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Critical Care Nephrology and Acute Kidney Injury

Acute Kidney Injury in Patients with Liver Disease

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Abstract

AKI is commonly encountered in patients with decompensated cirrhosis, and it is associated with unfavorable outcomes. Among factors specific to cirrhosis, hepatorenal syndrome type 1, also referred to as hepatorenal syndrome-AKI, is the most salient and unique etiology. Patients with cirrhosis are vulnerable to traditional causes of AKI, such as prerenal azotemia, acute tubular injury, and acute interstitial nephritis. In addition, other less common etiologies of AKI specifically related to chronic liver disease should be considered, including abdominal compartment syndrome, cardiorenal processes linked to cirrhotic cardiomyopathy and portopulmonary hypertension, and cholemic nephropathy. Furthermore, certain types of GN can cause AKI in cirrhosis, such as IgA nephropathy or viral hepatitis related. Therefore, a comprehensive diagnostic approach is needed to evaluate patients with cirrhosis presenting with AKI. Management should be tailored to the specific underlying etiology. Albumin-based volume resuscitation is recommended in prerenal AKI. Acute tubular injury and acute interstitial nephritis are managed with supportive care, withdrawal of the offending agent, and, potentially, corticosteroids in acute interstitial nephritis. Short of liver transplantation, vasoconstrictor therapy is the primary treatment for hepatorenal syndrome type 1. Timing of initiation of vasoconstrictors, the rise in mean arterial pressure, and the degree of cholestasis are among the factors that determine vasoconstrictor responsiveness. Large-volume paracentesis and diuretics are indicated to relieve intra-abdominal hypertension and renal vein congestion. Direct-acting antivirals with or without immunosuppression are used to treat hepatitis B/C–associated GN. In summary, AKI in cirrhosis requires careful consideration of multiple potentially pathogenic factors and the implementation of targeted therapeutic interventions.

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Introduction

AKI among individuals with cirrhosis is common, and it has been occurring more frequently over the last two decades. This has been observed among hospitalized patients with cirrhosis, where the burden of AKI has increased approximately 200% since 2004 and the burden of CKD has increased approximately 50% since 2004. Among liver transplant candidates, the burden of CKD has increased >200% since 2002, and the utilization of simultaneous liver-kidney transplantation has increased approximately 500% since 2000 (1,2). These trends are concerning because AKI and CKD are associated with poor clinical outcomes (1,3–5). For instance, patients with AKI or AKI superimposed on CKD have approximately three times greater mortality than those with either CKD alone or no kidney dysfunction (4,5). In addition, there is a growing recognition that episodes of AKI have a long-term effect on patients with cirrhosis. These episodes of AKI often lead to acute kidney disease, an indeterminate phase where it is not clear whether patients will achieve AKI reversal or acquire CKD (6). This interdependence between AKI and CKD has been established in cirrhosis. Patients with CKD are more likely to develop AKI (*i.e.*, AKI on CKD) and less likely to have AKI reversal; similarly, those with AKI are more likely to develop CKD (7). It is hypothesized that the emergence of nonalcoholic fatty liver disease and its associated comorbidities (*e.g.*, hypertension and diabetes mellitus) has led to a population with a greater susceptibility and decreased physiologic reserve to recover from AKI (2,7). These data highlight the importance of identifying the acuity, etiology, and severity of kidney dysfunction in patients with cirrhosis; the recognition of these independent syndromes has led to the proposal of a new nomenclature for the hepatorenal syndromes (Table 1).

Assessment of Kidney Function in Cirrhosis

Estimating GFR utilizing serum creatinine–based formulas is inaccurate in patients with cirrhosis (8). Serum creatinine concentration in cirrhosis is affected by decreased hepatic synthesis of creatine and cirrhosis-related loss of skeletal muscle (8). As a result, serum creatinine is inherently lower, and consequently, the eGFR is often greater than measured GFR (9). These limitations of commonly used eGFR estimators have led to the development of two cirrhosis-specific estimators: the Royal Free Hospital and the GFR Assessment in Liver Disease estimators (10,11). They represent an improvement in GFR estimation; however, they do not account for some limitations of serum creatinine (12). To address these limitations, cystatin C has been studied, although without the creation of a cirrhosis-specific GFR estimator; instead,

Table 1. Definitions of AKI, hepatorenal syndrome type 1/hepatorenal syndrome-AKI, acute kidney disease, and CKD

Syndrome	Old Term	Definition	Hepatorenal Syndrome Prerequisites	New Term
AKI	HRS-1	Stage 1: increase from baseline[a] sCr of either ≥0.3 mg/dl in 48 h or ≥1.5–1.9× baseline in the last 7 d or urinary output ≤0.5 mg/kg body weight in ≥6 h Stage 2: ≥2–2.9× baseline sCr Stage 3: ≥3× baseline sCr or sCr≥4 mg/dl or KRT	• Decompensated cirrhosis • Absence of shock • No treatment with nephrotoxic medications • No response to volume expansion • Absence of parenchymal disease (proteinuria: >500 mg/d; hematuria: <50 RBCs per HPF) • Suggestion of kidney vasoconstriction with FENa<0.2%	HRS-AKI
AKD	HRS-2	eGFR<60 ml/min per 1.73 m^2 for <3 mo		HRS-AKD
CKD[b]		eGFR<60 ml/min per 1.73 m^2 for ≥3 mo		HRS-CKD

HRS-1, hepatorenal syndrome type 1; sCR, serum creatinine; RBC, red blood cell; HPF, high-powered field; FENa, fractional excretion of sodium; AKD, acute kidney disease; HRS-2, hepatorenal syndrome type 2.
[a]Baseline sCr is defined as a stable sCr ≤3 months from the previous. If not available, a stable SCr closest to the current one. If no previous SCr at all, use the admission SCr.
[b]There are limited data regarding albuminuria in patients with cirrhosis; however, it is presumed that patients with cirrhosis follow the general nephrology literature regarding mortality risk with proteinuria. It is not clear if patients with cirrhosis follow the same thresholds.

studies have focused on cystatin C as a predictor for AKI or mortality (13). In a recent meta-analysis, equations combining creatinine and cystatin C were the least biased (14).

