Hyponatremia in Cirrhosis: An Update

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Hyponatremia is frequently seen in patients with ascites secondary to advanced cirrhosis and portal hypertension. Although not apparent in the early stages of cirrhosis, the progression of cirrhosis and portal hypertension leads to splanchnic vasodilation, and this leads to the activation of compensatory mechanisms such as renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and antidiuretic hormone (ADH) to ameliorate low circulatory volume. The net effect is the avid retention of sodium and water to compensate for the low effective circulatory volume, resulting in the development of ascites. These compensatory mechanisms lead to impairment of the kidneys to eliminate solute-free water in decompensated cirrhosis. Nonosmotic secretion of antidiuretic hormone (ADH), also known as arginine vasopressin, further worsens excess water retention and thereby hyponatremia. The management of hyponatremia in this setting is a challenge as conventional therapies for hyponatremia including fluid restriction and correction of hypokalemia are frequently inefficacious. In this review, we discuss the pathophysiology, complications, and various treatment modalities, including albumin infusion, selective vasopressin receptor antagonists, or hypertonic saline for patients with severe hyponatremia and those awaiting liver transplantation.

Am J Gastroenterol 2020;00:1–11. https://doi.org/10.14309/ajg.0000000000000786

INTRODUCTION

Hyponatremia is typically defined as a serum sodium concentration of less than 135 mEq/L. In patients with cirrhosis, by consensus, hyponatremia has been defined as a serum sodium of less than 130 mEq/L. In 1 study from Europe that included both inpatients and outpatients, 21.6% of patients with cirrhosis had sodium less than 130 mEq/L, 5.7% had less 125 mEq/L, and 1.2% had less than 120 mEq/L (1). Patients with cirrhosis and hyponatremia usually have decompensated liver disease, and hyponatremia before liver transplantation (LT) maybe an important prognostic marker in the post-transplant period (2). Although hyponatremia is a common electrolyte disorder encountered by physicians in clinical practice, its management in the setting of advanced liver cirrhosis can be challenging.

PATHOGENESIS

The pathophysiology of hyponatremia in cirrhosis is complex and multifactorial. Hyponatremia in cirrhotic patients is predominantly hypervolemic or dilutional. In less than 10% of the cases, hyponatremia is because of excessive diuretic use or gastrointestinal losses such as diarrhea (hypovolemic hyponatremia) (3). By contrast, hypervolemic hyponatremia is attributed to the impairment of the kidneys to eliminate solute-free water, resulting in a disproportionate accumulation of water in relation to sodium (4). Rarely, low serum sodium could be because of pseudo hyponatremia as in hyper triglyceridemia (>1,500 mg/dL) or because of high serum proteins (>10 g/dL), or translocational as in hyperglycemia, or because of mannitol infusion. In true hyponatremia, serum osmolality will be less than 280 mosmol/Kg, whereas in pseudo hyponatremia, serum osmolality will be normal (280–295 mosmol/Kg) and in translocational hyponatremia, serum osmolality will be more than 295 mosmol/Kg (Figure 1).

Splanchnic vasodilation

Splanchnic vasodilation, a hallmark of advanced cirrhosis and portal hypertension, results in reduced effective arterial blood volume that not only triggers antidiuretic hormone (ADH) secretion but also activates the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (Figure 2a,b). A myriad of factors is involved in the pathogenesis of splanchnic arterial vasodilation, the most important mediator being nitric oxide released from the endothelial cells (5–7). Other factors that contribute to vasodilation include vasoactive intestinal peptide, substance P, platelet activating factor, carbon monoxide, prostacyclin, hydrogen sulfide, endocannabinoids, adrenomedullin, and endothelium-derived hyperpolarizing factor (7,8). The systemic spread of bacterial products called pathogen-associated molecular patterns and danger-associated molecular patterns released by inflammation, apoptosis, and necrosis of the hepatocytes are also known to play a key role in this process (9). The bacterial translocation and neurohormonal activation ultimately lead to splanchnic arteriolar vasodilation, renal vasoconstriction, and retention of sodium and water leading to hyponatremia.

Extrahepatic hyporeactivity to vasoconstrictor agents such as thromboxane A2, angiotensin 2, ADH, and endothelin 1 is another characteristic feature seen in advanced cirrhosis that contributes to splanchnic vasodilation. Under normal conditions, smooth muscle contraction is mediated by G protein coupled transmembrane receptors such as alpha −1 adrenoceptor, angiotensin II type 1 receptor, and vasopressin receptor (4,5). Stimulation of these receptors activates protein kinase C that in

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Received March 23, 2020; accepted June 9, 2020; published online August 6, 2020

