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Editorial Board Member of *World Journal of Clinical Cases*, Chun-Lin Ou, Doctor, PhD, Associate Professor, Associate Research Scientist, Department of Pathology, Xiangya Hospital, Central South University, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China. ouchunlin@csu.edu.cn

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Kidney disease in patients with chronic liver disease: Does sex matter?

Katherine M Cooper, Alessandro Colletta, Kristen Moulton, Kenneth M Ralto, Deepika Devuni

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Katherine M Cooper, Alessandro Colletta, Department of Medicine, UMass Chan Medical School, Worcester, MA 01665, United States

Kristen Moulton, Deepika Devuni, Department of Medicine, Division of Gastroenterology, UMass Chan Medical School, Worcester, MA 01665, United States

Kenneth M Ralto, Department of Medicine, Division of Renal Medicine, UMass Chan Medical School, Worcester, MA 01665, United States

Corresponding author: Katherine M Cooper, MD, Doctor, Department of Medicine, UMass Chan Medical School, 55 Lake Ave, Worcester, MA 01665, United States.

katherine.cooper@umassmed.edu

Abstract

Kidney disease in patients with liver disease is serious and increases mortality. Up to 50% of patients hospitalized experience an episode of acute kidney injury. In general, men with liver disease are thought to be at increased risk of kidney disease. However, this association should be considered with caution because most studies use creatinine-based inclusion criteria, which is negatively biased against women. In this review, we synthesize data on sex differences in kidney disease in patients with chronic liver disease in the clinical setting and discuss potential physiologic underpinnings.

Key Words: Sex differences; Renal disease; Gender disparity; Hepatorenal syndrome; Renal replacement therapy

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Core Tip: Kidney disease in patients with chronic liver disease is common and associated with increased morbidity and mortality. Most literature on this topic is based in men. However, there are important sex differences to consider in pathophysiology and outcomes in men and women that are poorly addressed in the literature. Here, we synthesize data on sex differences in kidney disease amongst patients with liver disease.

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INTRODUCTION

Kidney disease is a serious comorbidity in patients with chronic liver disease (CLD). Both acute and chronic kidney diseases portend a worse prognosis in patients with CLD[1-3]. Sex differences in markers of kidney function have been a topic of interest in hepatology due to the relationship between serum creatinine and access to liver transplantation in women[4]. However, there are other differences regarding kidney disease in men and women that are infrequently addressed in the literature. We aim to review the existing literature to identify sex differences in the clinical course and outcomes of men and women with CLD complicated by renal impairment. We will discuss the potential pathophysiologic basis of sex differences, including differences in splanchnic vasodilation, autonomic regulation, portal hypertension, sarcopenia, hormones, and inflammation. We will also discuss future directions and alternative markers of kidney function that may reduce gender disparities in renal outcomes.

TERMINOLOGY

Kidney dysfunction occurs along a spectrum and is common in patients with CLD. Chronic kidney disease (CKD) affects 1 of 5 patients with cirrhosis[5] while acute kidney disease (AKD) and acute kidney injury (AKI) affect between one half and one third of decompensated patients[6]. The most common forms of AKI in patients with cirrhosis are pre-renal azotemia, acute tubular injury/necrosis, and hepatorenal syndrome (HRS)[7]. Other less common causes are IgA nephropathy, cholemic nephropathy, abdominal compartment syndrome, and nephritic syndromes related to viral hepatitis[8].

Of these pathologies, HRS is a unique entity with pathophysiology specific to advanced liver disease [9]. Prior to 2015, the diagnostic criteria for HRS included a final serum creatinine cutoff value of > 2.5 mg/dL[10,11]. However, this definition was thought to delay treatment and negatively affect outcomes [12]. Thus in 2015, the International Club of Ascites (ICA) revised the diagnostic criteria to be similar to those for AKI in other forms of critical illness without an absolute creatinine cutoff[13]. While these changes have reduced underdiagnosis of severe renal dysfunction, they have also: (1) Affected the interpretation and comparison of the literature published before and after this change period; and (2) allowed for more overlap between AKI syndromes. It is now more accepted that hepatorenal physiology occurs along a spectrum and may be present in conjunction with or independent of other causes of kidney injury[8]. The 2015 ICA guidelines also defined AKD and updated the definition of CKD (Figure 1).

There are currently no sex specific diagnostic criteria for AKI, AKD, or CKD in patients with CLD. We would like to highlight that it is unclear whether the change in diagnostic criteria will completely address underdiagnosis in women relative to men. While studies have shown that the required change of 30% serum creatinine occurs at similar rates between men and women with cirrhosis and AKI, this relies on capturing patients at baseline. Given that many patients with cirrhosis remain unrecognized until first decompensation[14], it is possible that women may already have renal impairment despite a normal presenting serum creatinine.

