**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 61986

**Manuscript Type:** FRONTIER

**Chronic renal dysfunction in cirrhosis: A new frontier in hepatology**

Kumar R *et al*. Chronic kidney disease in cirrhosis

Ramesh Kumar, Rajeev Nayan Priyadarshi, Utpal Anand

**Ramesh Kumar,** Department of Gastroenterology, All India Institute of Medical Sciences, Patna 801507, Bihar, India

**Rajeev Nayan Priyadarshi,** Department of Radiodiagnosis, All India Institute of Medical Sciences, Patna 801507, Bihar, India

**Utpal Anand,** Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Patna 801507, Bihar, India

**Author contributions:** Kumar R designed and wrote the manuscript, and collected relevant data; Priyadarshi RN and Anand U contributed in data collection and manuscript writing; all authors have read and approve the final manuscript.

**Corresponding author: Ramesh Kumar, MD, Associate Professor,** Department of Gastroenterology, All India Institute of Medical Sciences, Phulwari Sharif, Patna 801507, Bihar, India. docrameshkr@gmail.com

**Received:** December 24, 2020

**Revised:** January 17, 2021

**Accepted:** March 8, 2021

**Published online:**

**Abstract**

Chronic kidney disease (CKD) in patients with liver cirrhosis has become a new frontier in hepatology. In recent years, a sharp increase in the diagnosis of CKD has been observed among patients with cirrhosis. The rising prevalence of risk factors, such as diabetes, hypertension and nonalcoholic fatty liver disease, appears to have contributed significantly to the high prevalence of CKD. Moreover, the diagnosis of CKD in cirrhosis is now based on a reduction in the estimated glomerular filtration rate of < 60 mL/min over more than 3 mo. This definition has resulted in a better differentiation of CKD from acute kidney injury (AKI), leading to its greater recognition. It has also been noted that a significant proportion of AKI transforms into CKD in patients with decompensated cirrhosis. CKD in cirrhosis can be structural CKD due to kidney injury or functional CKD secondary to circulatory and neurohormonal imbalances. The available literature on combined cirrhosis-CKD is extremely limited, as most attempts to assess renal dysfunction in cirrhosis have so far concentrated on AKI. Due to problems related to glomerular filtration rate estimation in cirrhosis, the absence of reliable biomarkers of CKD and technical difficulties in performing renal biopsy in advanced cirrhosis, CKD in cirrhosis can present many challenges for clinicians. With combined hepatorenal dysfunctions, fluid mobilization becomes problematic, and there may be difficulties with drug tolerance, hemodialysis and decision-making regarding the need for liver *vs* simultaneous liver and kidney transplantation. This paper offers a thorough overview of the increasingly known CKD in patients with cirrhosis, with clinical consequences and difficulties occurring in the diagnosis and treatment of such patients.

**Key Words:** Acute kidney injury; Cirrhosis; Chronic kidney disease; Renal failure; Hepatorenal syndrome; Renal function

Kumar R, Priyadarshi RN, Anand U. Chronic renal dysfunction in cirrhosis: A new frontier in hepatology. *World J Gastroenterol* 2021; In press

**Core Tip:** The current definition of chronic kidney disease (CKD) in patients with liver cirrhosis is based on a 3-mo decline in the glomerular filtration rate of < 60 mL/min, and it may be structural or functional CKD, depending on the presence or absence of kidney injury. Emerging data show that the incidence of CKD has risen dramatically in patients with cirrhosis over the last decade. The main reasons behind the increased prevalence of CKD appear to be a growing recognition of this condition and a rising trend in the prevalence of diabetes, hypertension and nonalcoholic fatty liver disease. This paper offers a detailed overview of CKD in patients with cirrhosis, including the clinical implications and difficulties clinicians may face with regard to diagnosis and treatment.

**INTRODUCTION**

Most attempts to assess renal impairment in cirrhosis have so far concentrated on acute kidney injury (AKI), and as a result, detailed knowledge of AKI in cirrhosis is now available[1]. However, there is still scarce evidence on the prevalence, clinical impact and treatment of chronic kidney disease (CKD) in cirrhosis. A sharp rise in the diagnosis of CKD among patients with cirrhosis has been observed in recent years. The prevalence of CKD in hospitalized patients with cirrhosis, which used to be approximately 1% in 2005, has now risen to as high as 46.8% in 2019[2,3]. The growing prevalence of CKD in patients with cirrhosis may represent the convergence of several important epidemiological patterns: the continuing increase in the prevalence of metabolic risk factors such as obesity, hypertension and Medicine degree (DM); the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) as a major contributor to the burden of cirrhosis; and the aging cohort of cirrhosis[4-6]. Moreover, some emerging evidence indicates that the risk of developing de novo CKD remains high for AKI survivors[7]. Liver cirrhosis patients are susceptible to developing AKI due to circulatory abnormalities, neurohormonal changes and the involvement of risk factors such as bacterial infection, gastrointestinal bleeding, medication and paracentesis[1,8]. Depending on the severity, length and frequency, AKI increases the risk of developing incident CKD due to decreases in renal mass and nephron number, vascular insufficiency, and maladaptive repair mechanisms[9]. Therefore, rather than separate entities, AKI and CKD may represent a continuum. The term CKD now encompasses both structural CKD due to structural damage to the kidney and functional CKD due to circulatory and neurohormonal imbalances in cirrhosis. The differentiation between various forms of renal dysfunction in cirrhosis is crucial, as each requires a different treatment plan.

**DEFINITION AND CLASSIFICATION**

The definition of CKD in cirrhosis was originally based on a serum creatinine level of > 1.5 mg/dL until 2011, when an updated definition was introduced by a working group composed of experts from various disciplines[10]. The definition endorsed by kidney disease: Improving global outcomes was largely adopted by this group, and CKD was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min for more than 3 mo, measured using the Modiﬁcation of Diet in Renal Disease-6 (MDRD-6) equation. While the group further agreed that the MDRD-6 equation was not perfect for estimating GFR in patients with cirrhosis, it may still be adopted until better alternatives become available. Currently, the diagnosis of CKD does not require corroborating evidence of kidney damage, such as proteinuria, hematuria, abnormal renal imaging or pathology.

Kidney Disease: Improving Global Outcomes has classified CKD into structural and functional CKD on the basis of the presence or absence of kidney injury. The old entity, type 2 hepatorenal syndrome (HRS), now referred to as HRS-CKD, is essentially a functional CKD[11]. While functional CKD is considered potentially reversible, since biomarkers of renal tubular damage have been found in patients with HRS, this may not exactly be the case[12-14]. Patients with cirrhosis may have several risk factors for developing structural CKD per se, such as DM, NAFLD, and atherosclerosis[4-6]. In addition, persistent renal vasoconstriction in functional CKD can lead to structural changes, transforming it into structural CKD.

**THE GROWING PREVALENCE OF CHRONIC KIDNEY DISEASE IN CIRRHOSIS**

In recent years, not only has the prevalence of CKD increased significantly in the general population, but an increasing rise in the prevalence of CKD has also been reported in patients with cirrhosis (Table 1)[3,15-17]. The prevalence rates of CKD in cirrhosis, however, vary significantly across studies due to variations in parameters used to describe CKD and differences in the severity of patients with chronic liver disease (CLD).

In a study by Rustgi *et al*[18], although the prevalence of CKD among 94431 patients with cirrhosis collected from the insurance claim database was 3.37%, the proportion of patients with decompensated cirrhosis was higher in the combined CLD-CKD group (27.2% *vs* 11.8%), suggesting that the prevalence of CKD increases with the severity of CLD. In a recent retrospective analysis of a large cohort of patients with cirrhosis (*n* = 78640) awaiting liver transplantation (LT), while the prevalence of CKD was 7.8% in 2002, it increased to 14.6% in 2017. This is a documented increase in the CKD prevalence rate of 187% in just 15 years. Moreover, among 39719 LT recipients, 6269 (16%) patients met the CKD criteria at the time of last transplant[4]. Another study evaluating the prospectively managed database of the North American Consortium for the End-Stage Liver Disease Study reported a 46.8% prevalence of CKD among 2346 admitted patients with cirrhosis[3]. In an Indian study, the occurrence of CKD was observed in 32.8% of a large prospective cohort (*n* = 818) of patients with cirrhosis[16]. Functional CKD is considered to be relatively uncommon and accounts for only approximately 3.9% to 15.8% of renal impairments among hospitalized cirrhotic patients; however, new data need to be developed in light of the updated concept of CKD in cirrhosis[2,19].

**DETERMINANTS OF INCREASING CHRONIC KIDNEY DISEASE IN CIRRHOSIS**

Apart from the aging and the high incidence of AKI in cirrhosis, a rising recognition of this condition and a rising trend in the prevalence of DM, hypertension and NAFLD seem to be the key factors behind the increased prevalence of CKD in cirrhosis (Figure 1).