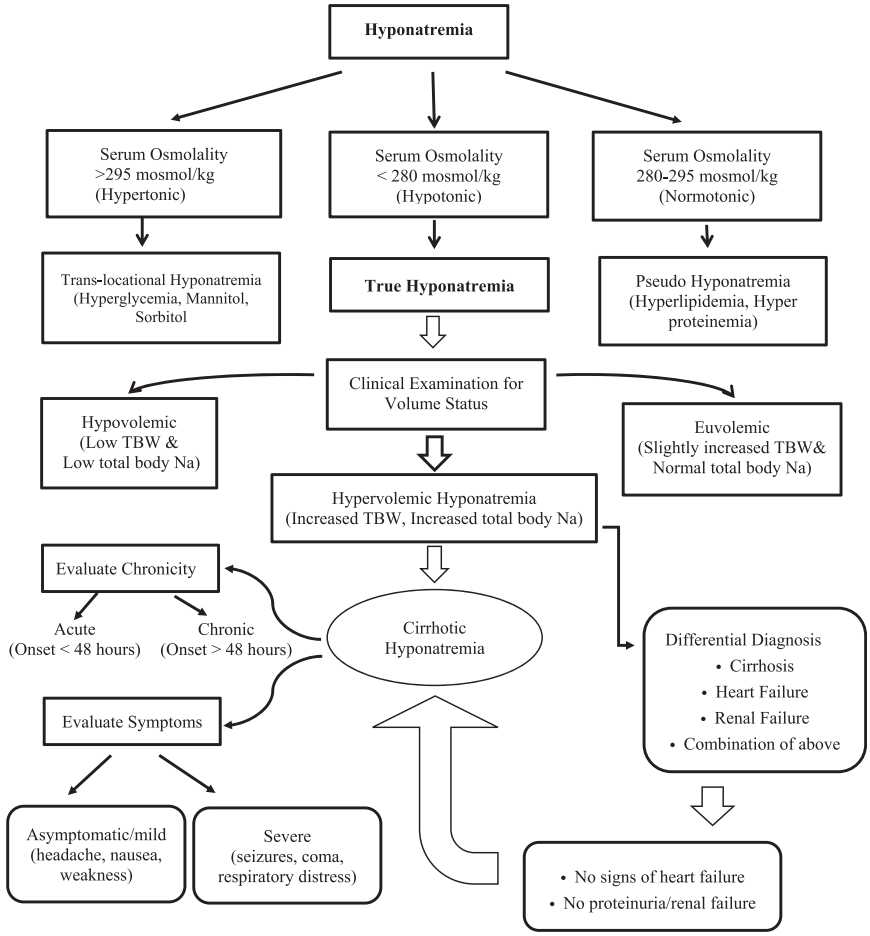

Figure 1. An algorithm for the diagnosis of hyponatremia in cirrhosis.

turn induces intracellular Ca^{2+} resulting in myosin light chain kinase phosphorylation and ultimately vascular smooth muscle contraction (10). It has been suggested that hyporesponsiveness to vasoconstrictors may be secondary to a functional defect at the level of the G protein receptor rather than an impairment of the signal transduction pathways (11).

Role of ADH

One of the key drivers for hyponatremia in cirrhosis is antidiuretic hormone (ADH), a polypeptide synthesized in the hypothalamus and stored in the posterior pituitary. The release of ADH from the neurohypophysis is regulated by changes in intravascular volume and serum osmolality. Under normal physiological conditions, the intact osmotic receptors in the hypothalamus interact with the renal tubules to regulate urinary volume and thereby maintain total body water within a narrow range (1.5–3 L/d), although under extreme conditions urine output can range from 0.5 L to 20 L depending on water intake and loss (4). Osmotic and nonosmotic stimuli trigger the secretion of ADH that initiate a cascade of events in the collecting ducts resulting in marked increase in water permeability compared with its basal state (Figure 3a,b). Nonosmotic stimuli (hypovolemia), that seem to play a predominant role (in contrast to osmotic stimuli under normal physiological conditions) in decompensated cirrhosis, activate baroreceptors located in the atria, ventricle, aortic arch, and carotid sinus via the parasympathetic pathway (5,6). These cascade of events trigger the release of ADH which then binds to V2 receptor on the basolateral membrane of the collecting ducts and thereby increasing intracellular levels of cyclic adenosine monophosphate and protein kinase A. This causes translocation of cytoplasmic vesicles carrying water channel protein (AQP2) to the apical membrane of the collecting duct rendering them permeable to large volumes of water, resulting in increase in total body water content and subsequent hypervolemic or dilutional hyponatremia (5,6).

CLINICAL IMPLICATIONS OF HYPONATREMEIA IN CIRRHOSIS

Clinicians need to be aware that rather than the absolute reduction in serum sodium, it is the rapidity of fall in sodium that determines the clinical outcome in this patient population. Nonetheless, it is difficult to identify and accurately define the consequences of hyponatremia per se in advanced cirrhosis because its manifestations are often difficult to distinguish from that of hepatic encephalopathy (HE). The symptoms are often nonspecific and include nausea, anorexia, mild cognitive impairment, headache, gait disturbance, and falls. Patients with a serum sodium >125 mEq/L are often asymptomatic, and symptoms usually arise when the sodium falls below this level (12). These patients are also known to have a reduced quality of life and frequent hospitalizations owing to a higher incidence of liver-related complications (13,14). Moreover, a small study has shown that correction of hyponatremia is associated with an improvement in cognition, health-