EPIDEMIOLOGY

Male sex is associated with increased risk of AKI in the general population, while population-based studies indicate that CKD affects more women than men[15,16]. Similarly, many studies evaluating AKI in patients with cirrhosis show a male predominance[7]. A recent 10-year analysis found that 60%-65% of hospitalizations for cirrhosis with AKI are in male patients. This study also observed a significant increase in the number of hospitalizations for female patients over the study period[17]. The economic burden of these hospitalizations is significant. Hospitalizations for cirrhosis complicated by AKI are almost twice as costly as those without AKI[18]. In 2019, the health care burden of HRS alone in the United States was 4.2 billion dollars[19]. Some data suggest that women may have more costly hospital stays when hospitalized with AKI compared to men[20].

Thus, while most data suggest that males experience more AKI episodes, these should be interpreted with caution. First, the data suggesting a greater incidence of AKI in men is not generalizable to the diagnosis of HRS-AKI, since most studies on decompensated cirrhosis are male predominant. Second, women are at increased risk of underdiagnosis of AKI compared to men due to lower baseline serum

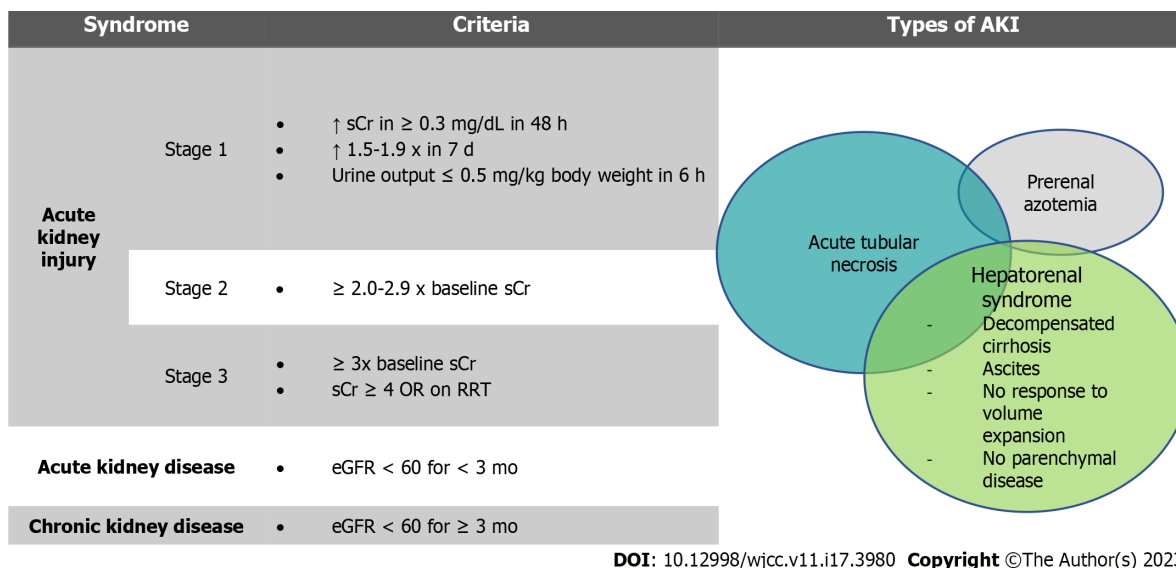


Figure 1 Definitions and diagnostic schema for kidney disease in patients with chronic liver disease based on updated 2015 guidelines. sCr: Serum creatinine; RRT: Renal replacement therapy; AKI: Acute kidney injury; AKD: Acute kidney disease; CKD: Chronic kidney disease; OR: Odds ratio; eGFR: Estimated glomerular filtration rate.

creatinine[21]. This disparity was likely exacerbated when diagnosis of HRS required an absolute serum creatinine level > 2.5 mg/dL[22]. Thus, studies conducted prior to 2015 may have failed to capture the true sex differences. Further, the male to female ratio in many HRS studies is similar to that in decompensated cirrhosis, which suggests a similar risk between sexes rather than an increased risk specific to men.

The relationship between sex and persistent kidney disease in patients with cirrhosis is less clear. Female sex has been associated with what was previously considered type 2 HRS, which is now more consistent with HRS-CKD[23]. Conversely, a large consortium study found that there was no difference in the risk of AKD in men and women hospitalized for cirrhosis with AKI[2]. Similarly, an analysis of hospitalized patients with cirrhosis found rates of established CKD to be similar in men and women. This study also found that males had decompensated liver disease significantly more often and did not control for how this affected risk of CKD[5]. However, of those that have received a liver transplant, female sex is a risk factor for post-transplant CKD; this may suggest more significant yet underestimated pre-transplant kidney dysfunction in women[24].