Evaluation of AKI in Cirrhosis

Acute impairment in kidney function is clinically assessed by changes in serum creatinine and/or urine output (15). History and physical examination remain the cornerstones of the approach to diagnosis and dictate the pretest probability of a specific etiology of AKI. The clinical context (*i.e.*, inpatient versus outpatient) often will inform the differential, including consideration for hepatorenal syndrome type 1 (HRS-1), a form of AKI unique to cirrhosis (Figure 1). Urine chemistries, complete urinalysis, and microscopic examination of the urinary sediment are essential elements of laboratory testing. Kidney ultrasonography is routinely used to rule out obstructive uropathy as a cause of AKI. Urine biomarkers have been tested to assess AKI in cirrhosis. These include neutrophil gelatinase–associated lipocalin, liver fatty acid–binding protein, kidney injury molecule-1, and tissue inhibitor of metalloproteinases-1, among others (Table 2) (16). These metrics capture either the degree of injury or the inflammatory response and have been linked with clinical outcomes. Prerenal azotemia and acute tubular injury combined account for the majority of the cases of AKI in cirrhosis. Although early reports linked HRS-1 to worse clinical outcomes than other AKI causes, a recent study reported similar 90-day mortality in HRS-1 compared with patients with acute tubular injury (17,18). Although clinical presentation and laboratory testing should point to specific etiologies, often clinically, these etiologies are challenging to distinguish, and they may overlap (19).

Etiology-Driven Management of AKI in Cirrhosis

Prerenal Azotemia and Ischemic Acute Tubular Injury

Individuals with decompensated cirrhosis are susceptible to prerenal azotemia resulting from gastrointestinal fluid losses induced by laxatives prescribed for prophylaxis for hepatic encephalopathy. In addition, urinary losses caused by diuretics prescribed for refractory ascites or secondary to poor cardiac output due to superimposed cardiorenal syndrome can lead to prerenal AKI (20). Ischemic acute tubular injury can result from prolonged prerenal azotemia or hemorrhagic shock due to variceal bleeding or be secondary to infections, like spontaneous bacterial peritonitis or septic shock (21). Urine sediment microscopy in cases of acute tubular injury often reveals the presence of characteristic muddy brown granular casts (22).

Regardless of the etiology or severity of prerenal azotemia, the treatment is centered on volume resuscitation. Intravascular assessment of volume status is often complex in patients with cirrhosis. A trial period of 24–48 hours of targeted volume resuscitation with albumin has been traditionally recommended. However, routine administration of volume expanders without a reasonable grasp on volume status might pose a risk of pulmonary edema (23,24). A combination of history, physical examination, laboratory data, and point-of-care ultrasound (POCUS) optimizes volume status assessment. In a single-center retrospective study with patients diagnosed with HRS-1, POCUS-based assessment led to the reclassification of the AKI etiology according to inferior vena cava diameter and collapsibility. Specifically, 21% of patients who were previously deemed clinically euvolemic had findings consistent with hypervolemia, and 23% exhibited hypovolemia despite presumed adequate volume resuscitation, suggesting the diagnostic utility of POCUS in this setting (25).