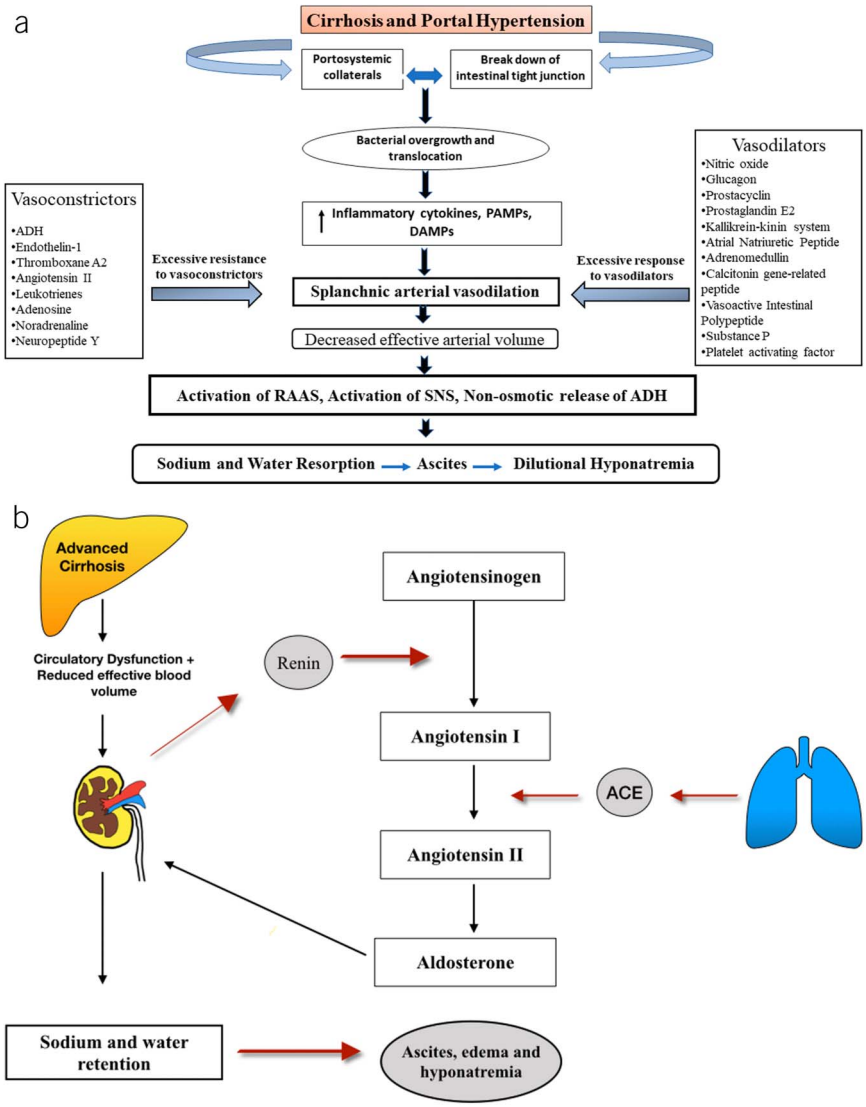

Figure 2. (**a**) Pathophysiology of splanchnic vasodilation, via activation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), and release of antidiuretic hormone (ADH). (**b**) Pathways of activation of renin-angiotensin-aldosterone system (RAAS).

related quality of life, and companion burden (14). A large prospective multicenter study that evaluated a large number of cirrhotic patients (n = 995) showed that hyponatremia was associated with a higher prevalence of refractory ascites, higher requirement of large-volume paracentesis, and a shorter time interval between paracentesis. There was also a higher incidence of HE, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS) in this group of patients (1). Another study in critically ill cirrhotic patients found that serum sodium <135 on the day of hospitalization was an independent risk factor for both in-hospital mortality and 6-month mortality (15).

Association between HE and hyponatremia

Hypotonic hyponatremia results in shift of water from the extracellular compartment to astrocytes to maintain osmotic balance that result in swelling of the astrocytes. Given the closed anatomic space of the skull, expansion of brain cells is limited; hence, they acclimatize by expulsion of intracellular solutes in the opposite direction so as to reduce intracellular osmolality (6). This is a two-step process that starts with movement of cations such as potassium across the cell membrane, followed by organic osmolytes such as myoinositol, glutamine, choline, and taurine (6). Regulation of brain volume by this process and subsequent attempt to main osmotic balance is pertinent to prevent severe neurological complications that could potentially result from hyponatremia. This defensive adaptive mechanism of astrocytes requires time and is seen in chronic hyponatremia, but not in acute hyponatremia because the astrocytes do not get time to adapt to the rapid change in serum sodium.

It has been suggested that low grade cerebral edema seen in hyponatremia may play a role in the pathogenesis of HE (16). Hyperammonemia (increased glutamine), oxidative stress, and inflammatory cytokines associated with advanced cirrhosis cause activation of N-methyl-D-aspartate glutamate receptors resulting in astrocyte swelling and dysfunction of the glial-neuronal communication pathway (17). Hyponatremia further aggravates astrocyte swelling and poses a secondary hit for the development of overt HE. A study in Spain found that hyponatremia (Na <130 mEq/L) was a

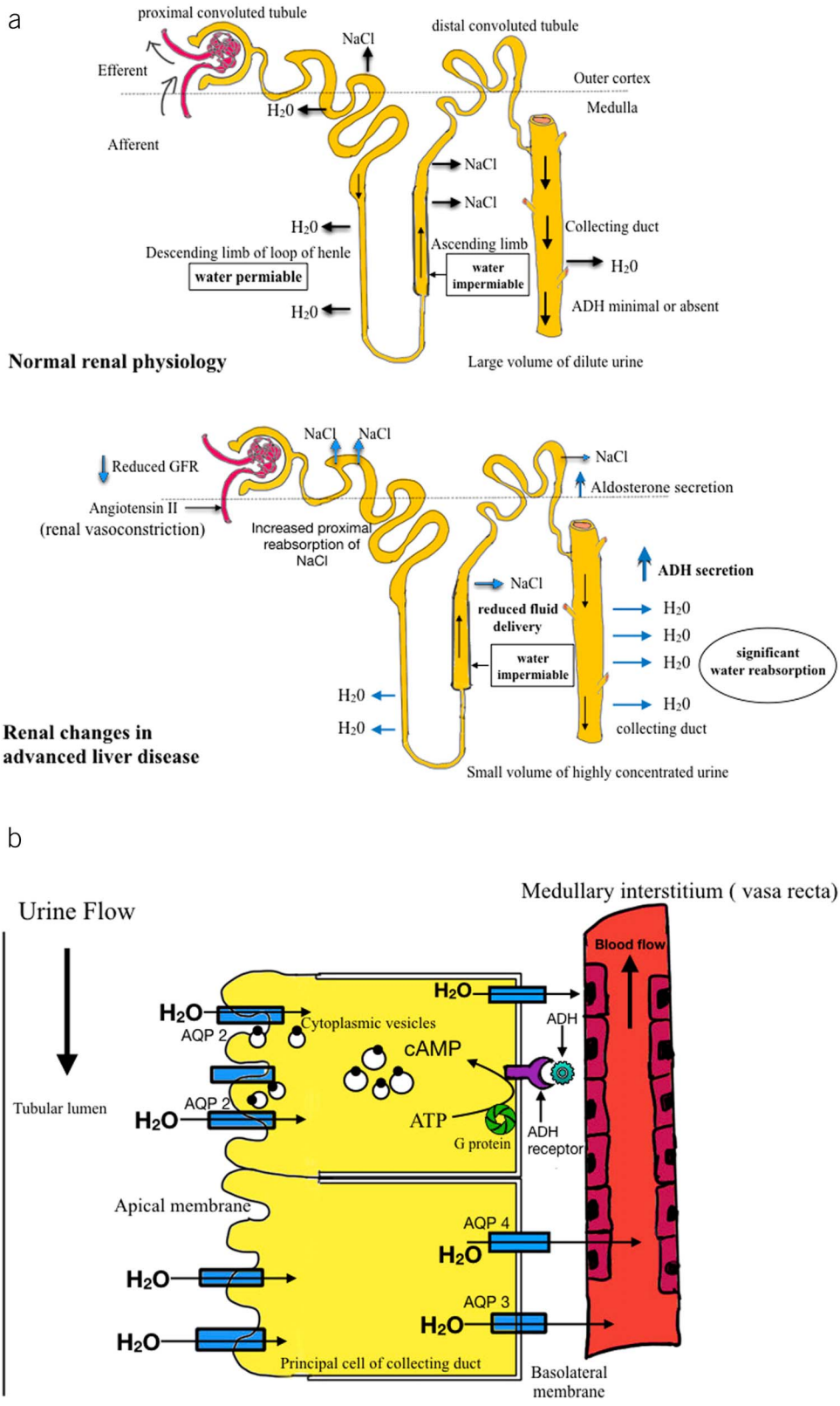

Figure 3. (**a**) Normal renal physiology of sodium and water homeostasis (top panel) and renal changes in portal hypertension leading to decrease in water clearance (bottom panel). (**b**) Mechanisms of excessive water absorption mediated by the release antidiuretic hormone (ADH).

