ELSEVIER

From Listing to Transplant: Nephrologic Monitoring in Cirrhotic Patients Awaiting Liver Transplantation

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ABSTRACT

Nephrologic monitoring of end-stage liver disease (ESLD) patients is part of evaluation for orthotopic liver transplantation (OLT). The numerous causes of renal dysfunction in ESLD patients sometimes relate to the extent of liver damage or sometimes more closely to organic nephropathy. The aim of this study was to evaluate renal function through a specific nephrologic form applied in our outpatient clinic to optimize nephrologic monitoring in ESLD patients awaiting OLT. We enrolled 69 cirrhotic patients (56 men, 13 women) awaiting OLT from April 2008 to January 2012. All patients were evaluated at listing and every 3 months until OLT. The most interesting result was the stable values of serum creatinine from listing to transplantation. We think that dedicated liver transplant nephrologic evaluation is important in the follow-up of ESLD patients awaiting OLT, because the presence of renal dysfunction may represent an important criterion for specific therapeutic interventions to minimize pre-OLT renal injuries that limit the effect of impaired renal function on patient outcomes.

LIVER cirrhosis represents the final stage of several chronic hepatic diseases.[1] It is most frequent in male adults. The most important causes are hepatitis C (HCV) or B (HBV) infection and excessive alcohol consumption.[2] In liver cirrhosis, renal and hepatic functions are often intertwined as a direct consequence of intrarenal vasoconstriction and inflammation promoted by hepatic failure[3] and more rarely through primary disease processes such as hepatorenal polycystic disease, Budd-Chiari syndrome, α1-antitrypsin deficiency, Wilson disease, and glycogen storage hyperoxaluria.

The poor prognosis of end-stage liver disease (ESLD) patients with renal dysfunction has led to the inclusion of serum creatinine (sCr) concentration in the Model for End-Stage Liver Disease (MELD) score that is used to prioritize patients for liver transplantation, seeking to reduce mortality on the waiting list.[4]

Although sCr is easy to determine, it can be inaccurate in patients with ESLD owing to decreased hepatic creatine synthesis, increased tubular creatinine secretion, decreased skeletal muscle mass, and various sCr measurement method.[5] Normal sCr levels in ESLD should be the lower limit of normal, usually 0.7–0.8 mg/dL. If the sCr is near to or above the upper limit of normal, one must perform a second-level investigation.[6,7] Some workers have proposed monitoring sCr in ESLD patients by considering changes from baseline concentrations rather than the absolute values.[8]

Ascites and water retention with subsequent increases in total body water and development of dilutional hyponatremia are associated in ESLD.[9] Hyponatremia may result from several factors related to cirrhosis and portal hypertension, the most prominent of which is increased release of arginine vasopressin.[9] Approximately 30%,[10] of patients with cirrhosis and ascites display hyponatremia (serum sodium <130 mEq/L) is associated with an increased risk of mortality among cirrhotic patients,[9,10] and individuals on liver transplant waiting lists.[11]

Kidney involvement in ESLD can be associated with portal hypertension.[12] Hepatorenal syndrome (HRS),

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Supported by the Consorzio Interuniversitario peri i Trapianti.

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0041-1345/13/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.07.035

a specific form of impaired renal function, is characterized by marked abnormalities in the arterial circulation, ascites, and endogenous vasoactive systems.[13,14] Activation of vasoconstrictor systems maintains normal arterial pressure but leads to ascites formation and eventually to renal failure.[15,16] In early stages of cirrhosis, when portal hypertension is moderate, increased cardiac output compensates for the modest reduction in systemic vascular resistance, permitting the arterial pressure and effective arterial blood volume to remain within normal limits.[15,16] In advanced stages of cirrhosis, systemic vascular resistance is markedly reduced; additional increases in cardiac output cannot normalize effective arterial blood volume.[15] Cardiac output decreases with cirrhosis progression and liver volume reduction[17] parameters that correlate with longer listing times.

