

Challenges in Renal Failure Treatment Before Liver Transplant

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KEYWORDS

- Acute kidney injury • Cirrhosis • Hepatorenal syndrome • Survival • Terlipressin
- Liver transplant

KEY POINTS

- Various causes of renal failure among cirrhotics exist and outcomes after liver transplantation (LT) are worse for patients with acute tubular necrosis than those with hepatorenal syndrome (HRS).
- HRS syndrome is still a frequent complication of cirrhosis and plays a detrimental role on survival before and after LT, compared with non-HRS patients.
- The diagnostic criteria of acute kidney injury for the diagnosis of HRS have been recently revised to allow prompt recognition of kidney disease and earlier treatment; studies are in progress to demonstrate the benefits of the revised classification.
- Treatment of HRS now includes surgery (transjugular intrahepatic portosystemic shunt), medical management (vasoconstrictors), and support therapy (renal replacement therapy or extracorporeal artificial liver).

INTRODUCTION

Patients on the waiting list for liver transplantation (LT) show usually cirrhosis and are prone to several complications, such as ascites, bacterial infections, gastrointestinal hemorrhage, hepatic encephalopathy, and renal failure.¹ Renal failure is an important complication in end-stage liver disease and it has been known for many years that it confers greater morbidity and mortality in patients awaiting LT compared with those patients without renal failure. In addition, cirrhotic patients have more complications and reduced survival after LT; serum creatinine after LT is an important predictor of post-LT survival. This is well acknowledged by the Model for End-Stage Liver Disease (MELD) score, which is now used by the United Network for Organ Sharing for

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prioritizing allocation of LTs instead of the older Child-Pugh score; it includes serum creatinine, in addition to parameters of liver function. This article reviews the most important and recent data regarding renal failure treatment in patients with cirrhosis awaiting LT, with special emphasis on diagnosis and management of HRS, which is the most important complication of advanced cirrhosis.

RENAL FAILURE IN CIRRHOSIS: EPIDEMIOLOGY AND OUTCOME

It has been recently calculated that up to 19% of hospitalized patients with cirrhosis and ascites show acute kidney injury (AKI). Also, chronic kidney disease occurs in approximately 1% of all patients with cirrhosis.² Multiple causes of renal failure in patients having cirrhosis exist. In some cases, renal failure is related to etiological factors that also lead to renal failure in patients without liver disease, such as consistent dehydration, hemorrhagic or septic shock, or nonsteroidal anti-inflammatory drugs. Renal failure among patients with cirrhosis can be the consequence of a parenchymal disease, including membranous nephropathy, immunoglobulin A glomerulopathy, and cryoglobulinemic glomerulonephritis. In cirrhotics, prerenal failure (42%) and acute tubular necrosis (ATN) (38%) are the most common reasons for acute renal failure; postrenal acute kidney failure is much less frequent (about 0.3%).^{3,4} Hepatorenal syndrome (HRS) is a prerenal renal failure without any identifiable kidney disease occurring in around 20% of patients with advanced liver disease.^{3,4} The cumulative probability of HRS in patients was prospectively addressed by Gines and colleagues⁵ in a large ($n = 229$) cohort of patients with cirrhosis and ascites; it was 18% after 1 year, rising to 39% at 5 years. The prevalence of HRS declined over recent years, probably a result of a better understanding of its pathogenesis and improved clinical management. Although multiple causes of renal failure in patients with cirrhosis exist, HRS is probably the most challenging to treat.

There is abundant evidence in the medical literature regarding the prognostic value of renal function parameters, particularly serum creatinine, in cirrhotic patients before LT. It is less clear whether the cause of renal failure is relevant to prognosis. This information may be important not only for clinical management of patients and classification of patients in therapeutic trials but also in decision-making in LT. Recent evidence promotes the notion that the cause of renal failure affects the outcome of renal failure. Martin-Llahi and colleagues⁶ studied 562 subjects with cirrhosis and renal failure who were consecutively hospitalized at a single institution over 6 years. They found that 3-month probability survival was 73% for parenchymal nephropathies, 46% for hypovolemia-associated renal failure, and 15% for HRS. In a multivariate analysis adjusted for potentially confounding variables, cause of renal failure was independently associated with prognosis, together with the MELD score, serum sodium, and hepatic encephalopathy at time of diagnosis of renal failure. Another study by Nadim and colleagues⁷ investigated the impact of AKI cause (ATN vs HRS) on survival and renal outcomes after LT. At 5 years, the incidence of chronic kidney disease (stage 4 or 5) was statistically higher in the ATN group versus the HRS group (56% vs 16%, $P < .001$). A multivariate analysis revealed that the presence of ATN at the time of LT was the only variable associated with higher mortality 1 year after LT (odds ratio 6.68, 95% CI 1.96–22.78, $P < .001$).⁷

HISTORICAL PERSPECTIVE

Frerichs⁸ and Flint⁹ were the first investigators to note an association among advanced liver disease, ascites, and oliguric renal failure in the absence of significant renal histologic changes. The term HRS was initially used in 1939 to report the

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