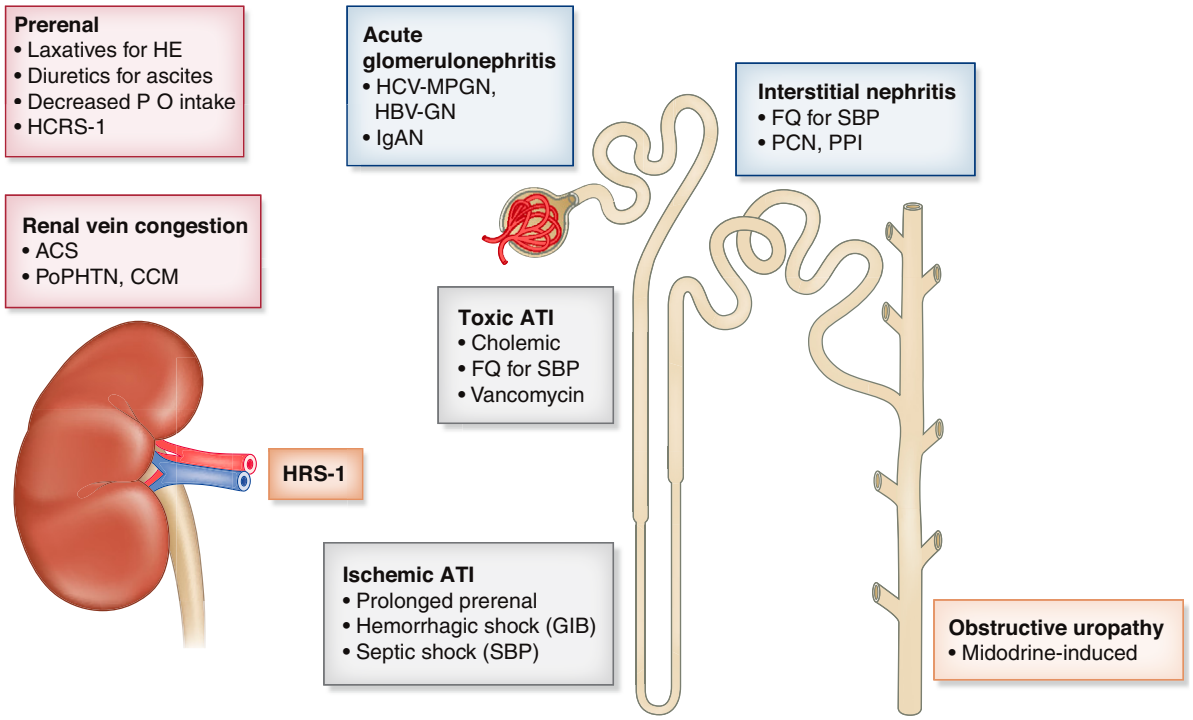

Figure 1. | **Etiology of AKI in cirrhosis.** Hepatorenal syndrome type 1 (HRS-1) is one of many potential causes of AKI. Prerenal azotemia can be caused by gastrointestinal fluid losses induced by laxatives prescribed for prophylaxis for hepatic encephalopathy (HE), urinary losses caused by diuretics prescribed for ascites, or poor cardiac output due to hepatocardiorenal syndrome 1 (HCRS-1). Ischemic acute tubular injury (ATI) can be caused by prolonged prerenal azotemia, hemorrhagic shock (*e.g.*, due to gastrointestinal bleeding [GIB]) or septic shock (*e.g.*, due to spontaneous bacterial peritonitis [SBP]). Toxic ATI can be caused by cholemic tubulopathy (bile acids) or certain drugs commonly prescribed in this setting, such as fluoroquinolones (FQs) or vancomycin. Renal vein congestion can cause AKI, as seen in abdominal compartment syndrome (ACS) caused by tense ascites, congestive heart failure from cirrhotic cardiomyopathy (CCM), or right ventricular failure from portopulmonary hypertension (PoPHTN). Acute GN can be caused by IgA nephropathy (IgAN) or hepatitis C (HCV)– or hepatitis B (HBV)–associated membranoproliferative GN (MPGN), often cryoglobulinemic. Acute interstitial nephritis can be caused by antibiotics prescribed for infections (*e.g.*, FQ or penicillin [PCN]) or proton pump inhibitors (PPIs). Obstructive uropathy is rare in cirrhosis, but it can occur in patients treated for HRS-1 with midodrine.

Hepatorenal Syndrome Type 1

HRS-1 is a unique form of AKI in patients with cirrhosis, portal hypertension, and ascites. The state of portal hypertension, peripheral arterial vasodilation, and decreased effective circulatory volume is associated with overactivation of the sympathetic nervous system and the renin-angiotensin system as well as marked renal vasoconstriction. The degree of kidney dysfunction required by the International Club of Ascites for the diagnosis has evolved over time. Currently, the definition adheres to the existing Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI (*i.e.*, it is currently defined as greater than or equal to stage 1 AKI and/or a decrease in urine output to ≤0.5 ml/kg body weight in ≥6 hours) (Table 1) (15). A diagnosis of HRS-1 is often difficult to make. Unclear baseline serum creatinine values or clinical presentations not fitting the classic phenotype of hypotension, ascites, oliguria, and bland urinary sediment often make the diagnostic approach a challenging task. Moreover, often these patients have several competing risk factors for AKI that confound the clinical picture. These include infectious complications, nephrotoxic medications, acute tubular injury, *etc*. Nevertheless, in the correct clinical context, the diagnosis of HRS-1 can be made with some certainty.

Several risk factors have been identified as predictors of HRS-1. (*1*) Baseline serum creatinine. Patients with higher serum creatinine are more likely to develop HRS-1 and less likely to have AKI reversal (2,26). (*2*) Systolic BP. Patients with lower mean arterial pressure (MAP) at baseline are more likely to develop HRS-1 and less likely to achieve AKI reversal (27). (*3*) Other hemodynamic parameters, such as the evolution of hepatocardiorenal derangements. Prolonged maintenance of a hyperdynamic state leads to decreased cardiac responsiveness and diastolic dysfunction and ultimately predisposes patients to circulatory dysfunction and the development of HRS-1 (20). (*4*) Acute-on-chronic liver failure, a syndrome of acute and severe hepatic decompensation with associated multiorgan failure that occurs after several types of triggers (*e.g.*, bleeding and infection) in patients with decompensated cirrhosis (28). Kidney dysfunction occurs in >50% of those patients hospitalized with acute-on-chronic liver failure—often a consequence of a precipitating event (*e.g.*, infection and hemorrhage). Specifically, spontaneous bacterial peritonitis is a frequent cause of AKI and acute-on-chronic liver failure, and as such, the empirical use of albumin has been shown to prevent AKI and HRS-1 among patients with spontaneous bacterial peritonitis (29).

Table 2. Kidney biomarkers investigated as diagnostic tools for AKI in the setting of cirrhosis

Biomarker	Biofluid	Nephron Damage Site	Differential Expression[a]			Area Under Curve: Acute Tubular Ischemia versus Prerenal/Hepatorenal Syndrome
			Prerenal	Hepatorenal Syndrome	Acute Tubular Ischemia	
NGAL	Urine/serum	Tubule	↑	↑↑	↑↑↑	0.79
IL-18	Urine	Tubular	↑	—	↑↑↑	0.71
KIM-1	Urine	Tubular	↑	—	↑↑	0.64
L-FABP	Urine	Tubular	↑	—	↑↑	0.69
Microalbumin	Urine	Glomerular	↑	—	↑↑↑	0.73
TIMP-2/IGFBP7	Urine	—	NS	NS	—	NR
miR-21	Serum	—	↑	↑↑	↑↑↑	0.97
miR-210	Serum	—	↓	↓↓	↓↓↓	0.80
miR-146a	Serum	—	↓	↓↓	↓↓↓	0.86
Adrenomedullin	Serum	—	↑	↑↑↑	↑↑	0.95–0.92
Thromboxane A2	Urine	—	↑	↑↑↑	↑↑	0.68–0.70

NGAL, neutrophil gelatinase–associated lipocalin; ↑, mild increase; ↑↑, moderate increase; ↑↑↑, marked increase; —, no data available; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid–binding protein; TIMP-2, TIMP metallopeptidase inhibitor 2; IGFBP7, insulin-like growth factor binding protein 7; NS, nonsignificant; NR, none reported; miR-21, microRNA-21; miR-210, microRNA-210; ↓, mild decrease; ↓↓, moderate decrease; ↓↓↓, marked decrease; miR-146a, microRNA-146a.