Renal dysfunction in ESLD patients, is mostly caused by ischemia due to intrarenal vasoconstriction and hypoperfusion,[15,18] which are usually related to volume depletion, renal vasoconstrictive drugs including diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal antiinflammatory drugs, and/or severe hypotension supported by gastrointestinal bleedings, ascites, paracentesis, reduced intake or fluid loss, excessive use of diuretics or laxatives, diarrhea, severe sepsis or spontaneous bacterial peritonitis (SBP), or septic shock.[14–16] Moreover, acute kidney injury can occur after administration of iodinated contrast agents often used to diagnose and monitor liver lesions.

These causes of renal ischemia should always be evaluated and considered to be exclusion criteria for the diagnosis of HRS, along with the presence of proteinuria, hematuria/hematic casts, or ultrasound alterations of the kidneys. In clinical practice, it is also important to perform a urinalysis and to measure the sodium concentration in urine to identify organic renal impairment.[19] These cases seem to show a correlation between the extent of liver damage and severity of renal lesions.[20] Hepatitis virus–related and alcoholic cirrhosis are in fact associated with membranous glomerulonephritis, membranoproliferative glomerulonephritis with the presence or absence of cryoglobulins (HCV), IgA nephropathy or postinfectious glomerulonephritis, ANCA-positive vasculitis, or renal tubular acidosis[21] and sometimes associated with systemic vasculitic manifestations, particularly in primary biliary cirrhosis or primary sclerosing cholangitis. These renal lesions cannot be predicted without a renal biopsy the opportunity for which may be limited because of coagulopathy abnormalities in patients with cirrhosis.[22] Finally, renal failure related to classic risk factors is associated with the presence of atherosclerotic risk factors, particularly diabetes and hypertension.

Evaluation of renal function in ESLD patients is part of the necessary monitoring to be accepted on to the waiting list for orthotopic liver transplantation (OLT). The presence of nephropathy or glomerular lesions before transplantation may play an important role in the development of acute or chronic renal failure after OLT.[23] Moreover, it may contribute to poor functional recovery in the post-transplantation period.[24] Among patients listed for OLT, evaluation of renal function, recognition of organic or functional nephropathy and all the hepatic-related conditions are important aspects that can affect the prognosis and the indication for liver-kidney transplantation versus liver transplantation alone. Therefore standardization of nephrologic monitoring could provide a mechanism for physicians to critically review outcomes and adjust selection criteria.[3] The aim of the present study was to evaluate renal function through a specific nephrologic form to optimize nephrologic monitoring in ESLD patients awaiting OLT.

MATERIAL AND METHODS

We enrolled 69 cirrhotic patients (56 men/13 women) awaiting OLT from April 2008 to January 2012. We collected specific historic information such as age, sex, etiology of liver disease, presence of HBV or HCV virus infection, hepatocellular carcinoma, presence of ascites, and risk factors for kidney dysfunction, such as diabetes mellitus and hypertension. All patients were evaluated at listing (T0) and every 3 months thereafter on the basis of the specific nephrologic form *modified* from Davis et al[25] applied in our outpatient clinic, with particular attention to medical history, renal and hepatic function, and factors that may be suspected of more specific kidney diseases. We also performed a physical examination and evaluated laboratory and instrumental tests. These parameters, divided into first- and second-level evaluations are reported in a collection data table (Table 1). An algorithm of nephrologic monitoring in cirrhotic patients awaiting OLT or kidney-liver transplantation is presented in Table 2.

Renal function was assessed by sCr, blood urea nitrogen (BUN), serum sodium, urinalysis, and glomerular filtration rate (GFR) estimated with the Modification of Diet in Renal Disease (MDRD) formula. Liver function was assessed by MELD score, albumin, bilirubin, and international normalized ratio (lNR).