***AKI to CKD transition***

AKI is an independent risk factor for developing CKD in the general population. AKI to CKD transition appears to reflect a continuum. In a meta-analysis of 13 studies, the pooled adjusted hazard ratio for developing CKD among patients with AKI was 8.8 (95% confidence interval: 3.1-25.5)[20]. AKI occurs very frequently in patients with decompensated cirrhosis because of pre-existing circulatory abnormalities, neurohormonal changes and the involvement of risk factors such as DM, bacterial infection, gastrointestinal bleeding, medications and therapeutic paracentesis[1,7,10,11]. Emerging data suggest that in patients with decompensated cirrhosis, a large proportion of AKI progresses to CKD. In a recent study, 25% of patients with decompensated cirrhosis with AKI who survived for at least 3 mo developed CKD, compared with only 1% of those without AKI[7]. Moreover, the odds of developing CKD in patients with decompensated cirrhosis with AKI were 31, suggesting that they are more prone to CKD development than general AKI patients. A higher transition from AKI to CKD was seen when the severity of AKI was higher and when it developed after hospitalization. In another study published in India, 32.8% of 818 patients with cirrhosis developed CKD, approximately 80% of patients with CKD had at least one episode of AKI, and one-third of patients with AKI had progression to CKD[16]. The mechanisms underlying AKI-CKD progression are still poorly understood. In general, it is believed to be a result of maladaptive repair in the interstitial, vascular and tubular structures of the kidney[9]. However, it is not clear whether the same mechanisms contribute to the development of CKD in cirrhosis. Patients with higher baseline levels of serum creatinine are more likely to develop AKI and less likely to recover from such AKI episodes[21]. Because DM and hypertension patients are more likely to have intrinsic renal disease, such as diabetic nephropathy or hypertensive nephrosclerosis, they are not only at higher risk of developing AKI episodes but also less likely to recover from these episodes due to a lower renal reserve.

***Increase in the multiple risk factors***

There has been a substantial increase in the multiple shared risk factors for cirrhosis and CKD over the years. NAFLD is independently and significantly associated with an increased incidence and prevalence of CKD[22,23]. In a recent meta-analysis that included nearly 64000 subjects, NAFLD was associated with an approximately 2-fold increased risk of both prevalent and incident CKD[23]. Multiple factors, such as the proinflammatory environment, insulin resistance, oxidative stress, and the activated renin-angiotensin system, may account for the accelerated development and progression of CKD in NAFLD subjects, apart from the common occurrence of DM and hypertension[24]. In addition, NAFLD has been strongly associated with atherosclerosis, as shown by increased intima media thickness or atherosclerotic plaques in the carotid arteries, and atherosclerosis has been associated with glomerulosclerosis, a process that can lead to CKD[25]. In one study, approximately 20%-25% of LT candidates were found to have severe coronary artery disease, suggesting that atherosclerosis in cirrhosis is not uncommon[26]. Over the last 2 decades, the prevalence of NAFLD and NAFLD-related cirrhosis has also increased considerably[27]. In a study, NAFLD accounted for a substantial rise in simultaneous liver and kidney transplantation (SLKT), from 8.2% in 2002 to 22% in 2011[28]. In cirrhosis, DM is highly prevalent, with recorded prevalence rates ranging from 35% to 71%, which is far higher than in the general population[29]. Glomerulopathy, which can progress to CKD, may be associated with certain specific causes of cirrhosis, such as hepatitis B virus (HBV) or hepatitis C virus (HCV). Glomerular involvement in patients with viral hepatitis occurs *via* an immune pathogenic mechanism. Circulating immune complexes containing viral antigens have been found in the kidney[30].

**CLINICAL IMPLICATIONS OF CHRONIC KIDNEY DISEASE IN CIRRHOSIS**

In several ways, CKD can affect the clinical manifestations, complications, therapeutic decisions, and outcomes of patients with cirrhosis.

***Impact on clinical manifestations***

Anorexia, anemia, ascites, bleeding tendency and encephalopathy can be independently due to both hepatic and renal diseases, so the contributions from individual diseases are often difficult to determine in patients with cirrhosis with CKD. This may create uncertainty about optimal therapeutic choices, such as requirements of renal replacement therapy. In patients with cirrhosis, CKD may contribute to ascites and edema in various ways, such as nephrogenic ascites, chronic fluid overload, hypoproteinemia, and cardiomyopathy[31]. Refractory ascites is almost universal in patients with functional CKD[32,33]. Due to multiple and complex hemostasis abnormalities, patients with concurrent hepatorenal dysfunction may have a higher tendency to bleed. On the other hand, even thrombotic complications are not unusual in such patients[34]. CKD is an independent cardiovascular mortality risk factor, and it can worsen anemia due to cirrhosis[35,36]. Both CKD and cirrhosis can cause immunodepression, leading to an increased risk of infection[37]. Patients with cirrhosis and CKD appear to have an increased risk of developing malignancy[27,38]. In recent years, NAFLD, which is significantly linked to CKD, has also emerged as one of the leading causes of hepatocellular carcinoma (HCC)[27]. Alcohol, HBV infection and HCV infection are other shared risk factors that can be associated with both HCC and CKD. HCC has been found to be associated with a higher prevalence of CKD than any other cancer[39]. After adjustment for many possible confounders, a lower GFR has been shown to be independently associated with a higher risk of incident renal cell and urothelial cancer[40]. CKD has been shown to be associated with increased mortality from liver, kidney, and urothelial cancers[41].

***Impact on complications and outcomes***

CKD in cirrhosis is associated with poor outcomes and an increased frequency of complications[3,7]. Wong *et al*[3] found that patients with cirrhosis with CKD had higher rates of superimposed AKI (68% *vs* 21%), need for dialysis (11% *vs* 2%) and 30-d mortality rates (16% *vs* 7%) than patients with cirrhosis without CKD. A 10 mL/min decrease in eGFR was found to be associated with a 13% increase in 30-d mortality in patients with cirrhosis. In a study by Bassegoda *et al*[7], patients with cirrhosis with CKD had a higher frequency of AKI (75% *vs* 45%), refractory ascites (25% *vs* 7%), bacterial infections (58% *vs* 34%) and LT requirement (25% *vs* 10%) compared with those without CKD[7]. In addition, the involvement of cirrhosis is independently related to a poor outcome in patients with CKD[42]. CKD impacts not only waitlist mortality but also worsens post-LT survival. Cullaro *et al*[4] reported that the one-year post-LT mortality rate in patients with CKD was 12%, compared with 9% in those without CKD. In addition, posttransplant renal outcomes may also be affected by the presence of CKD[13].

***Impact on health care utilization***

Wong *et al*[3] found that cirrhosis patients with CKD had higher rates of hospitalization during the preceding 6 mo (70% *vs* 63%) than those without CKD. Similarly, Bassegoda *et al*[7] reported a higher 3-mo readmission rate (67% *vs* 37%) in cirrhosis-CKD patients compared to cirrhosis alone. A recent study analyzed the usage of health care services and the cost burden associated with CKD in patients with CLD (*n* = 9869) compared to patients with CLD alone (*n* = 588586) by using real-world insurance claims data. In a propensity-matched cohort analysis, patients with combined CLD-CKD were found to have substantially greater annual per-person all-cause health care costs than patients with CLD alone[18].

**DIAGNOSTIC EVALUATION**

The diagnosis of CKD in cirrhosis is based on GFR. Abnormal urine analysis and/or abnormal findings on renal ultrasonography are usually found in advanced CKD and hence are not required for diagnosis. Cirrhosis can be diagnosed in patients with CKD by histopathology or hepatic ultrasound, as well as by clinical manifestations of portal hypertension and/or hepatic decompensation.

Since CKD diagnosis in cirrhosis requires a decrease in GFR to < 60 mL/min for 12 wk, a reliable and reproducible method is required to estimate GFR. The direct iothalamate clearance test is the gold standard for GFR measurement; however, the cumbersome technique and lack of widespread availability limit its usage in clinical practice[43]. Several indirect methods are available to calculate eGFR in clinical practice.

***Creatinine-based eGFR***

For the assessment of renal function, an eGFR based on the serum creatinine level is commonly used in clinical practice. In patients with cirrhosis, the most commonly used creatinine-based equation is the MDRD. However, serum creatinine levels in patients with cirrhosis may be unreliable due to hepatic dysfunction causing decreased production of creatine, reduced skeletal muscle mass causing decreased creatine-to-creatinine conversion, increased tubular secretion of creatinine, and underestimation of the serum creatinine level by hyperbilirubinemia[44-46]. Therefore, GFR in cirrhosis is typically overestimated by the creatinine-based equation, where a normal serum creatinine level cannot rule out renal dysfunction. In a meta-analysis, the formula based on creatinine was found to overestimate GFR by 18 mL/min[47]. However, despite limitations and until better substitutes become available, the latest creatinine-based MDRD equation (MDRD-6) has been recommended by expert panels to be used in patients with cirrhosis[4,44]. The MDRD-6 equation includes 6 variables: Age, sex, race, serum creatinine, serum albumin, and blood urea nitrogen.