strong and independent predictor for development of HE in cirrhotic patients with a hazard ratio (HR) of 8.36 (17). Furthermore, they also found that patients in whom serum sodium concentration decreased by at least 5 mEq/L during the first 3 months of the study had an increased risk of developing HE compared with patients in whom sodium level did not decrease by 5 mEq/L ($P < 0.05$).

Multiple studies have also demonstrated that the cerebral concentration of myoinositol and choline containing compounds are depleted in patients with cirrhosis and hyponatremia, which further disrupts the natural volume regulatory defense mechanisms and worsening symptoms of HE (18). Nonetheless, given the fact that hyponatremia in cirrhosis is a chronic process, severe neurological complications are usually uncommon.

Refractory ascites, renal failure, and hyponatremia

Refractory ascites (RA) develops in 5%–10% of patients with cirrhosis. RA is characterized by severe ascites (grade 3) often requiring repeated paracentesis despite maximum (or tolerated) diuretic regimen (spironolactone 400 mg/d and furosemide 160 mg/d) and sodium restriction, or early recurrence of grade 2 or grade 3 ascites despite large volume paracentesis (19–21). Diuretic induced complications such as HE, renal failure, hyponatremia, and hypo/hyperkalemia are also frequently seen in RA. The pathogenesis of RA involves similar pathways as hyponatremia. It is the end stage of progressive splanchnic vasodilation leading to arterial under-filling and subsequent activation of RAAS, sympathetic nervous system, and ADH (19,21). This leads to avid retention of sodium at the proximal convoluted tubule and an inability to excrete free water leading to hypervolemia. Moreover, a combination of decreased oncotic pressure (secondary to hypo albuminemia) and an increased intestinal capillary permeability leads to massive fluid accumulation in the peritoneal cavity. Decreased renal perfusion and subsequent renal insufficiency worsens ascites by decreasing the efficacy of diuretics, leading to RA.

The incidence of RA was to be higher in patients with hyponatremia (29.4% when sodium $<$ 130 mEq/L vs 18.5% when sodium is 131–135 mEq/L, $P < 0.001$); in this study, only 13.5% patients with normal serum sodium developed RA (1). RA is associated with a very poor prognosis, and in 1 study from Spain that followed 263 cirrhotic patients with ascites for 41 months found that 5-year probability of developing RA was only 11.4% but among those who developed RA, the 1-year survival was only 31.6% (22).

Based on the pathophysiology of ascites and hyponatremia, it is to be expected that a subset of these patients will progress to develop acute kidney injury (AKI) or HRS. The probability of developing HRS in ascites is anywhere between 11% and 40%, and hyponatremia is an independent risk factor for renal failure in patients with ascites (22,23). As to be expected, renal failure is more common in patients with hyponatremia with ascites (28%, 33.6%, and 40.5% when sodium is $>$ 135 mEq/L, 131–135 mEq/L, and $<$130 mEq/L, respectively) (1). Although the relationship is not linear, ascites, hyponatremia, and renal dysfunction are interrelated and is a reflection of progressive splanchnic vasodilation and compensatory mechanisms. Additional stresses such as SBP, infections, and gastrointestinal hemorrhage and medications including diuretic could further precipitate or worsen renal function. Large volume paracentesis in patients with refractory ascites can lead to more reduction of effective arterial volume, which can further lead to a condition known as postparacentesis circulatory dysfunction (PPCD) (24). PPCD is characterized by renal failure, hyponatremia, HE, and decreased survival. Plasma volume expansion with intravenous salt poor albumin at a dose of 8 g per liter of ascitic fluid removed, when more than 5 L of ascitic fluid is removed at any single session, has been shown to prevent not only PPCD but also hyponatremia and mortality (25).

Hyponatremia in acute on chronic liver failure

Acute on chronic liver failure (ACLF) is characterized by rapidly progressive liver failure in patients with established chronic liver disease resulting in multiorgan failure and a very high short-term mortality. Hyponatremia, seen in 22%–24% of patients, is a poor prognostic predictor in those with ACLF (26,27). In one study of 1,341 hospitalized patients with cirrhosis and acute decompensation, the prevalence of hyponatremia was 2-times higher in those with ACLF as compared to those without ACLF (24.3% vs 12.3 %, $P < 0.001$) (27). Patients with ACLF and hyponatremia were sicker and had a lower 90-day survival (35.8% vs 58.7%, $P = 0.001$) as compared to those without hyponatremia. Another small study showed that hyponatremia is an independent risk factor for progression into severe ACLF ($\geq$class 2) and death in hospitalized patients with cirrhosis and bacterial infection (SBP, urinary tract infection, pneumonia, or cellulitis) (28). Seventy percent of patients in this cohort with baseline hyponatremia and higher Model for End-Stage Liver Disease (MELD) scores developed ACLF. Chronic Liver Failure (CLIF) Consortium Acute Decompensation score has been proposed to estimate the prognosis of hospitalized cirrhotic patients with acute decompensation who do not develop ACLF. This score is based on the age of the patient, serum creatinine, INR, WBC count, and sodium levels. The CLIF Consortium Acute Decompensation score has been shown to be more accurate than MELD and MELD-Na score in predicting the outcome of these patients (29).

