefit both for the patient and graft when HVPG was incorporated in the evaluation.

This study has several limitations. This is a retrospective study which has its own inherent shortcomings. The patient numbers were small, which is to be expected at any single-center, but can be augmented with multi-center studies looking at the same data. We did not routinely perform portal pressure measurements via the transjugular approach as this newer recommendation was elucidated after a predominant number of the cirrhotic patients underwent

KTA. Cirrhotic patients also may have been missed on the initial datasheet evaluation due to poor documentation of cirrhosis in physician reports during kidney transplant workups.

We believe that we addressed a difficult issue in a population that is slowly growing. We demonstrated that cirrhotic KTA patients might be considered for CLKT as opposed to KTA due to poor patient and graft survival. Further evaluation with multi-center studies is needed with larger numbers of patients to truly define the proper management of the patient cohort.

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DISCLAIMER

The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Carl R. Darnall Army Medical Center, San Antonio Military Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, Department of Defense or the U.S. Government.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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Peer reviewers: Neda Svrtlih, Professor, MD, PhD, Department for Hepatitis, Medical Faculty, University of Belgrade, Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Bulevar oslobođenja 16, Belgrade, 11000, Serbia; Nasser Hamed Mousa, Associate Professor, Tropical Medicine and Hepatology, Mansoura University, Mansoura City, 35516/20, Egypt.