***Cystatin-based eGFR***

Cystatin C is a protein produced by all nucleated cells in the body that is exclusively removed by glomerular filtration. Hepatic function, muscle mass, sex, hyperbilirubinemia and tubular secretion do not affect the level of cystatin C. Therefore, cystatin C-based eGFR may be a better alternative to the serum creatinine-based equation for patients with cirrhosis[48-50]. However, the level of cystatin C is affected by hypoalbuminemia, elevated C-reactive protein and leukocytosis, which may limit its role in estimating GFR in cirrhosis[50,51]. Additionally, in patients with cirrhosis, the diagnostic performance of all cystatin C-based GFR equations has been found to be lower than in those without cirrhosis[44]. Combining serum creatinine and cystatin C in an equation appears to predict GFR more accurately than either alone[52]. However, eGFR measurement based on cystatin C has not yet been approved for routine use in patients with cirrhosis.

***Biomarkers of kidney damage***

The role of conventional urinary markers such as albuminuria is very limited in patients with cirrhosis, which may be because of hypoalbuminemia and relatively increased capillary permeability[44]. In addition, a normal proteinuria or urine examination may not exclude parenchymal changes in the kidney. The recent identification of many urinary biomarkers of renal tubular injury, such as urinary neutrophil gelatinase-associated lipocalin (uNGAL), interleukin-18, liver-type fatty acid-binding protein and kidney injury molecule-1, has revolutionized research into organic renal dysfunction[44,53-55]. These biomarkers have, however, been studied primarily in the context of AKI, and their role in the assessment of CKD is not yet clear. The most extensively assessed biomarker in cirrhotic patients has been uNGAL, an inflammatory biomarker produced by damaged renal tubular cells. The uNGAL levels can help distinguish organic from functional AKI; however, cutoff values for such discrimination lack specificity. In addition, the existence of concomitant infections or prolonged renal vasoconstriction in patients with HRS may significantly increase uNGAL levels, thereby limiting its discriminatory function in patients with cirrhosis[14,53]. In general, uNGAL has a positive correlation with the severity of renal dysfunction in patients with CKD, which indicates its prognostic significance for CKD[53]. However, the prognostic value of uNGAL in patients with cirrhosis with CKD is not known.

The profiles of urinary microRNAs may be an attractive noninvasive tool for future kidney damage assessment[54]. Other biomarkers, such as osteopontin and metalloproteinase-1 tissue inhibitor, are usually elevated in patients with CKD, but their clinical significance has not yet been established[55].

***Role of duplex Doppler ultrasonography***

Renal duplex Doppler ultrasound is a simple, noninvasive and efficient method that can be used in patients with cirrhosis to study intrarenal hemodynamics (Figure 2). It is a test to assess renal vascular resistance as a vasoconstriction marker, and the renal resistive index (RRI) can be used to detect early renal dysfunction in patients with cirrhosis[56]. In general, there is a progressive increase in RRI as cirrhosis patients move from without ascites to with ascites and then to HRS[57]. Since severe renal vasoconstriction is a feature of HRS, duplex ultrasonography can play a potential role in the assessment of functional CKD in patients with cirrhosis. Furthermore, the RRI can predict CKD progression as it correlates with renal histopathological changes such as glomerular sclerosis, interstitial fibrosis, and arteriolosclerosis[58].

***Differentiation between functional and structural CKD***

It is important to determine what proportion of CKD in cirrhosis is functional due to HRS and what proportion is associated with structural renal damage. Such differentiation has important therapeutic and prognostic implications. This would assist the clinician in deciding on the use of diuretics, vasoconstrictor treatment and the recommendation of LT *vs* SLKT. Structural CKD patients are more likely to be indolent and have higher survival rates than functional CKD patients[32]. However, in the absence of a renal biopsy, it is often difficult to differentiate a functional CKD from a structural CKD. Abnormal urine analysis (proteinuria > 500 mg/d or hematuria > 50/high power field) and/or abnormal findings on renal ultrasonography (reduced cortical thickness, increased cortical echogenicity and scarring) are features of advanced structural CKD (Figure 2). Currently, no accurate biomarkers are available that can diagnose subclinical renal parenchymal injury or differentiate between reversible and permanent renal injury. Importantly, prolonged renal vasoconstriction in patients with functional CKD may lead to irreversible structural changes in the kidney[32,33]. Studies on the outcome of LT in patients with type 2 HRS have found that 50%-60% of patients develop stage 3 CKD during the posttransplant period, even when HRS reverses[13,59]. Therefore, essentially a long-standing functional CKD can be regarded as structural CKD. In the absence of abnormal early imaging features and reliable biomarkers of CKD, renal biopsy remains the only choice to diagnose and further characterize CKD. However, due to coagulopathy, thrombocytopenia, and the presence of large ascites in cirrhosis, as well as scarred kidneys due to CKD, percutaneous renal biopsy may be technically challenging in patients with decompensated cirrhosis.

***Pitfalls in the diagnosis of CKD***

A dramatic rise in the diagnosis of CKD in patients with cirrhosis raises some concerns as to whether, in the absence of any corroborating evidence of renal injury, the dependence solely on eGFR leads to overdiagnosis of CKD[60]. An arbitrary single threshold of eGFR < 60 mL/min might have a high propensity to cause overestimation of CKD in elderly subjects. There is a natural steady decrease in GFR with increasing age, and eGFR levels between 50 and 60 mL/min can be insignificant for older individuals, with very little propensity to progress to symptomatic kidney disease[61]. The risks of overdiagnosis of CKD may be significant in patients with cirrhosis since many of them belong to the old age group. In addition, a varying degree of deterioration in GFR may occur in patients with decompensated cirrhosis due to neurohormonal alterations and circulatory dysfunction well before the detection of overt renal disease, which may lead to overdiagnosis of CKD. Therefore, on the basis of a single eGFR threshold and in the absence of any corroborating evidence of kidney damage, caution before labeling CKD in elderly patients with cirrhosis may be needed. Since creatinine-based equations tend to overestimate the GFR, they can underestimate CKD and thus may provide clinicians with false reassurance. Studies need to be performed to determine whether the diagnosis of CKD in patients with decompensated cirrhosis requires a different GFR cutoff.

**MANAGEMENT IMPLICATIONS**

The presence of CKD in patients with cirrhosis presents many challenges to clinicians with regard to medical care. In particular, fluid mobilization to control ascites and edema becomes a real challenge. The use of diuretic therapy has several limitations. As ascites often reaccumulates rapidly, patients require repeated large volume paracentesis. This puts them at risk of multiple complications, such as worsening circulatory dysfunction, infection and bleeding, in addition to causing discomfort to the patients.

***Diuretic therapy***

Diuretic therapy is often not prescribed in patients with functional CKD because of the concern that it may further worsen renal failure by causing intravascular volume loss and may precipitate electrolyte imbalance[33]. In patients with structural CKD, the use of diuretics seems appropriate to manage ascites and edema. However, a varying degree of diuretic resistance is usually present in patients with CKD. This occurs primarily because of decreased renal blood flow, hyperuricemia and organic anion accumulation[62]. The organic anions, uric acid and hypoalbuminemia interfere with the function of loop diuretics. A higher dose of diuretics is therefore required to overcome diuretic resistance in the presence of CKD.

There is a lack of evidence to guide clinicians as to which single or combination diuretic agent is most appropriate for these patients. Furosemide is primarily eliminated by the kidney, while torsemide has predominant hepatic clearance[63]. Therefore, if kidney dysfunction is a predominant issue, torsemide might be preferred over furosemide, while in the case of severe hepatic dysfunction, furosemide may be preferred over torsemide. A recent meta-analysis found that coadministration of albumin with furosemide had a modest effect on overcoming diuretic resistance in hypoalbuminemic patients[64]. Correction of metabolic acidosis and hyperuricemia, adequate restriction of fluid and salt intake, and avoidance of medications that interfere with peritubular diuretic uptake, such as nonsteroidal anti-inflammatory drugs and beta-lactam antibiotics, may be other measures to enhance the diuretic response[62]. Spironolactone should be better avoided in advanced CKD to prevent hyperkalemia.

***Vaptans***

Vaptan, an antagonist of vasopressin 2 receptor, may be considered in patients with CKD with cirrhosis who are intolerant to or poorly responsive to diuretics. Tolvaptan has been found to be potentially safe with an efficacy rate of 77% for the treatment of refractory ascites in decompensated cirrhosis patients with coexisting type 2 HRS[65]. Tolvaptan significantly increases urine volume in patients with CKD with liver cirrhosis without worsening renal dysfunction[66]. However, its diuretic response gradually diminishes with progression of the CKD stage[67]. Due to the possible risks of hepatocellular damage identified during a clinical trial involving patients with autosomal dominant polycystic kidney disease, the United States Food and Drug Administration issued a warning for tolvaptan use in 2013. However, very high doses of tolvaptan had been used for a long period of time in this study (120 mg/d for 3 years), and no such adverse effects have been reported from the study on patients with cirrhosis where the recommended dose was much lower.