[a]These data are extrapolated from studies that compared biomarker levels between different etiologies of AKI. Only NGAL, miR-21, mir-210, miR-146a, adrenomodulin, and thromboxane A2 were compared between prerenal, hepatorenal syndrome-AKI, and acute tubular ischemia (ATI). All others were compared between ATI and non-ATI (64–69). TIMP-2/IGFBP7 was compared between hepatorenal syndrome type 1 and no AKI (70).

The treatment of HRS-1 centered on reversing hemodynamics. This has focused mainly on vasoconstriction, and tested agents include ornipressin, vasopressin, midodrine/octreotide combination, terlipressin, and norepinephrine (20). Regardless of the vasoconstrictor of choice, several key factors have emerged, which appear to dictate outcomes (Figure 2): (*1*) timing of initiation (the earlier in the disease evolution [*i.e.*, at lower stages of AKI], the greater the likelihood of response to therapy) (26); (*2*) the effect on MAP (there is a nearly linear correlation between the increase in MAP and the likelihood of HRS-1 reversal; although the ideal MAP target is not clear, an increase of ≥15 mm Hg has been associated with improved outcomes) (30,31); (*3*) the degree of underlying liver disease (patients with an elevated total bilirubin level are less likely to respond to therapy; whether this is a direct effect of bile acid nephrotoxicity or a reflection of the underlying severity of illness is not known) (20); (*4*) reversal of the trigger (whether infection, hemorrhage, or another trigger, removal and treatment of the trigger dictate clinical outcomes); and (*5*) underlying cirrhotic cardiomyopathy or portopulmonary hypertension (underlying cirrhotic cardiomyopathy or portopulmonary hypertension plays an important role in determining if a patient will respond to vasoconstrictor therapy and have HRS-1 reversal).

On the basis of clinical trial evidence, norepinephrine and terlipressin are the most effective agents to treat HRS-1. Studies to date have varied in sample size, the severity of AKI at initiation, the degree of hepatic decompensation, interventions selected, and primary outcomes chosen. This variation has made it difficult to directly compare between vasoconstrictors, except for the more potent vasoconstrictors (*i.e.*, norepinephrine and terlipressin) showing a greater likelihood of reversal. Most recently, the CONFIRM trial randomized 300 patients to either terlipressin or placebo (23). Results demonstrated a higher rate of hepatorenal syndrome reversal with terlipressin as compared with the placebo group (32% versus 17%; $P=0.006$); however, the treatment group had higher rates of respiratory failure (10% versus 3%). It is not clear if this was a direct effect of terlipressin or related to increased albumin-based resuscitation in the treatment group (32). In addition to terlipressin, ornipressin and vasopressin have been examined in HRS-1 in small and uncontrolled studies (33,34). However, lack of strong evidence, V1 receptor selective (of vasopressin), and concerns for adverse effects may have mitigated the enthusiasm for those alternative vasopressin analogs.

Currently, terlipressin is not approved by the Food and Drug Administration in the United States. As a result, norepinephrine is the preferred agent for HRS-1 in patients in an intensive care unit. However, norepinephrine cannot be administered on the general wards. Thus, the combination of midodrine and octreotide is routinely used to treat HRS-1 outside of the intensive care unit. Interestingly, the use of midodrine and octreotide use originated from a nonparallel controlled study that compared five patients treated with midodrine and octreotide with eight patients treated with nonpressor doses of dopamine (35). Notably, midodrine and octreotide were titrated to achieve an increase in MAP by 15 mm Hg. The study showed the superiority of midodrine and octreotide over dopamine, and its use became vastly adopted, likely due to the ease of administration and relatively favorable safety profile. Subsequently, midodrine and octreotide have been shown to be inferior to both terlipressin and norepinephrine (36,37). Therefore, the existing evidence is insufficient to recommend midodrine and octreotide as vasoconstrictor therapy for HRS-1. Current clinical algorithms focus on the augmentation of MAP with the regimen chosen dictated by those that are clinically available (20). It should be noted that in the favorable scenario of HRS-1 reversal, if the pathophysiologic state that predisposed HRS-1 is still present, HRS-1 recurrence may