To date, there are limited studies evaluating sex differences in kidney disease in patients with specific etiologies of cirrhosis. A small analysis conducted in patients hospitalized with alcohol-related liver disease found males to make up a larger proportion of the AKI cohort than non-AKI cohort (76% vs 57%, $P = 0.006$), but did not identify male sex as a predictor of AKI on multivariate regression modeling[25]. Patterns in non-alcoholic fatty liver disease (NAFLD) are unique compared with those in other etiologies: Men appear to be at increased risk of CKD compared to women but they have similar risk of HRS[26]. A study using iothalamate clearance tests to study renal function in a cohort of NAFLD patients found that more women had a glomerular filtration rate (GFR) less than 60 mL/min than men prior to liver transplant (39% vs 27%)[27]. Unfortunately, there is limited data on kidney disease in autoimmune related liver diseases (*e.g.*, autoimmune hepatitis and primary biliary cirrhosis). As these diseases are female predominant, their underrepresentation in the literature further supports the bias surrounding CKD and AKI/AKI-HRS[28]. This concept is bolstered by lack of sex-specific data in cirrhosis from viral hepatitis, despite these being some of the most prevalent worldwide.

For HRS-AKI specifically, many studies have been performed in male predominant populations. However, a recent Cochrane meta-analysis demonstrates variability in sex composition among studies employing medical treatment for HRS. In the 25 studies included, females comprised 6%-61% of study participants with a pooled average of 28%[28]. A nationwide analysis of over 500000 patients hospitalized for cirrhosis noted that a higher proportion of men had a diagnosis of HRS compared to women (3.9% vs 3.3%, $P < 0.01$)[5]. While this evidence purports a higher risk of HRS in males, the authors did not provide diagnostic criteria used in this determination and thus this data should be interpreted with caution. Ultimately, high quality studies that directly compare the risk of HRS-AKI in men and women are lacking. Interestingly, there is a female predominance amongst pediatric patients who develop HRS as this most often occurs in the setting of biliary atresia, a female predominant congenital malformation[29]. Thus, studies in the pediatric population may provide a unique opportunity to limit the underrepresentation of female subjects and better understand sex differences in HRS.

CLINICAL DISEASE AND OUTCOMES

The negative impact of AKI on survival in this cohort is well recognized. Up to 50% of patients hospitalized with decompensated cirrhosis present with or develop AKI[7,30,31]. A recent meta-analysis of 32 high quality studies found that AKI was associated with significantly higher mortality in-hospital [odds ratio (OR) 5.92], at 30 d (OR 4.78), at 90 d (OR 4.34), and at 1 year follow-up (OR 4.82) compared to patients without AKI[32]. Of note, the authors did not present sex-specific differences in outcomes.

Women hospitalized with AKI may be less likely to recover normal renal function compared to men. Patidar *et al*[6] found that female sex was a predictor of persistently elevated serum creatinine 3 mo after an AKI event. While we are unaware of studies reporting sex specific data regarding response to treatment with midodrine-octreotide, there are definitive sex differences in response to terlipressin treatment for HRS-AKI. A study by Wong *et al*[33] demonstrated that male sex is a predictor of improvement of AKI in patients with HRS-AKI, regardless of initial AKI stage. Overall, they found that men were 1.58 times as likely to have a clinically significant reduction in serum creatinine compared to women after 14 d of treatment with terlipressin plus albumin.

A randomized, multicenter, placebo-controlled, double-blind study assessing the efficacy and safety of intravenous terlipressin plus albumin *vs* placebo plus albumin found that HRS reversal in female patients (15.6%) was lower than that in male patients (23.1%). Further, when evaluating for baseline factors predictive of a response to terlipressin and overall survival using multivariate logistic regression, male sex was a significant positive predictor of overall survival ($P = 0.02$)[34]. Frederick *et al*[35] analyzed pooled data from three landmark studies on terlipressin use in HRS and found that while both men and women have some improvement in serum creatinine with treatment, men were significantly more likely to achieve HRS-AKI reversal. The lower response in women may reflect more severe renal dysfunction at the time of treatment initiation. This is consistent with data showing worse kidney disease in women compared to men despite lower serum creatinine, due to inherent differences in muscle mass[36]. Despite these differences, there remain no sex specific recommendations to guide treatment[37].