***Vasoconstrictor therapy***

Midodrine is an orally available α1-agonist that serves as a vasoconstrictor and has been found to have an effect on the systemic hemodynamics of cirrhotic patients. However, midodrine trials in patients with cirrhosis have shown contradictory results. There is insufficient evidence about its use in patients with CKD. In patients with type 2 HRS, midodrine has only a slight beneficial effect on systemic hemodynamics, with no effect on renal hemodynamics[68]. Additionally, treatment with terlipressin or noradrenaline along with albumin appears to have a limited role in patients with CKD. While there are several cases of reversal of type 2 HRS, recurrence after withdrawal of therapy is very common. In addition, evidence on the impact of this treatment on the outcomes of patients is controversial. Few studies have assessed the efficacy of terlipressin in a limited number of patients with type 2 HRS, and the findings have been equivocal[69,70]. In a recent study, 46% of treated patients demonstrated reversal of type 2 HRS; however, nearly half of responders experienced relapse[71]. Furthermore, reversal of type 2 HRS before LT does not appear to provide a major benefit over patients who are untreated or who have failed treatment before LT[13]. Therefore, most of the current guidelines do not recommend vasoconstrictor treatment in functional CKD.

***Transjugular intrahepatic portosystemic shunt***

Transjugular intrahepatic portosystemic shunt**(**TIPS) decreases portal pressure, improves kidney function and relieves ascites. While it is being used increasingly to treat patients with refractory ascites and functional renal failure, there is limited evidence on its use in patients with advanced CKD. In a study on TIPS in 17 patients with cirrhosis with CKD, Lakhoo *et al*[72] found that ascites control occurred in 83% of patients but at the expense of a high incidence (47%) of new or worsening hepatic encephalopathy (HE). Michl *et al*[73] reported improvement in renal function and a decrease in the frequency of paracentesis following TIPS in 10 patients with cirrhosis, including three with structural kidney disease. A recent systematic review and meta-analysis found a potential survival benefit of TIPS in patients with HRS but with a high (49%) incidence of HE. In type 2 HRS, the pooled short-term and 1-year survival rates after TIPS were 86% and 64%, respectively. Moreover, 83% of patients with HRS experienced improvement in renal function after TIPS[74]. In summary, TIPS appears to be very effective in patients with functional CKD, and limited data indicate its effectiveness in structural CKD as well. However, TIPS may increase the incidence of HE, so it should be avoided in patients with encephalopathy, cardiopulmonary disease, and significant hepatic dysfunction.

***Cell-free and concentrated ascites reinfusion therapy***

Cell-free and concentrated ascites reinfusion therapy (CART) is an apheresis therapy in which ascitic fluid is filtered to remove unwanted cells, sterilely concentrated, and then intravenously reinfused[75]. It was introduced in Japan as a novel treatment for refractory ascites in patients with cirrhosis. The potential advantages of CART include its ability to maintain nutritional status, control ascites, and improve quality of life. Unlike large volume paracentesis, CART is not associated with the risk of hypoproteinemia, hemodynamic instability, renal dysfunction or fatigue. It has been used for both cirrhotic and malignant ascites; however, its safety and efficacy need to be assessed in CLD-CKD patients with refractory ascites. CART has been found to be equally as effective as large volume paracentesis plus albumin infusion[76]. However, its routine use can be limited by the high cost of the CART apparatus[77].

***Concerns related to medications***

Since the majority of drugs are metabolized and/or excreted by the hepatorenal system, it is a challenging task to prescribe medicines in patients with advanced cirrhosis with renal impairment[78]. There are no evidence-based guidelines for the use of medicines in such patients. Drugs with significant hepatotoxic or nephrotoxic potential or both need to be avoided in such patients. In addition, the dosage of several antibiotics needs to be modified in accordance with GFR. Nonselective β-blockers can increase mortality in patients with advanced cirrhosis with renal dysfunction due to their adverse impact on cardiac compensation[79]. Treatment with hepatitis B nucleos(t)ide analogues can also raise the risk of lactic acidosis if renal dysfunction is present[80].

***Treatment modifications according to the etiology of cirrhosis***

There are no large controlled studies available to direct appropriate antiviral therapy for patients with CKD with HBV cirrhosis. The use of tenofovir disoproxil fumarate has been associated with a mild risk of CKD progression, but a recent meta-analysis has shown that such a decrease in renal function is inappreciable compared with entecavir[81,82]. Nevertheless, entecavir tends to be the most preferred drug for these patients. However, entecavir therapy may not be as effective in patients with lamivudine resistance, so tenofovir alafenamide, an orally bioavailable tenofovir prodrug with a lower risk of renal toxicity, may be considered in such patients. In patients with HCV-cirrhosis and CKD, high sustained virologic response rates with glecaprevir/pibrentasvir combination in all genotypes and with elbasvir/grazoprevir in genotypes 1 and 4 can be achieved. However, these drugs are largely metabolized in the liver and are therefore not safe in advanced cirrhosis[83]. Patients with advanced decompensated cirrhosis and renal dysfunction are a difficult-to-treat category for which there are no guidelines for treatment; therefore, a treatment decision should be made on a case-by-case basis. While a treatment based on sofosbuvir is not recommended for patients with severe renal impairment, it may be used in patients with mild renal impairment[84]. In patients with nonalcoholic steatohepatitis-CKD, statins have been shown to decrease cardiovascular disease mortality, and sodium-glucose cotransporter-2 inhibitors have been found to slow the progression of CKD and minimize all-cause mortality[85]. However, it is important to determine the role of these drugs in nonalcoholic steatohepatitis-cirrhosis patients with CKD.

***Renal replacement therapy***

The shared symptoms between the two diseases and overestimation of eGFR make it difficult for patients with cirrhosis with CKD to determine the ideal time for commencing renal replacement therapy. The hemodynamic alterations of cirrhosis pose a challenge to maintaining hemodynamic stability during dialysis, where a sudden decrease in intravascular volume due to ultrafiltration may cause hypotension. A sharp change in blood osmolarity and electrolyte levels increases the risk of developing HE. In addition, thrombocytopenia, platelet dysfunction, and coagulopathy due to combined CKD-cirrhosis may increase the risk of bleeding complications. In these patients, peritoneal dialysis may be a better choice because it will not only resolve many problems associated with intermittent HD but will also allow ascitic fluid to be regularly evacuated[86,87]. Studies evaluating the survival of cirrhotic patients on peritoneal dialysis have reported a modest survival rate of 8 to 66 mo[88].

***LT vs SLKT***

Increased post-LT mortality is associated with any form of renal dysfunction. However, most studies evaluating the impact of renal function on post-LT survival do not differentiate between CKD and AKI[4,89,90]. Few studies have reported the progression of CKD, including the development of end-stage renal disease and increased post-LT mortality in cirrhotic patients with CKD receiving LT alone[90-92]. In a recent study, the presence of CKD at the time of LT increased the risk of post-LT mortality by 16%[4]. Thus, there has been a drive to perform more SLKT in patients with combined cirrhosis-CKD. However, in patients with cirrhosis, predicting renal recovery post-LT is difficult, and the degree or severity of CKD that warrants SLKT *vs* LT remains undefined. The 2012 SLKT summit guidelines indicate that SLKT should be considered for cirrhosis-CKD patients with an eGFR of ≤ 40 mL/min measured by the MDRD-6 equation[93]. Once again, however, the use of SLKT is highly variable, and the role of kidney transplantation in nondialysis CKD is controversial. Singh *et al*[94] recently reported the outcome of LT only in nine CKD-cirrhosis patients who had persistently low eGFR < 40 mL/min for ≥ 12 wk but relatively normal kidney biopsy findings. Post-LT, eGFR increased in all nine patients within a week and remained stable afterwards; one patient progressed to ESRD 9 years post-LT, and another patient expired 7 years after LT. While no definite conclusions can be drawn from this small study, there is an indication that, in the absence of other indicators of renal injury, low eGFR alone below an arbitrary cutoff value does not constitute an absolute requirement for SLKT in patients with liver cirrhosis. Functional CKD is potentially reversible after LT[13,52]. However, prolonged renal ischemia can cause permanent tubular or glomerular damage that may not recover with LT, leading to post-LT CKD progression. Because the assessment of renal function may be difficult in patients with advanced cirrhosis, a renal biopsy should be considered whenever possible for identifying parenchymal changes and to decide between LT and SLKT. In patients with low eGFR and kidney biopsy showing > 30% glomerulosclerosis and/or interstitial fibrosis, SLKT should be considered[93]. Future prediction models to assist in decision-making between SLKT and LT should consider integrating kidney injury markers, including new CKD biomarkers.

**CONCLUSION**

In conclusion, the incidence of CKD in patients with cirrhosis has increased significantly as a result of a rise in risk factors and a change in the diagnostic criteria from a fixed level of serum creatine to a dynamic change in GFR. The available data on this condition are extremely limited. Future studies on this subject are required to explain several contentious issues. Taking into account the problems related to the calculation of GFR in patients with cirrhosis, the main issue to be addressed would be the refining of diagnostic criteria. The other areas that require future research are the identification of reliable biomarkers of chronic kidney damage, the formulation of management strategies based on phenotypic features of CKD in cirrhosis, and the development of prediction models to assist in decision-making between SLKT and LT.