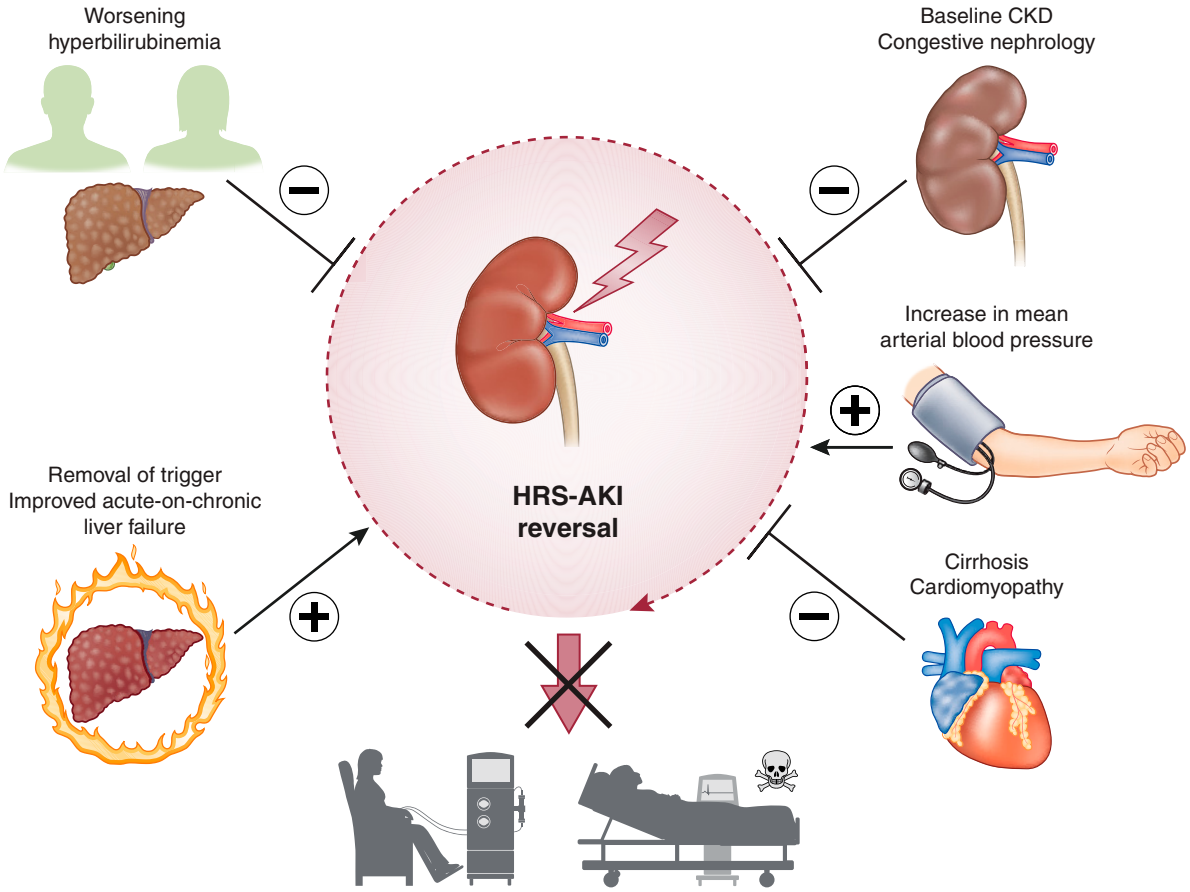

Figure 2. | **Determinants of HRS-1 reversal.** (*1*) Timing of initiation—the earlier in the disease evolution (*i.e.*, at lower stages of AKI), the greater the likelihood of response to therapy. (*2*) Effect on mean arterial pressure (MAP). There is a nearly linear correlation between the increase in MAP and the likelihood of HRS-1 reversal. Although the ideal MAP target is not clear, an increase of ≥15 mm Hg has been associated with improved outcomes. (*3*) The degree of underlying liver disease. Patients with an elevated total bilirubin level are less likely to respond to therapy; whether this is a direct effect of bile acid nephrotoxicity or a reflection of the underlying severity of illness is not known. (*4*) Reversal of the trigger. Whether infection, hemorrhage, or other trigger, removal and treatment of the trigger dictate clinical outcomes. (*5*) Underlying CCM or PoPHTN plays an important role in determining if a patient will respond to vasoconstrictor therapy and have HRS-1 reversal.

ensue (5%–60%), and retreatment should be pursued as indicated (20).

Cholemic Tubulopathy

In patients with hyperbilirubinemia, cholemic nephropathy (also termed cholemic nephrosis, cholemic nephropathy, or bile cast nephropathy) refers to a condition characterized by intratubular bile casts with impaired kidney function in the setting of cholestasis (30). It was originally described in individuals with cholangiocarcinoma or other causes of obstructive jaundice (38). The notion that cholemic nephropathy is implicated in the pathogenesis of HRS-1 was introduced by human autopsy studies reporting a significant proportion of patients with cirrhosis with histologic evidence of intratubular bile casts who had been diagnosed as having HRS-1 premortem (39,40). However, careful consideration is needed when translating animal studies and autopsy results. It remains unclear whether the presence of intratubular bile casts merely reflects reduced GFR and tubular stasis or signifies a potential role in inducing tubular injury (19). Nevertheless, bile acids may pose other effects leading to renal hemodynamic derangements and cardiac output compromise leading to renal hypoperfusion (41). Notably, the presence of renal tubular epithelial cell casts is described in patients with severe hyperbilirubinemia and suggests cholemic tubular injury. However, those casts can be found in the absence of AKI, and hence, their significance remains unclear (42). Finally, greater severity of hyperbilirubinemia has been associated with attenuated response to vasoconstrictors in HRS-1, suggesting that other pathogenic mechanisms might complicate those cases (43). Altogether, the evidence indicates that hyperbilirubinemia itself may independently contribute to the pathogenesis of AKI in cirrhosis, but more studies are needed to answer this question conclusively (Figure 3).

Drug-Induced AKI

Antimicrobials are frequently prescribed for patients with cirrhosis in the hospital setting. Antibiotics can, therefore, be the cause of AKI either by an allergic reaction