Acute renal failure (ARF) based on Acute Kidney Injury Network criteria was classified in 3 stages: ARF stage 1: sCr $\geq$150%–200% (1.5–2-fold) from baseline; ARF stage 2: for sCr $\geq$200%–299% (2–3-fold) from baseline; and ARF stage 3: sCr $\geq$300% (>3-fold) from baseline or sCr >354 mmol/L ($\geq$4 mg/dL).[26] Chronic renal failure (CRF) was defined as GFR <60 mL/min/1.73 m^2 for >3 months, regardless of the presence or absence of structural kidney damage, as evaluated with the MDRD formula as suggested by the Working Party proposal for cirrhotic patients and according to the practice guidelines from the Kidney Disease Outcomes Quality Initiatives (K/DOQI) Workgroup.[27]

Statistical Technique

Data are presented as mean $\pm$ SD for continuous variables and as n (%) for categoric variables. All analyses were performed with the use of SPSS 18.0 (SPSS, Chicago, Illinois) with $P < .05$ considered to be significant.

RESULTS

Among 69 cirrhotic patients of mean age 55.6 $\pm$ 9.2 years 28 (40.6%) suffered HCV infection, 15 (21.7%), HBV

Table 1. Nephrologic Form Used in Our Nephrologic Outpatient Clinic for ESLD Patients Awaiting OLT

Specific Anamnestic Information and Tests
Age
Sex
Etiology of liver disease
MELD score
Listing time
sCr >0.8 mg/dL
Hyponatremia, proteinuria, hematuria
Hypertension
Abnormal blood glucose levels
Diagnostic iodinated contrast
Use of diuretics (dosage >125 mg furosemide)
Ascitic decompensation
Refractory ascites
Paracentesis
Increase of sCr >50% from baseline or ≥0.3 mg/dL within 48 hours
Response to diuretic withdrawal/volume expansion with albumin
TIPS
Spontaneous bacterial peritonitis/infections
Bleeding or fluid loss
Urinary output (24 hours)
Diastolic dysfunction
Cardiac output
Hypotension
Liver size reduction
Physical Examination
Nutritional status (BMI)
Edema
Pleural effusion
Tense ascites
Neuropathy (diabetes, cryoglobulinemia)
Blood pressure (mm Hg)
Heart rate (bpm)
Lymphadenopathy
Signs of vasculitis (purpura, erythema, vitiligo, psoriasis, skin ulcerations, xerostomia, etc) and autoimmune tests

First-level evaluation. Modified from Davis et al.[25]
ESLD, end-stage liver disease; OLT, orthotopic liver transplantation; MELD, Model for End-Stage Liver Disease; sCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic shunt; BMI, body mass index; bpm, beats per minute.

Table 2. Algorithm of Nephrologic Form Used in Our Nephrologic Outpatient Clinic for ESLD Patients Awaiting OLT

First-Level Tests (All Patients Listed)
sCr
BUN
Urinalysis with urinary sediment
Creatinine/albumin rate
Creatinine clearance (mL/min)
Proteinuria (24 hours)
Renal ultrasound and color Doppler ultrasonography with resistive index measurement
Serum albumin
Serum sodium, serum potassium
Other Diagnostic Investigations if…
sCr >0.8 mg/dL in patients with decompensated cirrhosis, and/or
Positive urinalysis for presence of leukocytes, erythrocytes or casts in significative number, and/or
Microalbuminuria/proteinuria
Second-Level Diagnostic Investigations
Dosage electrolytes and urinary creatinine to calculate sodium escrection fraction and urinary osmolality
Determination of glomerular filtration with renal scintigraphy
Renal Biopsy if…
In patients with primitive renal disease, no available resistive index, or
Not reversible suspect disease in absence of contraindications
Indications of Kidney-Liver Transplantation
Patients with CRF with GFR <30 mL/min or in chronic renal replacement therapy or with fibrosis and/or glomerulosclerosis >30% at renal biopsy
Patients with ARF in renal replacement therapy for a period >6 weeks or HRS with sCr >2.5 mg/dL in renal replacement therapy >2 weeks
Patients with genetic syndromes involving kidney and liver: polycystic disease, glycogen disease