**REFERENCES**

1 **Bucsics T**, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. *Gastroenterol Rep (Oxf)* 2017; **5**: 127-137 [PMID: 28533910 DOI: 10.1093/gastro/gox009]

2 **Péron JM**, Bureau C, Gonzalez L, Garcia-Ricard F, de Soyres O, Dupuis E, Alric L, Pourrat J, Vinel JP. Treatment of hepatorenal syndrome as defined by the international ascites club by albumin and furosemide infusion according to the central venous pressure: a prospective pilot study. *Am J Gastroenterol* 2005; **100**: 2702-2707 [PMID: 16393223 DOI: 10.1111/j.1572-0241.2005.00271.x]

3 **Wong F**, Reddy KR, O'Leary JG, Tandon P, Biggins SW, Garcia-Tsao G, Maliakkal BJ, Lai JC, Fallon MB, Vargas HE, Subramanian R, Thuluvath PJ, Kamath PS, Thacker L, Bajaj JS. Impact of Chronic Kidney Disease on Outcomes in Cirrhosis. *Liver Transpl* 2019; **25**: 870-880 [PMID: 30908855 DOI: 10.1002/lt.25454]

4 **Cullaro G**, Verna EC, Lee BP, Lai JC. Chronic Kidney Disease in Liver Transplant Candidates: A Rising Burden Impacting Post-Liver Transplant Outcomes. *Liver Transpl* 2020; **26**: 498-506 [PMID: 31785069 DOI: 10.1002/lt.25694]

5 **Solà E**, Ginès P. Chronic Kidney Disease in Cirrhosis: Emerging Complication With Negative Impact in the Liver Transplant Setting. *Liver Transpl* 2020; **26**: 483-484 [PMID: 32031312 DOI: 10.1002/lt.25728]

6 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]

7 **Bassegoda O**, Huelin P, Ariza X, Solé C, Juanola A, Gratacós-Ginès J, Carol M, Graupera I, Pose E, Napoleone L, Albertos S, de Prada G, Cervera M, Fernández J, Fabrellas N, Poch E, Solà E, Ginès P. Development of chronic kidney disease after acute kidney injury in patients with cirrhosis is common and impairs clinical outcomes. *J Hepatol* 2020; **72**: 1132-1139 [PMID: 31953138 DOI: 10.1016/j.jhep.2019.12.020]

8 **Parke CY**, Martin P, Bunnapradist S. Renal dysfunction in cirrhosis. *Clin Liver Dis (Hoboken)* 2015; **5**: 150-153 [PMID: 31040973 DOI: 10.1002/cld.485]

9 **Chawla LS**, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012; **82**: 516-524 [PMID: 22673882 DOI: 10.1038/ki.2012.208]

10 **Wong F**, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, Angeli P, Moreau R, Davenport A, Jalan R, Ronco C, Genyk Y, Arroyo V. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011; **60**: 702-709 [PMID: 21325171 DOI: 10.1136/gut.2010.236133]

11 **Angeli P**, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015; **62**: 968-974 [PMID: 25638527 DOI: 10.1016/j.jhep.2014.12.029]

12 **Trawalé JM**, Paradis V, Rautou PE, Francoz C, Escolano S, Sallée M, Durand F, Valla D, Lebrec D, Moreau R. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. *Liver Int* 2010; **30**: 725-732 [PMID: 20040048 DOI: 10.1111/j.1478-3231.2009.02182.x]

13 **Tan HK**, Marquez M, Wong F, Renner EL. Pretransplant Type 2 Hepatorenal Syndrome Is Associated With Persistently Impaired Renal Function After Liver Transplantation. *Transplantation* 2015; **99**: 1441-1446 [PMID: 25643142 DOI: 10.1097/TP.0000000000000557]

14 **Fagundes C**, Pépin MN, Guevara M, Barreto R, Casals G, Solà E, Pereira G, Rodríguez E, Garcia E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012; **57**: 267-273 [PMID: 22521351 DOI: 10.1016/j.jhep.2012.03.015]

15 **Hill NR**, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0158765 [PMID: 27383068 DOI: 10.1371/journal.pone.0158765]

16 **Maiwall R**, Pasupuleti SSR, Bihari C, Rastogi A, Singh PK, Naik V, Singh A, Jain P, Kumar A, Mukund A, Mathur RP, Kumar G, Sarin SK. Incidence, Risk Factors, and Outcomes of Transition of Acute Kidney Injury to Chronic Kidney Disease in Cirrhosis: A Prospective Cohort Study. *Hepatology* 2020; **71**: 1009-1022 [PMID: 31313333 DOI: 10.1002/hep.30859]

17 **Chen CY**, Lin CJ, Lin CS, Sun FJ, Pan CF, Chen HH, Wu CJ. The prevalence and association of chronic kidney disease and diabetes in liver cirrhosis using different estimated glomerular filtration rate equation. *Oncotarget* 2018; **9**: 2236-2248 [PMID: 29416767 DOI: 10.18632/oncotarget.23368]

18 **Rustgi VK**, Li Y, John T, Catalano C, Elsaid MI. Health Care Resource Use and Cost Burden of Chronic Kidney Disease in Patients With Chronic Liver Disease: A Real-World Claims Analysis. *Hepatol Commun* 2020; **4**: 1404-1418 [PMID: 33024912 DOI: 10.1002/hep4.1573]

19 **Choi YJ**, Kim JH, Koo JK, Lee CI, Lee JY, Yang JH, Ko SY, Choe WH, Kwon SY, Lee CH. Prevalence of renal dysfunction in patients with cirrhosis according to ADQI-IAC working party proposal. *Clin Mol Hepatol* 2014; **20**: 185-191 [PMID: 25032185 DOI: 10.3350/cmh.2014.20.2.185]

20 **Coca SG**, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; **81**: 442-448 [PMID: 22113526 DOI: 10.1038/ki.2011.379]

21 **Cullaro G**, Park M, Lai JC. "Normal" Creatinine Levels Predict Persistent Kidney Injury and Waitlist Mortality in Outpatients With Cirrhosis. *Hepatology* 2018; **68**: 1953-1960 [PMID: 29698588 DOI: 10.1002/hep.30058]

22 **Sinn DH**, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, Ryu S, Chang Y, Lazo M, Guallar E, Cho J, Gwak GY. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: A cohort study. *J Hepatol* 2017; **67**: 1274-1280 [PMID: 28870674 DOI: 10.1016/j.jhep.2017.08.024]

23 **Musso G**, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, Hultcrantz R, Hagström H, Yoon SK, Charatcharoenwitthaya P, George J, Barrera F, Hafliðadóttir S, Björnsson ES, Armstrong MJ, Hopkins LJ, Gao X, Francque S, Verrijken A, Yilmaz Y, Lindor KD, Charlton M, Haring R, Lerch MM, Rettig R, Völzke H, Ryu S, Li G, Wong LL, Machado M, Cortez-Pinto H, Yasui K, Cassader M. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014; **11**: e1001680 [PMID: 25050550 DOI: 10.1371/journal.pmed.1001680]

24 **Targher G**, Chonchol MB, Byrne CD. CKD and nonalcoholic fatty liver disease. *Am J Kidney Dis* 2014; **64**: 638-652 [PMID: 25085644 DOI: 10.1053/j.ajkd.2014.05.019]

25 **VanWagner LB**. New insights into NAFLD and subclinical coronary atherosclerosis. *J Hepatol* 2018; **68**: 890-892 [PMID: 29410378 DOI: 10.1016/j.jhep.2018.01.023]

26 **Kalaitzakis E**, Rosengren A, Skommevik T, Björnsson E. Coronary artery disease in patients with liver cirrhosis. *Dig Dis Sci* 2010; **55**: 467-475 [PMID: 19242795 DOI: 10.1007/s10620-009-0738-z]

27 **Kumar R**, Priyadarshi RN, Anand U. Non-alcoholic Fatty Liver Disease: Growing Burden, Adverse Outcomes and Associations. *J Clin Transl Hepatol* 2020; **8**: 76-86 [PMID: 32274348 DOI: 10.14218/JCTH.2019.00051]

28 **Singal AK**, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. *Transplantation* 2014; **98**: 216-221 [PMID: 24621538 DOI: 10.1097/TP.0000000000000048]

29 **Kumar R**. Hepatogenous Diabetes: An Underestimated Problem of Liver Cirrhosis. *Indian J Endocrinol Metab* 2018; **22**: 552-559 [PMID: 30148106 DOI: 10.4103/ijem.IJEM\_79\_18]