For patients with HRS-AKI and poorly controlled ascites, transjugular intrahepatic shunt (TIPS) has been utilized[38]. Trivedi *et al*[39] studied outcomes for HRS-AKI after TIPS and found that male patients had better outcomes than female patients. Men with HRS-AKI treated with TIPS experienced a reduction in mortality compared to medical management. Conversely, women with HRS-AKI treated with TIPS had no mortality benefit compared to medical management. Moreover, women were at a striking six-fold increased risk of death after TIPS compared to men. Of note, the use of TIPS in management of HRS-AKI is not well studied and is not recommended by the American Association for the Study of Liver Disease (AASLD) at this time[9].

Patients who do not respond to medical therapy for HRS require renal replacement therapy (RRT), often as a bridge to liver transplant evaluation. While women respond less to treatment, sex differences in utilization of RRT are inconsistent. A 15-center consortium study found that women with AKI received RRT more often than men, despite a similar change in serum creatinine from baseline[31]. In patients not listed for transplant, a larger proportion of women received RRT than men[40]. Conversely, a large study evaluating over 3 million hospitalizations for decompensated cirrhosis over a 6-year period found male sex to be an independent predictor of AKI requiring RRT. Specifically, the study found that AKI requiring RRT occurred in 2.2% of male hospitalizations for decompensated cirrhosis compared to 2.1% of female hospitalizations for decompensated cirrhosis. Interestingly, the study did not comment on sex differences in AKI without RRT. Further, AKI requiring RRT was associated with increased hospital complications and death, but the authors did not comment on sex differences in these events. Most importantly, the study did not discuss access to transplantation and how this affected the relationship between sex and RRT utilization[41]. The heterogenous nature of these findings is not surprising given the complexity of pursuing dialysis in patients with cirrhosis. Specifically, dialysis candidacy is closely associated with access to and candidacy for liver transplantation in patients with irreversible severe AKI associated with hepatic decompensation[42,43]. As such, requiring dialysis is not necessarily associated with receiving dialysis in patients who are deemed not to be candidates for liver transplantation. Interestingly, amongst patients with lower GFR, female transplant candidates have increased mortality relative to male candidates when there are no differences in transplant access[36].

Once initiated on dialysis, there appear to be no differences in renal outcomes or mortality in the acute setting. A study by Wang *et al*[44] utilized multivariable competing risks analysis to identify predictors of kidney recovery with death and transplant as competing events and found no differences between men and women. This has also been shown among both transplant and non-transplant candidates for whom RRT was initiated for ATN-AKI or HRS-AKI[40]. Similarly, there are no known sex differences in renal recovery or mortality once initiated on chronic maintenance RRT[45]. There appear to be sex differences in post liver transplant outcomes for men and women with pre-liver transplant AKI. A study performed in living donor liver transplant recipients found that men with HRS may be at reduced risk of death after transplant compared to women with HRS ($P = 0.07$)[46].

PATHOPHYSIOLOGY

The remainder of this review will focus on physiologic processes that may contribute to sex-based differences in kidney disease. Most of this section will focus on HRS given its specificity to advanced liver disease and unique pathophysiology. Specifically, HRS is a functional renal disorder caused by a complex cascade of circulatory and inflammatory changes that result in dysregulated renal vasoconstriction and reduced renal perfusion (Figure 2)[9]. In general, severe portal hypertension in the setting of CLD leads to low systemic vascular resistance (SVR) and splanchnic vasodilatation. Together, splanchnic vasodilation and low SVR result in reduced effective circulating volume which activates central baroreceptors and the renin-angiotensin-aldosterone system (RAAS). The RAAS activation increases over time with the declining ability of the cirrhotic liver to degrade renin. In parallel, systemic inflammation related to translocation of enteric bacteria results in nitric oxide production which exacerbates peripheral vasodilation and central hypovolemia. The interplay of hemodynamic changes with systemic inflammation ultimately predisposes patients to hemodynamic collapse when exposed to physiologic stressors such as gastrointestinal bleeding, dehydration, or infection. The second hit typically leads to a further impairment of circulatory dysfunction and worsening renal perfusion and ultimately development of severe AKI.

Portal pressure and splanchnic circulation

Sex differences in splanchnic circulation and portal pressures may contribute to differences in HRS-AKI outcomes. First, sex differences in splanchnic autoregulation have been demonstrated in the literature. Specifically, women have been found to have smaller splanchnic vasoconstrictor reserve than men[47]. For example, women have been shown to have lower tilt table tolerance associated with failure to increase splanchnic blood flow relative to circulation. Though this improves with octreotide administration, sex differences persist despite treatment with somatostatin analogue[48]. The latter finding may suggest that women have a decreased response to midodrine and octreotide based HRS protocols, though no studies have investigated this further.