Modified from Davis et al.[25]
BUN, blood urea nitrogen; CRF, chronic renal failure; GFR, Glomerular Filtration Rate (estimated by Modification of Diet in Renal Disease formula); ARF, acute renal failure; HRS, hepatorenal syndrome; other abbreviation as in Table 1.

infection, 26 (37.7%) hepatocellular carcinoma, 9 (13%) hypertension, and 22 (31.9%) diabetes mellitus.

At T0, mean values of sCr were 0.89 ± 0.29 mg/dL, bilirubin 4.09 ± 4.84 mg/dL, INR 1.45 ± 0.31, MELD score 14.98 ± 4.42, albumin 3.49 ± 0.55 mg/dL, and serum sodium 136.62 ± 5.54 mEq/L. Proteinuria and hematuria were present in 3 subjects (4.3%). We could perform a renal biopsy in only 1 patient with HBV-related cirrhosis, hematuria, and a serum creatinine of 1.2 mg/dL. It revealed IgA nephropathy with middle to moderate interstitial fibrosis, tubular atrophy, and arteriolosclerosis. In this case a second-level evaluation by renal scintigraphy showed a GFR of 45 mL/min/1.73/ m^2.

The median waiting time on the list was 357 days (interquartile range, 125–580). During follow-up, 28/69 patients (40.6%) developed ascites, 8 (11.6%) developed hepatic encephalopathy, and 8 (11.6%) underwent transjugular intrahepatic portosystemic shunt. No patients displayed cryoglobulinemia or manifestations of systemic vasculitis.

The prevalence of CRF was 13% ($n = 9$), and of ARF 30.4% ($n = 21$), namely, 10 ARF stage 1, 7 ARF stage 2, and 4 ARF stage 3. All patients with ARF showed ascitic decompensation, urinary tract infection/SBP, paracentesis, use of high diuretic doses and negative water balance. We considered baseline sCr (sCr-b) to be the lowest value of sCr during the observation period: 21 subjects (30.4%) presented with a sCr-b >0.8 mg/dL. Among those with ARF, 6 (28.6%) presented a sCr-b >0.8 mg/dL. Despite episodes of ARF, there were no differences between sCr values at T0 and at time of OLT.

DISCUSSION

Hepatic function and renal failure are closely related among ESLD patients.[28] Renal dysfunction is primarily related to disturbances in circulatory functions, triggered by portal hypertension leading to reversible intrarenal vasoconstriction and hypoperfusion.[15] Pre-OLT kidney function is an important predictor of post-OLT kidney function. Renal

dysfunction, in the setting of OLT, is associated with greater short- and long-term patient mortality rates.[29,30] In a previous study, we observed an association between pre-OLT CRF with CRF at 6 months after OLT.[24]

Therefore, monitoring of renal function in patients with ESLD is important. It requires a standardized assessment to achieve a reduction in the incidence of pre-OLT renal failure and better post-OLT outcomes. Therefore, we used specific nephrologic from account for all possible causes of renal dysfunction in the context of liver cirrhosis to predict the probability of renal recovery after OLT and appropriateness of a concurrent kidney transplantation.[31]

Monitoring ESLD patients every 3 months after listing allowed us to identify subjects with episodes of ARF caused by ascites decompensation, urinary infection/SBP, paracentesis, use of high diuretic doses, and negative water balance. The most interesting result of our study was the stable values of sCr from listing to transplantation. Despite the descriptive nature of our study, we think that a dedicated liver transplant nephrologic evaluation is important for the follow-up of ESLD patients awaiting OLT, because the presence of renal dysfunction represents an important criterion for specific therapeutic interventions to minimize pre-OLT renal injury and improve patients survival by limiting the impact of impaired functions.