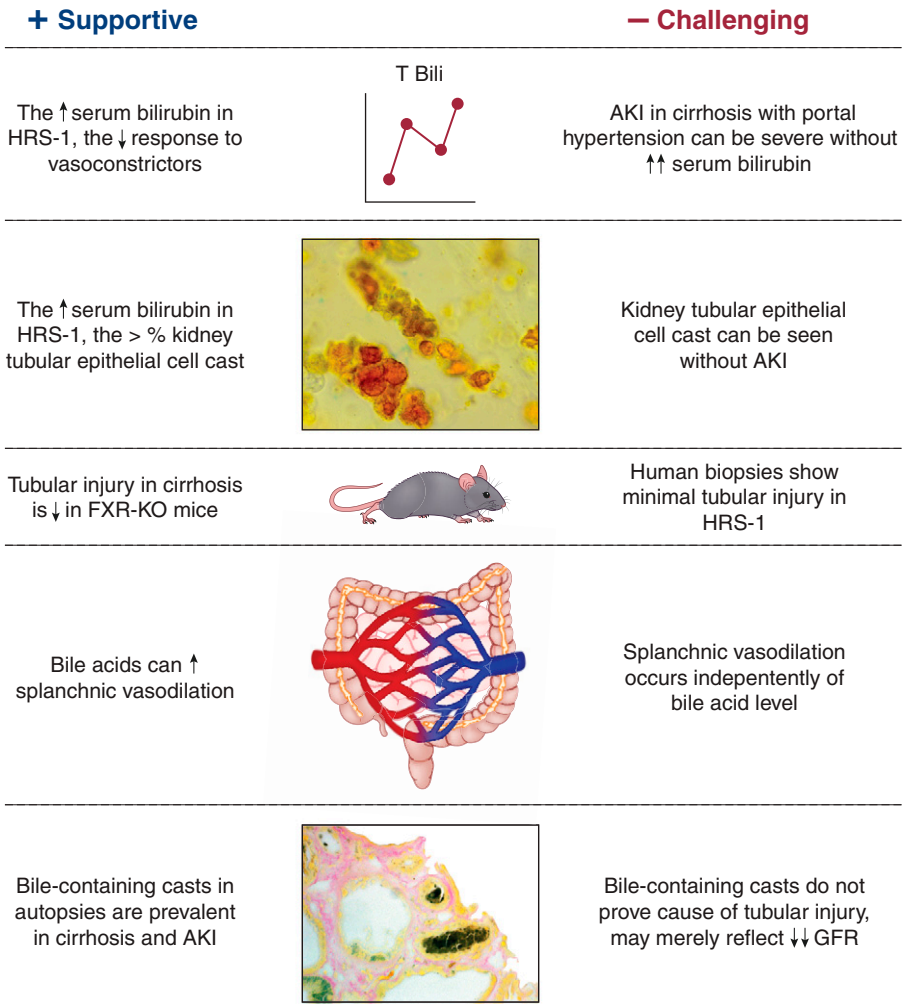

Figure 3. | **Assessment of the existing evidence for cholemic tubulopathy as a cause of AKI in cirrhosis.** Some studies showed that the greater the elevation of serum bilirubin concentration, the lower the likelihood of response to vasoconstrictors in HRS-1. However, this observation is not uniform across studies. Kidney tubular epithelial cell casts (RTECCs) are found more commonly among patients with elevated serum bilirubin concentrations. However, the correlation of high serum bilirubin level and abundance of RTECCs has also been reported in the absence of AKI, thus challenging the notion that RTECCs present in the urinary sediment of patients with cirrhosis and AKI are necessarily reflective of the AKI pathogenesis. In an animal model of cirrhosis, amelioration of tubulointerstitial injury in mice lacking receptors for bile acids (farnesoid X receptor knockout [FXR-KO] mice) was observed. However, seminal studies of HRS-1 showed mostly intact kidney parenchyma. Bile acids have been shown to elicit splanchnic vasodilation. However, splanchnic vasodilation occurs regardless of serum bile acid or bilirubin (T Bili) concentration. Autopsy studies reported high prevalence of bile casts filling the tubular lumen of patients with cirrhosis who died with a diagnosis of HRS-1. However, the presence of bile casts in tubular lumen does not prove causality and may merely reflect tubular stasis and severely reduced GFR.

leading to acute interstitial nephritis (AIN) or by direct tubular cell toxicity leading to toxic acute tubular injury.

Staphylococcal infections requiring treatment with vancomycin are not uncommon in cirrhosis. Vancomycin is known to cause toxic acute tubular injury in the general population, and it can present clinically as a precipitous rise in serum creatinine (44). Vancomycin nanospheres have been described to precipitate intratubular obstruction, an entity named vancomycin cast nephropathy (45). Currently, studies depicting the risk of vancomycin-associated AKI in patients with cirrhosis are lacking. Nevertheless, patients with decompensated cirrhosis exposed to vancomycin should be cautiously watched for AKI development.

Reports of ciprofloxacin-induced crystal tubulopathy have emerged (46). Although there are no specific reports of this nephrotoxic effect of ciprofloxacin in cirrhosis, these antimicrobials are often prescribed in cirrhosis. Therefore, the possibility of ciprofloxacin-induced tubulopathy should be considered as a potential cause of AKI in this population.

Fluoroquinolones are routinely used for prophylaxis and treatment of spontaneous bacterial peritonitis in patients with decompensated cirrhosis and ascites. Fluoroquinolone-induced AKI secondary to AIN has been reported in the general population (47). Piperacillin, nafcillin, other cephalosporins, and vancomycin can also cause AIN. Similarly, proton pump inhibitors, a common cause of AIN, are also frequently prescribed in cirrhosis (48). However, there is

limited literature about the risk of medication-induced AIN in patients with cirrhosis. Nevertheless, the presence of sterile pyuria in a patient exposed to an antibiotic or proton pump inhibitor should alert the practitioner to the possibility of AIN.

Glomerulonephritis

Patients with cirrhosis are at considerable risk for acquiring certain glomerulopathies (49). From autopsy and kidney biopsy data, glomerular involvement in cirrhosis is reported to be around 50%, although the majority of cases may only exhibit minor histologic changes without clinical manifestations (49). In a cohort of patients with cirrhosis, examination of kidney specimens by light microscopy and immunofluorescence at autopsy revealed that 61% of patients had IgA nephropathy and 31% had normal parenchyma (50).

Immunoglobulin A Nephropathy. Hepatic IgA nephropathy is the most common secondary form of IgA nephropathy and the most common type of GN in decompensated cirrhosis, accounting for 50%–90% of the cases (51). The majority of cases of hepatic IgA nephropathy are asymptomatic or manifest slow disease progression (52). It is suggested that defective hepatic processing of IgA secondary to reduced sialo-glycoprotein receptor on hepatocytes in conjunction with portosystemic shunting may cause IgA to deviate from hepatic uptake and depolymerize, subsequently leading to immune complex deposition within the mesangium (52). Management is aimed at supportive strategies with angiotensin-converting enzyme or angiotensin receptor blockers for BP and proteinuria control. Recently, sodium-glucose cotransporter-2 inhibitors have been shown to reduce the risk of progression of CKD in patients with primary IgA nephropathy and albuminuria in a prespecified secondary analysis of the DAPA-CKD trial (53). However, the role of sodium-glucose cotransporter-2 inhibitors in hepatic IgA nephropathy is not known.

Hepatitis C– and Hepatitis B–Associated Glomerulopathies. With the advent of new antiviral therapies, patients with hepatitis B (HBV) and hepatitis C (HCV) infections are achieving viral suppression and cure, respectively. However, patients can still develop immune-complex GN despite viral suppression as B cell dysregulation may persist (54).