Although American Association for the Study for Liver Disease recommends albumin infusion after large volume paracentesis only when $>$ 5 L of ascitic fluid is removed, in those with ACLF this threshold may be lower (30,31). In an randomized study, paracentesis ($<$5 L) for grade 3 ascites in patients with ACLF without albumin infusion (n = 40) was associated with an increased incidence of hyponatremia (67.5% vs 22.5%, $P < 0.001$), AKI (62.5% vs 30%, $P = 0.001$), and in-hospital mortality (62.5% vs 27.5%, $P = 0.003$) compared with patients (n = 40) who received albumin (31). Although this was a small study, it reinforces the importance of maintaining the delicate intravascular volume in patients with advanced cirrhosis.

Implications for liver transplatation

Effective January 2016, United Network for Organ Sharing incorporated serum sodium into MELD score (MELD-Na) for organ allocation in registrants with MELD $>$11 after multiple studies indicated that addition of serum sodium concentration better predicts waitlist mortality in candidates awaiting LT compared with MELD alone (32). In patients awaiting LT, each mmol reduction in serum sodium between 125 and 140 mEq/L was associated with a hazard ration of 1.05 (33). One of the concerns of incorporating serum sodium into organ allocation system is laboratory variations in serum sodium measurements or fluctuations in serum sodium after therapeutic interventions (34). In addition, serum sodium could be deliberately manipulated in both directions by therapeutic interventions or fluid intake. Although decreasing serum sodium by increased water intake or diuretics may favor the patient by increasing MELD-Na, treatment of hyponatremia by fluid restriction, or vaptans may mask the true disease state.

Although it is indisputable that hyponatremia before LT is associated with increased intensive care unit length of stay, hospital length of stay, mechanical ventilation, sepsis, renal failure, and neurological complications, there are conflicting reports regarding the impact of pretransplant hyponatremia on post-LT survival (35–39). According to one study in the United States that analyzed 2,175 patients in the pre-MELD era (before 2002) using

a large multicenter LT database, of which 31% had hyponatremia (Na <135mEq/L) before transplant, the investigators found no change in 90-day post-LT survival in this group of patients as compared to recipients with normal sodium concentration (35). Similar observations were also made in other studies (40,41). However, a study from the United Kingdom that consisted of 5,152 LT recipients found that patients with sodium level <130 mEq/L (10%) had a higher risk-adjusted mortality at 3 years (HR −1.28; $P < 0.02$) as compared to patients with normal sodium (the excess mortality was confined to the first 90 days post-transplant (HR 1.55; $P < 0.002$) (36). Recipient hypernatremia (Na > 145 mEq/L) was also associated with increased 90-day mortality. Another single-center study from Spain that consisted of a relatively small number of LT recipients (n = 241) also reported a reduced short-term survival in patients with hyponatremia (sodium <130 mEq/L) as compared to patients without hyponatremia (84% vs 95%, $P < 0.05$) and attributed this to an increased incidence of major complications such as sepsis, renal failure, and neurological disorders seen in this group of patients in the immediate post-transplant period (2). Nonetheless, according to the largest and the most recent study conducted in the MELD era (n = 19,537), pretransplant hyponatremia was not associated with decreased post-transplant survival (37).

It is interesting to note that although the European studies found that pretransplant hyponatremia had a detrimental impact on survival in the post-transplant period, this finding was not observed in the US studies. One possible explanation is that the recipients with hyponatremia in the UK study received a higher proportion of suboptimal donor liver as compared to patients without hyponatremia (21 % vs 17 %), and this could have had an impact on post-transplant survival (36,38). In addition, unlike the United States, there is no common organ allocation policy in European countries; therefore, recipients at the time of LT may have had more decompensated liver disease compared with their US counterparts (38).

Osmotic demyelination syndrome

Osmotic demyelination syndrome (ODS), a rare and potentially fatal complication characterized by destruction of the myelin sheath in the pontine and extrapontine areas of the brain such as cerebellum, cerebral cortex, subcortex, and thalamus is a consequence of rapid over correction of hyponatremia in the perioperative period (39,42). The rapid rise in extracellular sodium results in shrinkage of the glial cells leading to axonal shear damage, tight junction disruption, and apoptosis (39). The incidence of ODS in LT recipients is small and ranges from 0.5% to 1.5% (35,38,43,44). Apart from hyponatremia, other risk factors include severe hypophosphatemia, severe hypokalemia, hypoglycemia, previous history of HE, and male sex (38,45). According to 1 meta-analysis that investigated 59 cases of ODS in LT recipients, only 3.7% patients (n = 2) had serum Na <120 mEq/L, whereas most recipients (63%) had Na levels between 121 and 135 mEq/L (45). Rather than the absolute value of sodium, it is the overcorrection over a short period of time that poses the greatest risk for development of ODS. The use of crystalloids, blood products, continuous renal replacement therapy, and sodium bicarbonate to manage acidosis in the intraoperative period often contributes to this rapid change in sodium (38,46).

Clinical features of ODS include a wide spectrum of neurological manifestations that range from change in mental status to dysarthria, dysphagia, dystonia, ataxia, parkinsonism, and agitated delirium (39,45). In extreme cases locked in syndrome, persistent encephalopathy, quadriparesis, and seizures may be seen. ODS in LT recipients is associated with an increased risk of mortality and disability compared with non-LT recipients; moreover, LT recipients are less likely recover from the neurological complications of ODS compared with their counterparts. Diagnosis of ODS is confirmed by MRI brain and includes characteristic features such as hyperintense lesions demonstrated on T2-weighted and fluid-attenuated inversion recovery imaging in the central pontine and extrapontine structures, whereas hypointense lesions are seen on T1-weighted sequences (42,45). Serial imaging is recommended in suspected cases of ODS because changes on MRI brain may lag behind clinical symptoms by 1–4 weeks (46).

MANAGEMENT

It is imperative that clinicians distinguish hypervolemic hyponatremia from hypovolemic hyponatremia before treatment can be initiated. Hypovolemic hyponatremia is seldom seen in cirrhotic patients and is associated with excess diuretic use or gastrointestinal fluid loss because of diarrhea and vomiting. Hypovolemic hyponatremia, unlike hypervolemic hyponatremia, is characterized by the absence of ascites and edema; treatment involves discontinuation of diuretics and initiation of intravenous saline to expand plasma volume.