30 **Venkataseshan VS**, Lieberman K, Kim DU, Thung SN, Dikman S, D'Agati V, Susin M, Valderrama E, Gauthier B, Prakash A. Hepatitis-B-associated glomerulonephritis: pathology, pathogenesis, and clinical course. *Medicine (Baltimore)* 1990; **69**: 200-216 [PMID: 2142748]

31 **Franz M**, Hörl WH. The patient with end-stage renal failure and ascites. *Nephrol Dial Transplant* 1997; **12**: 1070-1078 [PMID: 9175077 DOI: 10.1093/ndt/12.5.1070]

32 **Martín-Llahí M**, Guevara M, Torre A, Fagundes C, Restuccia T, Gilabert R, Solá E, Pereira G, Marinelli M, Pavesi M, Fernández J, Rodés J, Arroyo V, Ginès P. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011; **140**: 488-496.e4 [PMID: 20682324 DOI: 10.1053/j.gastro.2010.07.043]

33 **Salerno F**, Cazzaniga M, Merli M, Spinzi G, Saibeni S, Salmi A, Fagiuoli S, Spadaccini A, Trotta E, Laffi G, Koch M, Riggio O, Boccia S, Felder M, Balzani S, Bruno S, Angeli P; Italian Association of the Hospital Gastroenterologists (AIGO) investigators. Diagnosis, treatment and survival of patients with hepatorenal syndrome: a survey on daily medical practice. *J Hepatol* 2011; **55**: 1241-1248 [PMID: 21703199 DOI: 10.1016/j.jhep.2011.03.012]

34 **Mannucci PM**, Tripodi A. Hemostatic defects in liver and renal dysfunction. *Hematology Am Soc Hematol Educ Program* 2012; **2012**: 168-173 [PMID: 23233577 DOI: 10.1182/asheducation-2012.1.168]

35 **Thomas R**, Kanso A, Sedor JR. Chronic kidney disease and its complications. *Prim Care* 2008; **35**: 329-344, vii [PMID: 18486718 DOI: 10.1016/j.pop.2008.01.008]

36 **Gkamprela E**, Deutsch M, Pectasides D. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. *Ann Gastroenterol* 2017; **30**: 405-413 [PMID: 28655976 DOI: 10.20524/aog.2017.0152]

37 **Kato S**, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3**: 1526-1533 [PMID: 18701615 DOI: 10.2215/CJN.00950208]

38 **Wong G**, Hayen A, Chapman JR, Webster AC, Wang JJ, Mitchell P, Craig JC. Association of CKD and cancer risk in older people. *J Am Soc Nephrol* 2009; **20**: 1341-1350 [PMID: 19406977 DOI: 10.1681/ASN.2008090998]

39 **Na SY**, Sung JY, Chang JH, Kim S, Lee HH, Park YH, Chung W, Oh KH, Jung JY. Chronic kidney disease in cancer patients: an independent predictor of cancer-specific mortality. *Am J Nephrol* 2011; **33**: 121-130 [PMID: 21242672 DOI: 10.1159/000323740]

40 **Lowrance WT**, Ordoñez J, Udaltsova N, Russo P, Go AS. CKD and the risk of incident cancer. *J Am Soc Nephrol* 2014; **25**: 2327-2334 [PMID: 24876115 DOI: 10.1681/ASN.2013060604]

41 **Weng PH**, Hung KY, Huang HL, Chen JH, Sung PK, Huang KC. Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort. *Clin J Am Soc Nephrol* 2011; **6**: 1121-1128 [PMID: 21511834 DOI: 10.2215/CJN.09011010]

42 **Kim AJ**, Lim HJ, Ro H, Jung JY, Lee HH, Chung W, Chang JH. Liver cirrhosis leads to poorer survival in patients with end-stage renal disease. *Korean J Intern Med* 2016; **31**: 730-738 [PMID: 27017394 DOI: 10.3904/kjim.2014.328]

43 **Hsu CY**, Bansal N. Measured GFR as "gold standard"--all that glitters is not gold? *Clin J Am Soc Nephrol* 2011; **6**: 1813-1814 [PMID: 21784836 DOI: 10.2215/CJN.06040611]

44 **Francoz C**, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. *J Hepatol* 2016; **65**: 809-824 [PMID: 27238754 DOI: 10.1016/j.jhep.2016.05.025]

45 **Papadakis MA**, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Prospective study. *Am J Med* 1987; **82**: 945-952 [PMID: 3578363 DOI: 10.1016/0002-9343(87)90156-2]

46 **Woitas RP**, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, Spengler U, Bidlingmaier F, Sauerbruch T. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem* 2000; **46**: 712-715 [PMID: 10794756]

47 **Skluzacek PA**, Szewc RG, Nolan CR 3rd, Riley DJ, Lee S, Pergola PE. Prediction of GFR in liver transplant candidates. *Am J Kidney Dis* 2003; **42**: 1169-1176 [PMID: 14655188 DOI: 10.1053/j.ajkd.2003.08.017]

48 **Demirtaş S**, Bozbaş A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. *Clin Chim Acta* 2001; **311**: 81-89 [PMID: 11566167 DOI: 10.1016/s0009-8981(01)00546-0]

49 **Orlando R**, Mussap M, Plebani M, Piccoli P, De Martin S, Floreani M, Padrini R, Palatini P. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem* 2002; **48**: 850-858 [PMID: 12029000]

50 **Mindikoglu AL**, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology* 2014; **59**: 1532-1542 [PMID: 23744636 DOI: 10.1002/hep.26556]

51 **Stevens LA**, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, Froissart M, Kusek JW, Zhang YL, Coresh J, Levey AS. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009; **75**: 652-660 [PMID: 19119287 DOI: 10.1038/ki.2008.638]

52 **Krones E**, Fickert P, Zitta S, Neunherz S, Artinger K, Reibnegger G, Durchschein F, Wagner D, Stojakovic T, Stadlbauer V, Fauler G, Stauber R, Zollner G, Kniepeiss D, Rosenkranz AR. The chronic kidney disease epidemiology collaboration equation combining creatinine and cystatin C accurately assesses renal function in patients with cirrhosis. *BMC Nephrol* 2015; **16**: 196 [PMID: 26627205 DOI: 10.1186/s12882-015-0188-0]

53 **Bolignano D**, Coppolino G, Campo S, Aloisi C, Nicocia G, Frisina N, Buemi M. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with severity of renal disease in proteinuric patients. *Nephrol Dial Transplant* 2008; **23**: 414-416 [PMID: 17893105 DOI: 10.1093/ndt/gfm541]

54 **Szeto CC**, Wang G, Ng JK, Kwan BC, Mac-Moune Lai F, Chow KM, Luk CC, Lai KB, Li PK. Urinary miRNA profile for the diagnosis of IgA nephropathy. *BMC Nephrol* 2019; **20**: 77 [PMID: 30832601 DOI: 10.1186/s12882-019-1267-4]

55 **Xu TY**, Zhang Y, Li Y, Zhu DL, Gao PJ. The association of serum inflammatory biomarkers with chronic kidney disease in hypertensive patients. *Ren Fail* 2014; **36**: 666-672 [PMID: 24575880 DOI: 10.3109/0886022X.2014.890002]

56 **Mindikoglu AL**, Dowling TC, Wong-You-Cheong JJ, Christenson RH, Magder LS, Hutson WR, Seliger SL, Weir MR. A pilot study to evaluate renal hemodynamics in cirrhosis by simultaneous glomerular filtration rate, renal plasma flow, renal resistive indices and biomarkers measurements. *Am J Nephrol* 2014; **39**: 543-552 [PMID: 24943131 DOI: 10.1159/000363584]

57 **Fouad YM**, Mokarrab H, Elgebaly AF, El-Amin H, Abdel-Raheem EM, Sharawy MA, Shatat ME. Renal duplex Doppler ultrasound in patients with HCV related liver cirrhosis. *Trop Gastroenterol* 2009; **30**: 213-218 [PMID: 20426281]

58 **Spatola L**, Andrulli S. Doppler ultrasound in kidney diseases: a key parameter in clinical long-term follow-up. *J Ultrasound* 2016; **19**: 243-250 [PMID: 27965714 DOI: 10.1007/s40477-016-0201-x]

59 **Rodriguez E**, Henrique Pereira G, Solà E, Elia C, Barreto R, Pose E, Colmenero J, Fernandez J, Navasa M, Arroyo V, Ginès P. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: Effects on kidney function and transplantation outcomes. *Liver Transpl* 2015; **21**: 1347-1354 [PMID: 26178066 DOI: 10.1002/lt.24210]

60 **De Broe ME**, Gharbi MB, Zamd M, Elseviers M. Why overestimate or underestimate chronic kidney disease when correct estimation is possible? *Nephrol Dial Transplant* 2017; **32**: ii136-ii141 [PMID: 28380639 DOI: 10.1093/ndt/gfw267]

61 **Wetzels JF**, Kiemeney LA, Swinkels DW, Willems HL, den Heijer M. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int* 2007; **72**: 632-637 [PMID: 17568781 DOI: 10.1038/sj.ki.5002374]