Hepatitis C–Associated Glomerulonephritis. A glomerular pattern of injury encountered in patients with cirrhosis due to HCV is that of membranoproliferative GN (44). Cryoglobulinemia is often present. Patients can present with nephrotic and nephritic manifestations with impaired kidney function in up to 25% of the cases, often as AKI (44). KDIGO and American Association for the Study of Liver Diseases recommend direct-acting antiviral agents as an initial therapy for HCV-associated GN in patients with stable kidney function and subnephrotic proteinuria (55). In patients who do not respond solely to antivirals, especially in those with cryoglobulinemic features, addition of immunosuppression with rituximab is indicated. Plasma exchange along with immunosuppression may be needed for cryoglobulinemic flares with nephrotic syndrome and/or rapidly progressive GN (45).

Hepatitis B and Glomerulonephritis. GN associated with HBV can occasionally lead to AKI in cirrhosis. Membranous and membranoproliferative patterns of glomerular injury and type 3 cryoglobulinemia have been reported in association with HBV (56). HBeAg is small and cationic, and it gets deposited in the subepithelial space, precipitating podocyte injury (46). HBsAg and HBcAg are larger in size and anionic with restriction of IgG-HbsAg to the subendothelial space, precipitating endocapillary injury (46). Immunosuppressive agents may accelerate HBV replication and should be avoided in patients with untreated HBV (46). Patients with replicative HBV (HBeAg positivity and/or viral DNA levels of >2000 IU/ml) and GN should receive treatment with nucleoside (lamivudine and entecavir) or nucleotide (tenofovir and adefovir) reverse transcription inhibitors. KDIGO additionally recommends a trial of plasma exchange if cryoglobulin levels >500 mg/dl in patients with symptomatic vasculitis and HBV-associated cryoglobulinemia (57).

Renal Venous Congestion

In decompensated cirrhosis, renal vein congestion as a cause of AKI can be encountered due to abdominal compartment syndrome/intra-abdominal hypertension caused by tense ascites or in congestive heart failure from right ventricular failure from cirrhotic cardiomyopathy and portopulmonary hypertension (58). In compensated cirrhosis, cardiac output is increased to maintain circulatory homeostasis. With disease progression, cirrhotic cardiomyopathy—a state of dysregulated systolic and diastolic function in response to physical stress with no overt left ventricular failure at rest—may develop (59). The pathophysiology relates to impaired β-adrenergic receptor signaling pathways and increased activity of nitric oxide and the endocannabinoid system (60). Large-volume paracentesis to relieve abdominal pressure and renal vein congestion has been reported to increase urine output with a transient rise in GFR in patients with decompensated cirrhosis (19).

Obstructive Acute Tubular Injury

A combination of midodrine, octreotide, and albumin is often used to manage HRS-1. Midodrine has α-adrenergic effects and increases vesical sphincter tone and detrusor-sphincter dyssynergia, leading to a risk of urinary retention and hydroureteronephrosis, particularly in the elderly and those with neurogenic bladder (61). Hence, we recommend vigilance in patients with decompensated cirrhosis who receive midodrine as part of treatment for HRS-1.

Role of Kidney Replacement Therapy in the Management of AKI

The management of patients with AKI and liver disease is dictated by the underlying etiology. With failure of medical management, KRT is considered on a case-by-case basis. For patients who are deemed eligible for liver transplantation, KRT can be offered until kidney function recovers. For patients who are being evaluated for liver transplantation and disposition is not clear, it is reasonable to offer KRT while deciding on the transplantation status. However, for patients who are ineligible for liver transplantation, a