Treatment of hypervolemic hyponatremia is more difficult (Figure 4). Withholding diuretics can be challenging in cirrhotic patients because this is often associated with worsening of ascites requiring repeated paracentesis. There is evidence to suggest that quality of life could be improved with successful management of hyponatremia (14,47,48).

Water restriction

Traditionally fluid restriction (1–1.5 L/d) has been considered the first-line option for treating hyponatremia associated with cirrhosis. To be effective, fluid intake has to be limited to 500 cc/d below the combined 24-hour urine output and insensible losses (5). The goal is to achieve a state of negative water balance. Sodium restriction should be continued along with fluid restriction. However, adhering to strict water restriction is often difficult because of poor compliance, and patients may be asked to suck on ice chips to help quench the sensation of thirst resulting from increased ADH (5). Although commonly practiced, and recommended, clinical studies have shown limited efficacy with fluid restriction alone and if there is no improvement in serum sodium in the first 24–48 hours, other options should be considered (49,50).

Discontinuation of diuretics and correction of hypokalemia

Management of hypervolemic hyponatremia also includes temporary discontinuation of diuretics and cautious correction of hypokalemia. Sodium and potassium being osmotically active are exchangeable and as the supplemented potassium enters the cells, intracellular sodium shifts in the opposite direction causing serum sodium to rise even without exogenous administration (51). Correcting hypokalemia without accounting for the rise in serum sodium can result in rapid overcorrection of hyponatremia leading to ODS (52). Hypokalemia is also known to precipitate and worsen HE through increased ammoniagenesis in the kidney via production of renal glutaminase, which reiterates the importance of adequately managing this electrolyte abnormality (5,53).

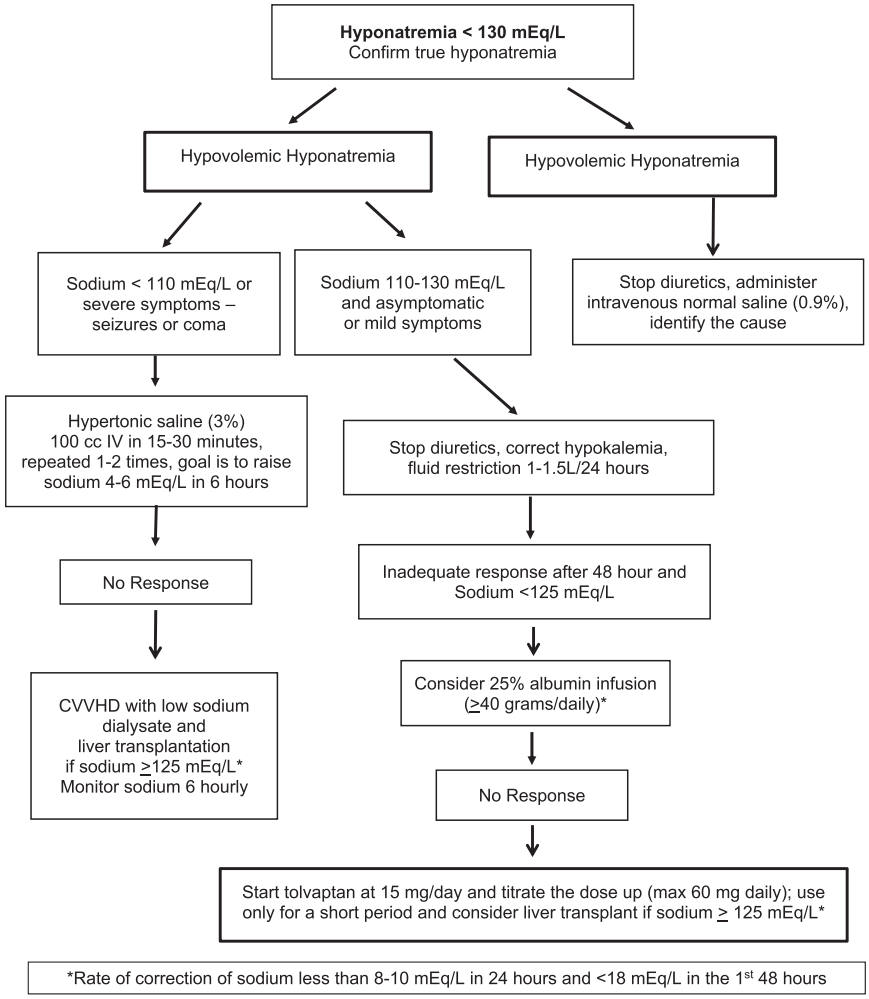

Figure 4. An algorithm for the management of hyponatremia in cirrhosis.

Albumin

Albumin infusion is another therapeutic option that may improve hyponatremia associated with cirrhosis. Although the exact mechanism is unknown, it is hypothesized that intravenous albumin can increase urinary free-water clearance by expanding intravascular volume, leading to a rise in serum sodium (54). A recent retrospective multicenter study, which analyzed 1,126 patients with cirrhosis with hyponatremia (Na $<$ 130 mEq) on hospital admission, reported a higher rate of hyponatremia resolution (69% vs 61%, $P = 0.009$) in patients who received IV albumin (n = 777) compared with those who did not (55). Patients in the study group received 25% albumin at a dose of 200 g (interquartile range 100, 400). Patients who received albumin infusion were also found to have a higher maximum Na (137.13 vs 135.00 mEq/L, $P < 0.0001$) and a much higher delta Na (8.47 vs 5.81 mEq/L, $P < 0.001$) compared with their counterparts. This study also demonstrated that infusion of albumin in cirrhotic patients, irrespective of its primary indication (SBP, AKI, postlarge volume paracentesis, or hyponatremia without other complications), was associated with an improvement in serum sodium levels. Moreover, the resolution of hyponatremia was associated with an improved 30-day survival.