Conversely, there are established sex differences in treatment response for HRS using TIPS. The goal of a TIPS procedure is to redirect flow in the portal system to minimize complications of portal hypertension, as reflected by a reduction in the hepatic venous pressure gradient (HVPG). The HVPG serves as a diagnostic tool in portal hypertension and has prognostication value for related clinical outcomes (ascites, varices, and HRS)[49]. An HVPG greater than or equal to 12 mmHg has been associated with advanced fibrosis and clinically significant portal hypertension[50]. However, this cutoff is derived from mostly male predominant studies. A recent study by Wortham *et al*[51] showed that men and women may respond differently to similar portal pressure. The study followed 20 patients (12 female, 8 male) with compensated cirrhosis who were monitored for clinical decompensation over a three-year period. They found that females tended to decompensate more than males (7 females *vs* 1 male, $P = 0.13$) and the HPVG at the time of decompensation was similar between groups. More females decompensating at similar HPVG suggest that women may not tolerate higher portal pressures as well as men. Ultimately, differences in tolerance to elevated portal pressures and changes in splanchnic hemodynamics may contribute to lower response to TIPS in women or may suggest different contributions of portal hypertension to the development of HRS across genders. Unfortunately, this is not well explored in the literature and no study has specifically assessed sex differences in HVPG with regards to predisposition for development of HRS.

Circulation and microvasculature

Current data suggest that women respond differently to terlipressin treatment than men. Pooled data from 535 patients across three randomized control trials found that women were less likely to have improvement in serum creatinine with terlipressin[35]. This discrepancy in response persists when matching males and females by serum creatinine. While there is no clear reason for this incongruence, systemic vasoregulation is likely at the crux of these findings.

First, there are established sex differences in RAAS response as men and women are known to respond differently to both RAAS activation and inhibition[52]. For example, women have enhanced response to angiotensin stimulation at the level of the kidneys[53,54]. Hyperresponsiveness has been shown to accelerate renal disease and decompensation in mice models of congestive heart failure, another state of decreased renal perfusion[55]. Unfortunately, this has yet to be studied within the context of cirrhosis. However, given that RAAS dysregulation is a key component of HRS development, it is difficult to discount this as a potential driving factor in sex differences.

Receptor level differences in vasoregulatory response may contribute to differences in treatment response observed between sexes. Terlipressin acts predominantly through vasopressin receptor 1 (V1R). Interestingly, pre-clinical models have found that females may have increased V2 receptor expression in the kidney compared to males[56]. Studies in other human organ tissue have also shown that males have increased V1R binding activity than females. It is possible that there is increased V2 stimulation relative to V1 stimulation in women, which may evoke a weaker treatment response.