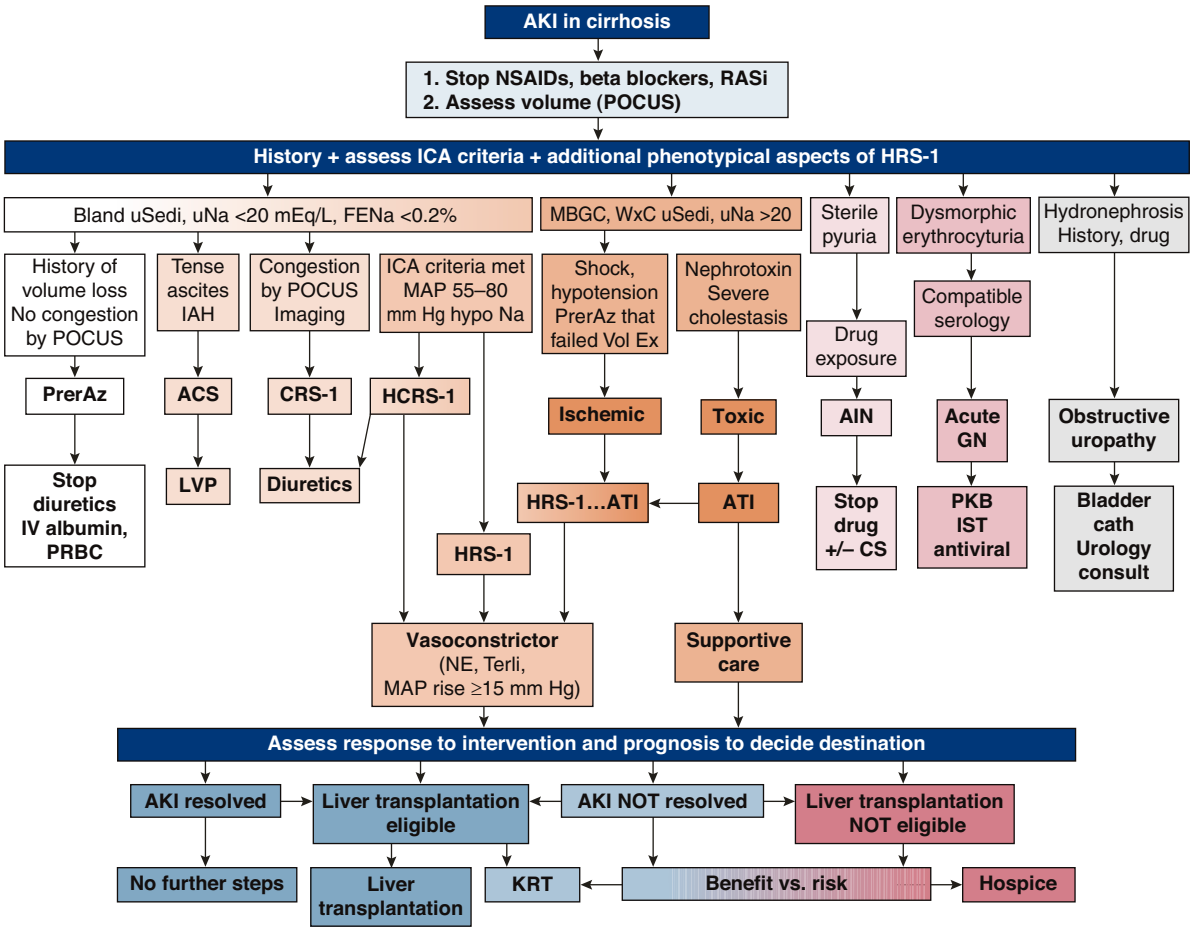

Figure 4. | **Algorithm to guide the diagnosis and management of in-hospital AKI in the context of cirrhosis.** Discontinuation of nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, and renin-angiotensin system inhibitors (RASis) applies to all cases. Upon recognition of AKI, objective assessment of volume status should incorporate point-of-care ultrasonography (POCUS) coupled with a careful review of diagnostic elements suggestive of HRS-1 not restricted to those listed as the International Club of Ascites (ICA) criteria. Clinical history and findings in urinary sediment microscopy (uSedi), urine sodium (uNa), and fractional excretion of sodium (FeNA) should then guide the next steps in the differential diagnosis. History of volume loss and POCUS findings can point to prerenal azotemia (PrerAz). In those cases, discontinuation of diuretics, volume expansion (Vol Ex) with intravenous (IV) albumin, and/or packed red blood cells (PRBCs), when appropriate, are warranted. Evidence of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) should prompt therapeutic large-volume paracentesis (LVP). Echocardiography, POCUS findings, and pulmonary congestion by imaging may suggest cardiorenal syndrome type 1 (CRS-1) resulting from cirrhotic cardiomyopathy, high-output heart failure, or severe portopulmonary hypertension. In those cases, diuretics may be indicated. When all ICA criteria are met and other phenotypical elements consistent with HRS-1 are present (*i.e.*, hyponatremia [hypo Na] and MAP denoting "low normal" BP), HRS-1 must be considered, and vasoconstrictor therapy should be initiated (with norepinephrine [NE] or terlipressin [Terli], MAP rise goal of ≥15 mm Hg). There is insufficient evidence supporting the use of the combination of midodrine and octreotide in HRS-1. Presence of abundant "muddy brown" granular casts (MBGCs) and/or waxy casts (WxCs) in uSedi is consistent with ATI that can originate from ischemic (shock, prolonged PrerAz, or PrerAz that fails Vol Ex) or toxic (nephrotoxins or cholemic) insults. In those cases, supportive care is the cornerstone of management. It is important to recognize the possibility of overlap of ATI and HRS-1 physiology or of HRS-1 and CRS-1 (HCRS-1). Sterile pyuria in the context of exposure to a drug should raise suspicion for acute interstitial nephritis (AIN) and should be managed by drug discontinuation and consideration for corticosteroids (CSs). Dysmorphic erythrocyturia and/or cellular casts in uSedi and viral or autoimmune serology may suggest acute GN. Percutaneous kidney biopsy (PKB) may be needed to guide the need for immunosuppression therapy (IST) and/or antiviral therapy. Obstructive uropathy can rarely occur in patients exposed to midodrine or due to other causes unrelated to cirrhosis. Bladder catheterization (cath) and consultation with urology are appropriate in this setting. After a therapeutic intervention has been executed, it is critical to assess the clinical response to the intervention, liver transplantation eligibility, need for KRT, and risks and benefits of each intervention to be able to choose the optimal treatment approach at this stage. Thus, hospice care may be the most appropriate step in some cases.

multidisciplinary approach, including patients and their families, needs to be considered, weighing the potential risks and benefits. With no signs of AKI reversibility and multiorgan failure in an intensive care setting, offering KRT could be deemed futile (62). Continuous KRT is the modality of choice for hemodynamically unstable patients, whereas intermittent hemodialysis can be attempted in more stable patients (63).

Summary

The burden of kidney dysfunction in patients with cirrhosis is rising (1,4). AKI in patients with cirrhosis is not limited to HRS-1. The differential diagnosis includes other cirrhosis-specific causes (*e.g.*, prerenal gastrointestinal losses, cirrhotic cardiomyopathy, portopulmonary-related venous congestion, *etc.*) and noncirrhosis-specific causes (*e.g.*, medication effect, acute tubular injury, obstructive uropathy, *etc.*). Management should be tailored according to the cause of AKI (Figure 4). Vasoconstrictor therapy is a specific treatment for those diagnosed with HRS-1. KRT should be offered to patients who fail medical therapy and either are eligible for liver transplantation or have a meaningful chance of kidney recovery or benefit from the intervention.

Disclosures

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Author Contributions

G. Cullaro, S.R. Kanduri, and J.C.Q. Velez conceptualized the study; J.C.Q. Velez was responsible for formal analysis; G. Cullaro, S.R. Kanduri, and J.C.Q. Velez were responsible for methodology; G. Cullaro and J.C.Q. Velez were responsible for project administration; G. Cullaro and J.C.Q. Velez were responsible for visualization; G. Cullaro, S.R. Kanduri, and J.C.Q. Velez wrote the original draft; and G. Cullaro, S.R. Kanduri, and J.C.Q. Velez reviewed and edited the manuscript.

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