Another open-label randomized clinical trial in Italy that analyzed the effect of long-term administration of human albumin in patients with cirrhosis and refractory uncomplicated ascites also had a favorable outcome in the resolution of hyponatremia. In this study, patients were randomized into 2 groups: standard medical treatment (SMT), which consisted of aldosterone antagonist and furosemide, and SMT plus albumin infusion and assessed outcome after 18 months (56). Patients received 20% human albumin infused at a dose of 40 g twice weekly for the initial 2 weeks, and then 40 g weekly thereafter. At the end of the trial, they found that the incidence rate of hyponatremia (Na $<$ 130 mEq/L) in the albumin group was lower than the SMT group with an incidence rate ratio of 0.51 ($P < 0.001$). Patients who received long-term albumin along with SMT were also found to have improved survival, improved quality of life, reduced number of hospital admissions and a reduction in the incidence rate of paracentesis, refractory ascites, SBP, and HE grade 3–4. Although the results from this study are promising, long-term albumin infusion is an expensive treatment modality that revolves around patient compliance, care coordination between health care providers, insurance companies, and home health agencies, and these factors may be cumbersome in the real world.

Hypertonic saline (3% Na)

Hypertonic saline (513 mEq/L Na) is usually not recommended for dilutional hyponatremia associated with liver cirrhosis

because the high salt content can lead to worsening of ascites, edema or pulmonary edema, and more importantly rapid overcorrection of serum sodium may lead to ODS. It is reserved for patients with profound hyponatremia (Na < 110 mEq/L) or symptomatic cases such as seizures, cardiopulmonary distress, or coma (5). It may also be an option in patients with severe hyponatremia awaiting LT in a few days (5,46).

Acute (<24 hour duration) symptomatic hyponatremia can be treated with a 100 cc bolus of 3% saline (100 cc over 15–30 minutes), and this may be repeated up to 3 times (a total of 300 cc) if symptoms persist (51,57). In acute cases, hypertonic saline infusion under close monitoring usually does not lead to neurological complications, although one has to be extremely cautious. The goal here is to raise serum sodium by 4–6 mEq/L in the first 6 hours. In chronic hyponatremia that is either symptomatic or severe (<110 mEq/L), hypertonic saline may be administered through a continuous infusion at a rate of 15–30 cc/hr (51,57). Serum sodium in such cases should not increase by more than 8 mEq/L per day, particularly in the first 24 hours. Because rapid overcorrection poses a risk for ODS in chronic hyponatremia, it is important that clinicians anticipate free water diuresis that may ensue after administration of hypertonic saline that could rapidly raise serum sodium (51). Desmopressin (DDAVP) may be an option in such instances and can help counter the rapid over correction (5).

DDAVP, an antidiuretic agent, is a synthetic analogue of vasopressin that acts on V2 receptors in the basolateral membrane resulting in increased water reabsorption, thereby reducing serum sodium concentration. This can be administered intravenously or subcutaneously at a dose of 1–2 μg and is repeated every 6–8 hours for 24–48 hours until target sodium is achieved (58). Traditionally, DDAVP was used for the treatment of diabetes insipidus and bleeding disorders such as von Willebrand disease. However, recent studies have demonstrated its efficacy in reducing sodium levels caused be inadvertent overcorrection of hyponatremia. One study that analyzed efficacy of DDAVP in 20 intensive care unit patients with severe hyponatremia (Na < 120 mEq/L) found that the rate of sodium correction reduced from 0.81mEq/L per hour (without DDAVP) to 0.02 mEq/L after DDAVP administration (59). This was also associated with a significant rise in urine osmolality (86 vs 209 mEq/L, $P = 0.002$, before DDAVP vs after DDAVP respectively) and a significant decrease in urine output (650 vs 93.5 mL/hr, $P = 0.003$, before DDAVP vs after DDAVP, respectively). DDAVP should ideally be administered proactively anticipating a rapid rise in serum sodium in patients who are at high risk for ODS rather than a reactive or rescue strategy, where DDAVP is administered after overcorrection of serum sodium because this approach has been found to be less efficacious (60,61).

Vasopressin receptor antagonists

Vasopressin receptor antagonists or vaptans are a class of nonpeptide drugs that block the action of ADH on V1 and V2 receptors. These drugs have been extensively studied over the past 2 decades for its potential to raise serum sodium concentration in euvolemic and hypervolemic hyponatremia. Although V1 receptors are found on the vascular smooth muscle cells, V2 receptors are located on the basolateral membrane of the renal collecting duct and antagonizing these receptors result in excretion of dilute urine and subsequent rise in serum sodium (62).

Conivaptan, a nonselective vasopressin receptor antagonist that blocks both V1 and V2 receptor, was approved by the Food and Drug Administration (FDA) in 2004. However, its actions on V1 receptor is associated with hypotension and variceal bleeding, which limits its use in cirrhosis (63). Tolvaptan is the only orally available vaptan and acts exclusively on V2 receptors. SALTWATER was a multicenter trial that analyzed the effect of tolvaptan on 111 patients with hyponatremia and followed them longitudinally for a mean of 1.9 years (64). Most patients in this study had hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion or heart failure, and only 18% had liver cirrhosis as a cause of hyponatremia. Tolvaptan was administered at a starting dose of 15 mg that was increased to 30 and 60 mg if the patient continued to have hyponatremia. At the conclusion of the trial, the investigators observed that the serum sodium increased from a mean of 130.8 mEq/L at baseline to >135 mEq/L, and this effect was more evident in patients with syndrome of inappropriate antidiuretic hormone secretion and congestive heart failure, whereas those with cirrhosis had a trend lower final serum sodium levels. Another small scale study (n = 9) in Europe that studied the efficacy of tolvaptan exclusively in patients with cirrhosis and severe hyponatremia (≤125 mEq/L) had disappointing results because only 2 of the 9 patients had improvement in serum sodium (>130 mEq/L) at the end of treatment (65). Similarly, a subanalysis of the SALT trial (a randomized controlled trial that analyzed efficacy of tolvaptan) that investigated the impact of tolvaptan in cirrhosis with mild and marked hyponatremia found no significant difference ($P < 0.08$) in the absolute change in serum sodium in the tolvaptan group (n = 35) vs placebo (n = 32) at day 30 compared with baseline in patients with marked hyponatremia (baseline Na < 130 mEq/L) (66).