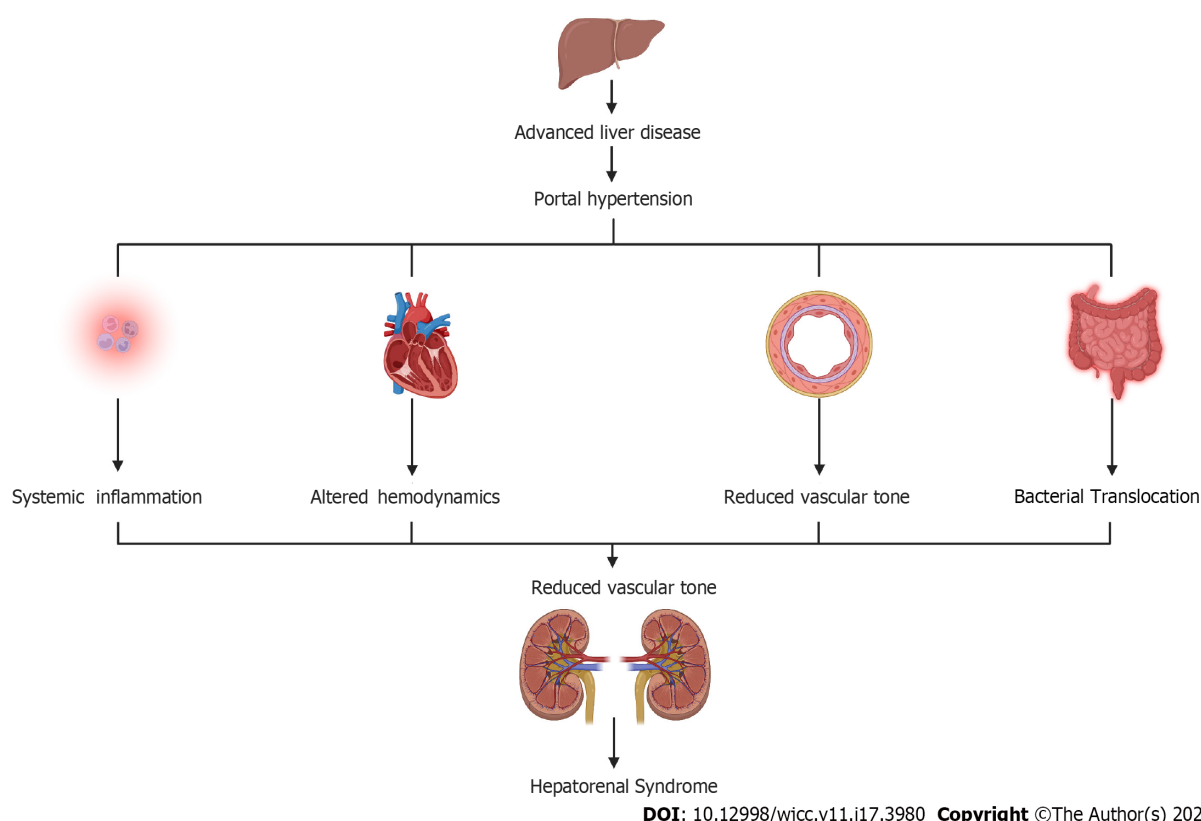


Figure 2 Hepatorenal physiology: A simplified perspective. Hepatorenal physiology includes a cascade of multi-systemic effects that initiate with portal hypertension. Portal hypertension is associated with increased inflammation, reduced effective circulating volume, systemic vascular resistance, altered cardiac hemodynamics, and gut bacterial translocation. Subsequent increased circulation of vasodilators including nitric oxide and prostaglandins, and activation of the renin-angiotensin-aldosterone system result in dysregulated renal vasoconstriction and decreased renal perfusion. Note: The cascade of pathophysiology in hepatorenal syndrome is complex and understanding is developing; this is a simplified figure created for the purpose of this publication. Created in BioRender.com.

Endothelin-1 (ET-1) is a vasoconstrictor that acts *via* endothelin-A receptors at the level of the kidneys and thus has potential implications in the dysregulation of renal microcirculation in HRS[57,58]. While terlipressin is not known to act directly on endothelin receptors, Abdel-Razik *et al*[59] found that a positive renal response to terlipressin was associated with early reduction of serum ET-1 Levels. Interestingly, women express fewer endothelin A receptors than men systemically. Differences in endothelin-A receptor expression may explain why terlipressin treatment is associated with a greater rate of HRS reversal in men[35]. Similarly, it may account for sex differences in rate of HRS, as women are less prone to ET-1 mediated vasoconstriction of renal microvasculature. Conversely, it may suggest different underlying HRS pathophysiology in men and women.

Sex hormones and body composition

Differences in sex hormones may portend differing risk profiles for HRS by gender. Estrogen has been shown to have multiple protective effects on the kidneys, including reduction of apoptosis, promoting mesangial cell enhancement, and regulating the renin-angiotensin system[60,61]. Conversely, androgens have been shown to have a negative impact due to promotion of tubular injury and upregulation of the renin-angiotensin system[62,63]. Furthermore, a study evaluating the relationship between renal function and muscle mass reported that loss of testosterone promotes sarcopenia which may exacerbate renal dysfunction independent of other causes.

While no studies have assessed sex hormones in HRS specifically, animal studies have shown estrogen to be protective against toxin driven hepatorenal toxicity[64]. In clinical practice, post-menopausal women have been shown to be at higher risk for kidney injury compared to pre-menopausal women, likely due to loss of estrogen mediated protection[65,66]. However, no studies evaluating AKI risk by menstrual state have been conducted in patients with CLD.

It is important to note that elevated levels of estradiol and progesterone are present at baseline both in men and women with cirrhosis due to impaired metabolism[67]. It is unclear whether this creates a dose dependent protective response in women or counteracts androgen mediated damage in men. In future studies, evaluating sex differences of HRS in the pediatric population could provide further insight to these relationships given presumably less profound sex differences in muscle mass and steroid hormones in pediatrics compared to adults.

Inflammation

Systemic inflammation is common in CLD and increases with disease progression[68]. Two key inflammatory markers are interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) which have been shown to have predictive power in hepatic decompensation, including HRS[69,70]. Patients with HRS-AKI have marked systemic inflammation with altered cytokine profile relative to patients with decompensated cirrhosis without HRS-AKI. Further, inflammatory markers have implications in treatment response and monitoring. Sole *et al*[71] showed that response to terlipressin is associated with a change in cytokine levels and significant reduction in IL-6 and TNF- α .