62 **Wilcox CS**. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 2002; **13**: 798-805 [PMID: 11856788]

63 **Brater DC**. Diuretic therapy. *N Engl J Med* 1998; **339**: 387-395 [PMID: 9691107 DOI: 10.1056/NEJM199808063390607]

64 **Kitsios GD**, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care* 2014; **29**: 253-259 [PMID: 24268626 DOI: 10.1016/j.jcrc.2013.10.004]

65 **Zhang X**, Wang SZ, Zheng JF, Zhao WM, Li P, Fan CL, Li B, Dong PL, Li L, Ding HG. Clinical efficacy of tolvaptan for treatment of refractory ascites in liver cirrhosis patients. *World J Gastroenterol* 2014; **20**: 11400-11405 [PMID: 25170228 DOI: 10.3748/wjg.v20.i32.11400]

66 **Tanaka A**, Katsuno T, Ozaki T, Sakata F, Kato N, Suzuki Y, Kosugi T, Kato S, Tsuboi N, Sato W, Yasuda Y, Mizuno M, Ito Y, Matsuo S, Maruyama S. The efficacy of tolvaptan as a diuretic for chronic kidney disease patients. *Acta Cardiol* 2015; **70**: 217-223 [PMID: 26148383 DOI: 10.1080/ac.70.2.3073514]

67 **Ikeda S**, Ohshima K, Miyazaki S, Kadota H, Shimizu H, Ogimoto A, Hamada M. Impact of chronic kidney disease on the diuretic response of tolvaptan in acute decompensated heart failure. *ESC Heart Fail* 2017; **4**: 614-622 [PMID: 29154417 DOI: 10.1002/ehf2.12190]

68 **Werling K**, Chalasani N. What is the Role of Midodrine in Patients with Decompensated Cirrhosis? *Gastroenterol Hepatol (N Y)* 2011; **7**: 134-136 [PMID: 21475424]

69 **Ghosh S**, Choudhary NS, Sharma AK, Singh B, Kumar P, Agarwal R, Sharma N, Bhalla A, Chawla YK, Singh V. Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study. *Liver Int* 2013; **33**: 1187-1193 [PMID: 23601499 DOI: 10.1111/liv.12179]

70 **Alessandria C**, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. *Eur J Gastroenterol Hepatol* 2002; **14**: 1363-1368 [PMID: 12468959 DOI: 10.1097/00042737-200212000-00013]

71 **Nguyen-Tat M**, Jäger J, Rey JW, Nagel M, Labenz C, Wörns MA, Galle PR, Marquardt JU. Terlipressin and albumin combination treatment in patients with hepatorenal syndrome type 2. *United European Gastroenterol J* 2019; **7**: 529-537 [PMID: 31065370 DOI: 10.1177/2050640619825719]

72 **Lakhoo J**, Gunasekaran SS, Lokken RP, Lipnik AJ, Ray CE Jr, Bui JT, Gaba RC. Does advanced chronic kidney disease impact transjugular intrahepatic portosystemic shunt efficacy and safety? *Acta Gastroenterol Belg* 2017; **80**: 243-248 [PMID: 29560689]

73 **Michl P**, Gülberg V, Bilzer M, Waggershauser T, Reiser M, Gerbes AL. Transjugular intrahepatic portosystemic shunt for cirrhosis and ascites: Effects in patients with organic or functional renal failure. *Scand J Gastroenterol* 2000; **35**: 654-658 [PMID: 10912668 DOI: 10.1080/003655200750023642]

74 **Song T**, Rössle M, He F, Liu F, Guo X, Qi X. Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: A systematic review and meta-analysis. *Dig Liver Dis* 2018; **50**: 323-330 [PMID: 29422242 DOI: 10.1016/j.dld.2018.01.123]

75 **Ito T**, Hanafusa N. CART: Cell-free and Concentrated Ascites Reinfusion Therapy against malignancy-related ascites. *Transfus Apher Sci* 2017; **56**: 703-707 [PMID: 28916401 DOI: 10.1016/j.transci.2017.08.018]

76 **Graziotto A**, Rossaro L, Inturri P, Salvagnini M. Reinfusion of concentrated ascitic fluid versus total paracentesis. A randomized prospective trial. *Dig Dis Sci* 1997; **42**: 1708-1714 [PMID: 9286238 DOI: 10.1023/a:1018865516168]

77 **Fukui H**, Kawaratani H, Kaji K, Takaya H, Yoshiji H. Management of refractory cirrhotic ascites: challenges and solutions. *Hepat Med* 2018; **10**: 55-71 [PMID: 30013405 DOI: 10.2147/HMER.S136578]

78 **Amarapurkar DN**. Prescribing medications in patients with decompensated liver cirrhosis. *Int J Hepatol* 2011; **2011**: 519526 [PMID: 21994861 DOI: 10.4061/2011/519526]

79 **Sersté T**, Melot C, Francoz C, Durand F, Rautou PE, Valla D, Moreau R, Lebrec D. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 2010; **52**: 1017-1022 [PMID: 20583214 DOI: 10.1002/hep.23775]

80 **Kumar R**, Agrawal S. Rapid Onset of Fatal Lactic Acidosis Complicating Tenofovir Therapy in a Diabetic Patient with Cirrhosis: A Cautionary Tale. *J Clin Exp Hepatol* 2017; **7**: 80-81 [PMID: 28348477 DOI: 10.1016/j.jceh.2016.08.010]

81 **Wong GL**, Chan HL, Tse YK, Yip TC, Lam KL, Lui GC, Szeto CC, Wong VW. Chronic kidney disease progression in patients with chronic hepatitis B on tenofovir, entecavir, or no treatment. *Aliment Pharmacol Ther* 2018; **48**: 984-992 [PMID: 30125952 DOI: 10.1111/apt.14945]

82 **Lee HY**, Oh H, Park CH, Yeo YH, Nguyen MH, Jun DW. Comparison of renal safety of tenofovir and entecavir in patients with chronic hepatitis B: Systematic review with meta-analysis. *World J Gastroenterol* 2019; **25**: 2961-2972 [PMID: 31249453 DOI: 10.3748/wjg.v25.i23.2961]

83 **Mücke MM**, Mücke VT, Lange CM, Zeuzem S. Special populations: treating hepatitis C in patients with decompensated cirrhosis and/or advanced renal impairment. *Liver Int* 2017; **37 Suppl 1**: 19-25 [PMID: 28052635 DOI: 10.1111/liv.13279]

84 **Kanda T**, Lau GKK, Wei L, Moriyama M, Yu ML, Chuang WL, Ibrahim A, Lesmana CRA, Sollano J, Kumar M, Jindal A, Sharma BC, Hamid SS, Dokmeci AK, Mamun-Al-Mahtab, McCaughan GW, Wasim J, Crawford DHG, Kao JH, Yokosuka O, Sarin SK, Omata M. APASL clinical practice recommendation: how to treat HCV-infected patients with renal impairment? *Hepatol Int* 2019; **13**: 103-109 [PMID: 30539517 DOI: 10.1007/s12072-018-9915-5]

85 **Papademetriou M**, Athyros VG, Geladari E, Doumas M, Tsioufis C, Papademetriou V. The Co-Existence of NASH and Chronic Kidney Disease Boosts Cardiovascular Risk: Are there any Common Therapeutic Options? *Curr Vasc Pharmacol* 2018; **16**: 254-268 [PMID: 28676027 DOI: 10.2174/1570161115666170621081638]

86 **Howard CS**, Teitelbaum I. Renal replacement therapy in patients with chronic liver disease. *Semin Dial* 2005; **18**: 212-216 [PMID: 15934968 DOI: 10.1111/j.1525-139X.2005.18315.x]

87 **Chaudhary K**, Khanna R. Renal replacement therapy in end-stage renal disease patients with chronic liver disease and ascites: role of peritoneal dialysis. *Perit Dial Int* 2008; **28**: 113-117 [PMID: 18332442]

88 **Marcus RG**, Messana J, Swartz R. Peritoneal dialysis in end-stage renal disease patients with preexisting chronic liver disease and ascites. *Am J Med* 1992; **93**: 35-40 [PMID: 1626571 DOI: 10.1016/0002-9343(92)90677-4]

89 **Nair S**, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179-1185 [PMID: 11981768 DOI: 10.1053/jhep.2002.33160]

90 **Gonwa TA**, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? *Am J Transplant* 2006; **6**: 2651-2659 [PMID: 16939515 DOI: 10.1111/j.1600-6143.2006.01526.x]

91 **Ruebner R**, Goldberg D, Abt PL, Bahirwani R, Levine M, Sawinski D, Bloom RD, Reese PP. Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. *Am J Transplant* 2012; **12**: 2958-2965 [PMID: 22759237 DOI: 10.1111/j.1600-6143.2012.04177.x]

92 **Bloom RD**, Reese PP. Chronic kidney disease after nonrenal solid-organ transplantation. *J Am Soc Nephrol* 2007; **18**: 3031-3041 [PMID: 18039925 DOI: 10.1681/ASN.2007040394]