REFERENCES

1. Brandão DF, Ramalho LN, Ramalho FS, et al. Liver cirrhosis and hepatic stellate cells. *Acta Cir Bras*. 2006;1:54–57.
2. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. *Am Fam Physician*. 2006;74(5):756–762.
3. Davis CL, Gonwa TA, Wilkinson AH. Pathophysiology of renal disease associated with liver disorders: implications for liver transplantation. Part I. *Liver Transpl*. 2002;8:91–109.
4. Arroyo V, Fernández J. Management of hepatorenal syndrome in patients with cirrhosis. *Nat Rev Nephrol*. 2011;7(9):517–526.
5. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–409.
6. Rastogi A, Wilkinson AH. Current management of renal dysfunction in the cirrhotic patient review. *Aliment Pharmacol Ther*. 2005;21:949–961.
7. Johnson RJ, Feehally J. Investigation of renal disease. In: Johnson RJ, Feehally J, eds. *Comprehensive Clinical Nephrology*. London: Mosby; 2003.
8. Ribeiro de Carvalho J, Alves Villela-Nogueira C, Raggio Luiz R, et al. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. *J Clin Gastroenterol*. 2012;46:e2l–e26.
9. Ginés P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. *Hepatology*. 1998;28(3):851–864.
10. Arroyo V, Rodés J, Gutierrez Lizarraga MA, et al. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. *Am J Dig Dis*. 1976;21:249–256.
11. Llach J, Ginés P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology*. 1988;94:482–487.
12. Fernandez-Esparrach G, Sanchez-Fueyo A, Ginés P, et al. A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol*. 2001;34:46–52.
13. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359:1018–1026.
14. Restuccia T, Guevara M, Ginés P, et al. Impact of pre-transplant treatment of hepatorenal syndrome with vasopressin analogues on outcome after liver transplantation: a case-control study. *J Hepatol*. 2003;38:69A (abstr).
15. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology*. 1988;8: 1151–1157.
16. Arroyo V, Ginés P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology*. 1996;23:164–176.
17. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology*. 2005;42:439–447.
18. Arroyo V, Rodés J, Gutierrez Lizarraga MA, et al. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. *Am J Dig Dis*. 1976;21:249–256.
19. Lata J. Hepatorenal syndrome. *World J Gastroenterol*. 2012;18(36):4978–4984.
20. Baxter JH, Ashworth CT. Renal lesions in portal cirrhosis. *Arch Pathol*. 1946;41:476–488.
21. Jouët P, Meyrier A, Mal F, et al. Transjugular renal biopsy in the treatment of patients with cirrhosis and renal abnormalities. *Hepatology*. 1996;24(5):1143–1147.
22. Sam R, Leehey DJ, Picken MM, et al. Transjugular renal biopsy in patient with liver disease. *Am J Kidney Dis*. 2001;37: 1144–1151.
23. Crawford DH, Endre ZH, Axelsen RA, et al. Universal occurrence of glomerular abnormalities in patients receiving liver transplant. *Am J Kidney Dis*. 1992;19:339–344.
24. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349: 931–940.
25. Davis CL, Feng S, Sung R, et al. Simultaneous liver-kidney transplantation: evaluation to decision making. *Am J Transplant*. 2007;7:1702–1709.
26. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut*. 2011;60:702–709.
27. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1–S266.
28. Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279–1290.
29. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology*. 2002;35:1179–1185.
30. Gonwa TA, Klintmalm GB, Levy M, et al. Impact of pre-transplant renal function on survival after liver transplantation. *Transplantation*. 1995;59:361–365.
31. Cholongitas E, Shusang V, Marelli L, et al. Renal function assessment in cirrhosis–difficulties and alternative measurements review. *Aliment Pharmacol Ther*. 2007;26(7):969–978.