While there are studies showing sex specific inflammatory responses in certain subsets of CLD[72], this type of literature in HRS is lacking. Most HRS studies are male predominant and do not comment on sex differences in systemic inflammation. However, there are physiologic differences that may serve as a basis for sex differences in inflammation. As described, females express fewer endothelin-A receptors than males and prolonged ET-1 activity is associated with the release of inflammatory cytokines, including TNF- α and IL-6, in smooth muscle cells in the vasculature and mesangial cells in the kidney[73-75]. This calls to question whether ET-1 promotes local inflammation at the level of the renal vasculature and whether that inflammation contributes to sex differences in HRS incidence and treatment response[76]. Tissue hypoxia is known to increase local inflammation in the kidney[77]. Studies assessing the relationship between anemia and HRS development have found low serum hemoglobin to be associated with HRS type 2[78]. As anemia is more common and is more pronounced in males with CLD[79], it is possible that hypoxia related inflammation predisposes males to the more profound inflammatory response in HRS-AKI.

Pathologic bacterial translocation and infection cause a significant and systemic inflammatory response and are well-known triggers of HRS[80,81]. Unfortunately, there are no studies assessing sex differences in inflammatory response to infection in patients with HRS. Ultimately, given the profound effect of inflammation on the development of HRS, further studies are needed to determine if a relationship between gender and inflammation exists.

EVOLUTION OF HRS DIAGNOSIS AND THE CREATININE CONUNDRUM

Serum creatinine is the standard biochemical marker of renal function in most health care settings, yet it has several limitations in patients with liver disease. Serum creatinine underestimates the severity of kidney dysfunction in patients with CLD due to a reduction in the hepatic synthesis of creatinine, severe malnutrition, sarcopenia, and anasarca[82-84]. This is more pronounced in women due to the inherent differences in muscle mass between sexes. Thus, absolute creatinine values and creatinine based GFR calculations fail to represent kidney function equally across genders as described; reliance on absolute serum creatinine level cutoffs likely results in both underdiagnosing and delaying diagnosis of HRS in women[85,86]. Further, the Model for End-stage Liver Disease-Sodium (MELD-Na) includes serum creatinine as one of its four values. The MELD-Na score not only predicts mortality in patients with end-stage liver disease but also directly determines priority on the liver transplant waitlist. The use of serum creatinine in the MELD-Na score has been shown to perpetuate disparities in access to liver transplantation in women.

Multiple studies that utilized creatinine-based definitions of AKI discuss the differential impact of creatinine by sex. In a study by Mindikoglu *et al*[36], women on the liver transplant list had not only lower serum creatinine compared to men, but also lower true GFR. Despite more severe renal impairment, women were also less likely to receive dialysis than men due to the use of creatinine based GFR estimations. O'Leary *et al*[31] found that women required dialysis and had a worse prognosis compared to men despite similar levels of serum creatinine. Similarly, Frederick *et al*[35] attributed differences in response rate to terlipressin in part to delayed diagnosis and treatment in female patients due to lower overall serum creatinine. Underdiagnosis of renal dysfunction in women is also supported by the literature[36,87]. A study by Yoo *et al*[87] found that creatinine overestimated GFR significantly more often in females than in males (152/192 females and 303/587 males). The authors concluded that serum creatinine concentrations were controlled by different mechanisms in men compared to women[87].

New strategies monitor kidney function in patients with decompensated liver disease are under investigation. Measuring GFR directly (using exogenous substances) may better approximate renal function in women[88]. However, this is time consuming and difficult to complete during acute decompensation and in the hospital setting. Likewise, using urine output-based definitions of kidney injury in theory would have less sex differences because these are based on volume per kilogram. While less expensive than obtaining a measured GFR, monitoring intake and output in the hospital is labor intensive and requires patients' strict adherence or the insertion of urethral catheters, which: (1) Increases risk of infection, and (2) is not indicated in most patients outside of the intensive care setting. MicroRNAs have garnered attention as innovative markers to evaluate kidney injury in cirrhotic patients due to their ability to differentiate ATN and HRS. However, pre-clinical models have shown that these markers are expressed variably across sexes[89]. Fortunately, there is increasing literature on