In randomized controlled trials, tolvaptan use was associated with non–life-threatening adverse effects such as thirst, polyuria, and fatigue in 3%–10% of treated subjects (67). Although rare, serious complications such as ODS, acute renal failure and gastrointestinal hemorrhage have also been reported (68). Nonetheless, FDA has limited the use of tolvaptan to no longer than 30 days and recommends against its use in patients with underlying liver cirrhosis (69). The caution was issued following reports of elevated liver enzymes, and serious liver injury in 3 patients in a clinical trial where the efficacy of higher doses of tolvaptan was investigated in patients with autosomal dominant polycystic kidney disease (70). The safety of long-term use of vaptans beyond 1 month has not been established yet. The early enthusiasm with these drugs was tempered by reports of adverse events, absence of long-term benefit in survival, or other outcomes such as variceal bleeding, HE, SBP, HRS, or renal failure. The authors are of the opinion that tolvaptan may be used in patients with severe hyponatremia imminently awaiting LT because the potential for hepatotoxicity is less of a concern in this setting. The European Association for the Study of the Liver clinical practice guidelines for the management of patients with decompensated cirrhosis caution against the routine use of tolvaptan in hyponatremia and recommend its use only in controlled clinical trials (71).

Perioperative management of hyponatremia before LT

Optimal management of hypervolemic hyponatremia before LT can be challenging and requires a comprehensive and multidisciplinary approach by a team of hepatologists, nephrologists, anesthesiologists, and transplant surgeons. Efforts should be made to optimize serum sodium levels to >125 mEq/L before LT because patients with severe pretransplant hyponatremia are more prone to develop neurological complications such as ODS

after transplantation (35,41,72). Most LT programs in the United States do not proceed with transplant if sodium is <120 mEq/L, and currently, there are no specific protocols regarding perioperative management of severe hyponatremia (38).

The initial management strategy includes fluid restriction up to 1–1.5 L/d, correcting hypokalemia, discontinuing diuretics, and trial of 25% albumin infusion. Any potential precipitating causes and complications of cirrhosis also need to be addressed. Serum sodium should be checked every 6–8 hours in the preoperative and postoperative period so as to monitor for rapid over correction of more than 8 mEq/L in the first 24 hours. For patients anticipating LT within 7 days and whose serum Na remains less than 120 mEq/L despite the initial efforts, experts recommend a cautious trial of tolvaptan starting at a dose of 15 mg twice daily but not exceeding more than 120 mg/d (38). LT surgery per se is associated with severe blood loss and resuscitation efforts with fresh frozen plasma, and packed red blood cells or isotonic crystalloids often contribute to the rapid rise in serum sodium. Efforts should be made to reduce the sodium content of products used for volume resuscitation; for instance, 0.45% saline could be used instead of normal saline (0.9%) solution. Intraoperative metabolic acidosis that is commonly encountered in these patients could be reversed by trishydroxymethyl aminomethane (Tris or THAM) rather than sodium bicarbonate (38). Tris is a weak amino alcohol that can buffer acidosis by binding to both carbon dioxide and metabolic acids (73). Unlike sodium bicarbonate, it does not raise sodium levels nor does it produce carbon dioxide, making it an ideal buffer in the operating room for hyponatremic patients undergoing LT. Tris is however contraindicated in patients with acute kidney failure because it is renally excreted (73). Although tris is available in Europe, its production in the United States was discontinued in 2016 by its only manufacturer (Pfizer) (74).

For patients who receive a large Na load intraoperatively through blood transfusion and IV fluids, continuous venovenous hemofiltration (CVVH) with a diluted solution maybe an option to counter the rapid shift in serum sodium (38). According to recent but limited data, CVVH may be attempted perioperatively or intraoperatively in LT recipients with hyponatremia after reducing the sodium concentration of the replacement fluid (RF) (75,76). This can be achieved by adding sterile water to the dialysate solution (77). If during surgery a large volume of blood transfusion is anticipated, the dialysate solution can be diluted intraoperatively, and the rate of dialysis can be titrated depending on change in serum sodium. At present, all CVVH replacement solutions have a sodium concentration of 140 mEq/L and customized dialysis solutions are not available commercially for purchase (78). Hence, these hypotonic solutions would have to be prepared locally by the hospital pharmacy. The following formula can be used be to calculate the volume of sterile water to be added to the RF (75,78).

$$\text{Volume of sterile water to add} = \frac{\text{RF volume} \times (\text{Initial RF}[Na^+] - \text{Desired RF}[Na^+])}{\text{Desired RF } [Na^+]}$$

All commercially available dialysate solutions come at a standard RF volume of 5 L with an initial RF Na+ of 140 mEq/L. It is important to keep in mind that these hypotonic dialysate solutions will also have a reduced concentration of potassium and bicarbonate, hence necessary electrolyte replacements will have to be performed intraoperatively and postoperatively. Although early reports of this novel strategy are promising, there is a paucity of data on the efficacy and safety of this modality of treatment.

CONCLUSIONS

Hyponatremia is the most common electrolyte disorder seen in cirrhosis, and it is associated with an increased morbidity and reduced survival after LT. Hypervolemic hyponatremia develops gradually over a period of time, hence patients are often asymptomatic. Initial treatment involves fluid restriction, correcting hypokalemia, and discontinuing diuretics. Hypertonic saline maybe an option in acute symptomatic hyponatremia, although its use in cirrhosis is usually discouraged because of worsening ascites and risk of rapid overcorrection. The development of V2 receptor antagonists provided a promising treatment option; however, reports of serious liver damage has deterred its use in patients with underlying liver disease. LT remains the only curative treatment for hyponatremia associated with advanced liver disease. Every effort should be made to reduce rapid over correction of sodium in the perioperative and intraoperative period through a multidisciplinary approach. Once the symptoms because of hyponatremia are brought under control, the rate of correction should be less than 8 mEq/L per day to avoid irreversible neurological complications. In LT candidates, the peri- and intra-operative care should be coordinated by hepatologists, nephrologists, intensive care physicians, pharmacists, and anesthesiologists.

CONFLICTS OF INTEREST

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Specific author contributions: J.A. and S.J. wrote the first draft, J.A. and P.J.T. created the figures, P.J.T. revised and finalized the final manuscript.
Financial support: None to report.
Potential competing interests: None to report.

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