93 **Nadim MK**, Davis CL, Sung R, Kellum JA, Genyk YS. Simultaneous liver-kidney transplantation: a survey of US transplant centers. *Am J Transplant* 2012; **12**: 3119-3127 [PMID: 22759208 DOI: 10.1111/j.1600-6143.2012.04176.x]

94 **Singh N**, Ahmadzadeh S, Shokouh-Amiri H, Qazi YA, Sequeira A, Samant H, McMillan R, Zibari GB. Kidney outcomes in patients with liver cirrhosis and chronic kidney disease receiving an orthotopic liver transplant alone. *Clin Transplant* 2017; **31** [PMID: 28504869 DOI: 10.1111/ctr.13008]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that they haveno conflict of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** December 24, 2020

**First decision:** January 10, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** India

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B, B

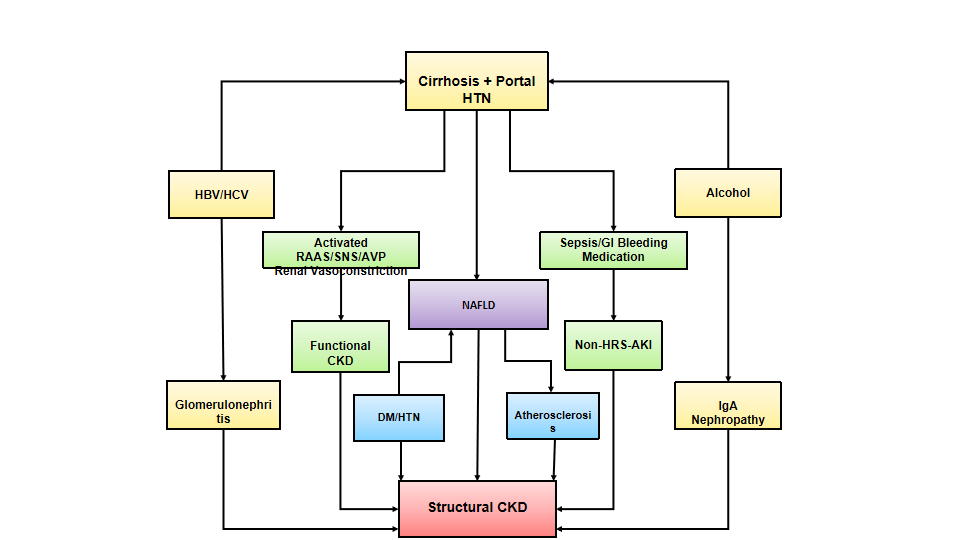
Grade C (Good): C

Grade D (Fair): 0

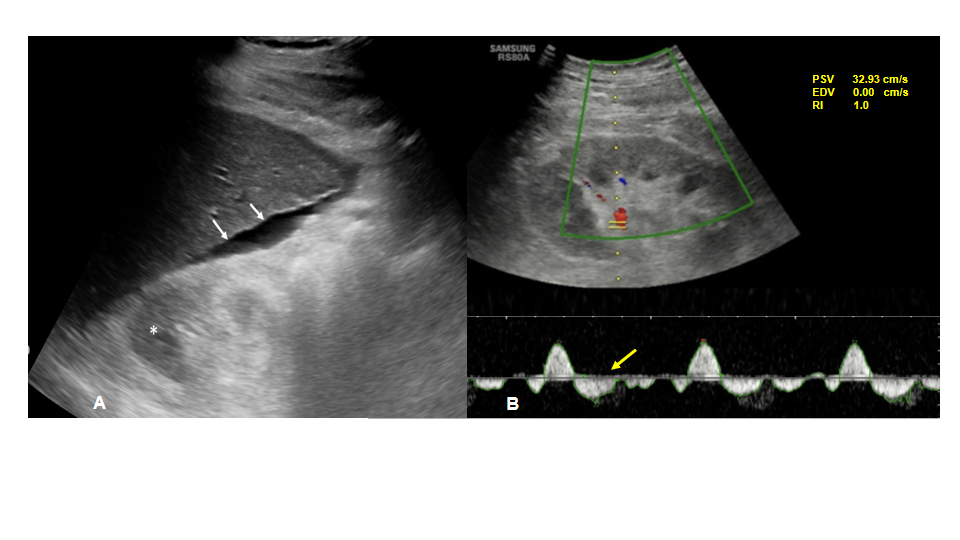
Grade E (Poor): 0

**P-Reviewer:** Li J, Naganuma H, Xu XY **S-Editor:** Zhang L **L-Editor: P-Editor:**

**Figure Legends**

****

**Figure 1** **Risk factors associated with chronic kidney disease in patients with liver cirrhosis.**A rising trend in the prevalence of medicine degree, hypertension and non-alcoholic fatty liver disease seem to be the key factors behind the increased prevalence of chronic kidney disease in cirrhosis. The risk of developing de-novo chronic kidney disease remains high for acute kidney injury survivors.CKD: Chronic kidney disease; HTN: Hypertension; HBV: Hepatis B virus; HCV: Hepatitis C virus; RAAS: Renin-angiotensin-aldosterone system; SNS: Sympathetic nervous system; AVP: Arginine vasopressin; GI: Gastrointestinal; NAFLD: Non-alcoholic fatty liver disease; HRS: Hepatorenal syndrome; AKI: Acute kidney injury.

****

**Figure 2 Ultrasonographic image of a 65-year-old diabetic patients with liver cirrhosis and chronic kidney disease.**A: The liver outline is irregular (white arrows) and there is ascites around it. The right kidney is small and the parenchymal echogenicity is increased with loss of corticomedullary differentiation (asterisk), suggesting chronic kidney disease; B: Doppler sonogram of the same kidney showed reversal of diastolic flow (yellow arrow) with absent end-diastolic velocity, indicating very high resistance vessels.

**Table 1 Incidence and prevalence of chronic kidney disease in cirrhosis patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Study subjects (*n*)** | **Criteria for CKD diagnosis** | **Incidence or prevalence of CKD** |
| Cullaro *et al*[4], 2020 | 39719 LT recipient cirrhosis patients | CKD-EPI equation based eGFR < 60 mL/min for 90 d or ≥ 42 d of hemodialysis | 16% patients (*n* = 6269) met CKD criteria at the time of LT |
| Bassegoda *et al*[7], 2020 | 409 hospitalized cirrhosis patients, 168 with AKI | MDRD-4 equation based eGFR < 60 mL/min > 3 mo | Among survived patients at 3 mo, 9.1% (26/285) developed CKD, Incidence of CKD among cirrhosis-AKI patients was 25% (24/97) |
| Rustgi *et al*[18], 2020 | 598455 CLD patients, including 94431 patients with cirrhosis | As per the record, based on International Classification of Disease (ICD-9) code | Among 94431 cirrhosis patients, prevalence of CKD was 3.37% |
| Wong *et al*[3], 2019 | 2346 non-electively admitted patients with cirrhosis | MDRD-4 equation based eGFR < 60 mL/min for > 3 mo | Prevalence of CKD was 46.8% (*n* = 1099) |
| Maiwall *et al*[16], 2020 | 818 cohort of both hospitalized and outdoor cirrhosis patients | MDRD-6 equation based eGFR < 60 mL/min for > 3 mo and abnormal urine microscopy > 12 wk | Incidence of CKD was 32.8% (*n* = 269) |
| Chen *et al*[17], 2018 | 7440 adult patients with cirrhosis | MDRD-6, CKD-EPI and MDRD-4 equation based eGFR < 60 mL/min for > 3 mo | CKD was present in 46.0%, 45.7% and 45.6% of patients using the MDRD-6, CKD-EPI and MDRD-4 equations, respectively |
| Choi *et al*[19], 2014 | 643 hospitalized cirrhosis patients | MDRD-6 equation based eGFR < 60 mL/min for > 3 mo | Prevalence of CKD was 3.4% (*n* = 22) |
| Martín-Llahí *et al*[32] , 2011 | 463 hospitalized cirrhosis patients with renal impairment | Old criteria for HRS based on serum creatinine: > 1.5 mg/dL | Proportion of CKD-HRS was 3.9% (*n* = 22) |
| Salerno *et al*[33], 2011 | 263 hospitalized cirrhosis patients with renal impairment | Old criteria for HRS based on serum creatinine: > 1.5 mg/dL | Proportion of CKD-HRS was 18.5% (*n* = 40) |
| Péron *et al*[2], 2005 | 932 hospitalized cirrhosis patients with renal impairment | Old criteria for HRS based on serum creatinine: > 1.5 mg/dL | Proportion of CKD was 10 (1.07%), Proportion of CKD-HRS was 07 (0.75%) |

CKD: Chronic kidney disease; LT: Liver transplantation; CKD-EPK: Chronic kidney disease epidemiology collaboration; eGFR: Estimated glomerular filtration rate; AKI: Acute kidney injury; MDRD: Modification of diet and renal disease; CLD: Chronic liver disease; HRS: Hepatorenal syndrome.