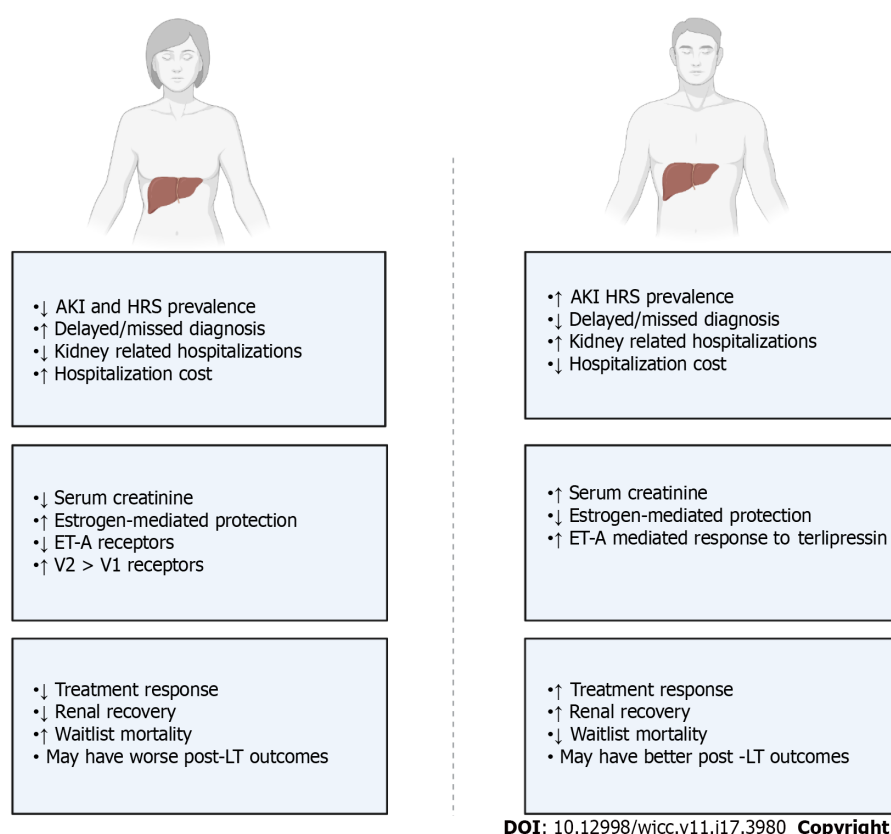


Figure 3 Summary of sex-based differences in cirrhosis related kidney disease. AKI: Acute kidney injury; HRS: Hepatorenal syndrome; ET-A: Endothelin-A. Created in BioRender.com.

alternative biomarkers for renal function. Two newer markers shown to be predictive of renal dysfunction in cirrhosis include cystatin C and neutrophil gelatinase-associated lipocalin (NGAL)[90].

NGAL is a small protein produced by the distal nephron in response to kidney injury[91]. Unlike serum creatinine concentrations, its value does not vary widely with age, gender, muscle mass, muscle metabolism, and hydration status[91]. Huelin *et al*[92] showed that urinary NGAL has high accuracy in differentiating between ATN, HRS, and pre-renal azotemia. Gambino *et al*[93] identified a urinary NGAL level of 220 ng/mL to be sensitive and specific in differentiating these pathologies, predicting treatment response to terlipressin, and predicting mortality. Unfortunately, this study did not have equal gender representation with 76.5% of participants being male. Interestingly, of the patients who died during the hospitalization, only 70% were male ($P = 0.135$). Although this did not reach the threshold for significance, the trend raises the question of whether a larger and more balanced study population would lead to different results.

Cystatin C has gained attraction for its superiority in assessing GFR and lack of sex specificity. This is because cystatin C is produced by all nucleated cells and serum levels are independent of muscle mass [94]. Cystatin C is better correlated with GFR than serum creatinine in patients of all Child-Pugh classes and more accurately estimates GFR for patients with a true GFR less than 70 mL/min[95,96]. Further, serum cystatin C level is an independent predictor of HRS[97]. Unlike creatinine, cystatin C does not depend on muscle mass or age and is not influenced by inflammatory disorders or malignancy. Multiple studies have found cystatin C to be a more neutral marker of renal function. First, the sensitivity of cystatin C is significantly higher ($P < 0.05$) than that of creatinine in women with cirrhosis [95]. Furthermore, Mindikoglu *et al*[36] found no association between cystatin C and biologic sex after controlling for potential confounding factors[98]. Lastly, Torner *et al*[99] found that cystatin C was a predictor of mortality in both male and female patients with HRS compared to creatinine which only predicted mortality in males.

CONCLUSION

Despite kidney disease in patients with cirrhosis being thoroughly studied and well documented in the literature, information regarding sex differences in liver disease is overall lacking (see summary Figure 3). It is known that serum creatinine continues to pose a barrier to care for women with cirrhosis who develop renal dysfunction. Additionally, the use of creatinine in MELD-Na scoring limits and may

even preclude access to liver transplant in women with more advanced renal dysfunction, whose creatinine does not accurately represent their true GFR. However, the historical use of serum creatinine as a marker for AKI in cirrhosis complicates interpretation of existing data relative to sex. Newer studies that employ updated AKI definitions demonstrate sex differences in clinical course and outcomes, suggesting that there are likely underlying pathophysiologic differences beyond serum creatinine between men and women. Given that there are known differences in renal physiology and risk of renal dysfunction between men and women, further research is needed to define sex specific diagnostic and treatment recommendations for kidney disease in patients with cirrhosis.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Katherine M Cooper 0000-0002-6030-4773.

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