Hyponatremia in cirrhosis
Pathophysiology, prevalence, prognostic value, treatment

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Abstract

Hypervolemic hyponatremia is common in patients with decompensated cirrhosis, resulting from solute-free water retention caused by the stimulation of V2 receptors of the distal nephron by relatively high circulating levels of arginine vasopressin (AVP, a nonapeptide). A nonosmotic secretion of AVP by the hypothalamo-neurohypophysial system is responsible for high plasma AVP concentrations. This hypersecretion of AVP is triggered by a decrease in effective arterial blood volume and arterial pressure caused by splanchnic/systemic vasodilation. Hyponatremia is an independent predictor of mortality in patients with cirrhosis ; however, it is still unknown if hyponatremia by itself plays a role or if it is a simple marker of the severity of liver disease. Pharmacological treatments of hypervolemic hyponatremia using drugs that antagonize the binding of AVP to V2 receptors are under evaluation in patients with cirrhosis. (Acta gastroenterol. belg., **2008**, 71, **379-385**).

Low serum sodium concentration (i.e., hyponatremia) is a common finding in patients with cirrhosis (1). It is thought to result from solute-free water retention caused by relatively high circulating levels of the anti-diuretic hormone, arginine vasopressin (AVP, a nonapeptide) (2-4). This review summarizes current knowledge on pathophysiology, prevalence, clinical significance and treatment of hyponatremia in patients with cirrhosis.

Definition of hyponatremia

Before commenting on low serum sodium concentrations in cirrhosis, it is important to have some general information. Hyponatremia is defined as a decrease in the serum sodium concentration to a level below 135 mmol/L (14) or 136 mmol/L (4), depending on the authors. Tonicity (also known as effective osmolality) refers to the contribution to osmolality of solutes, such as sodium and glucose, which cannot move freely across cell membranes, thereby inducing transcellular movements of water (4). Whereas hypernatremia always denotes hypertonicity, hyponatremia can be associated with low, normal, or high tonicity (4). Dilutional hyponatremia, which is the most common form of hyponatremia, is caused by water retention. If water intake exceeds the capacity of the kidneys to excrete water, dilution of body solutes results, causing hypo-osmolality and hypotonicity. Hypotonic hyponatremia can be associated, however, with normal or even high serum osmolality if sufficient amounts of solutes that can permeate cell membranes have been retained (4,15). The nonhypotonic hyponatremias are hypertonic (or translocational) hyponatremia, isotonic hyponatremia, and pseudo-hyponatremia (4).

Hypotonic (dilutional) hyponatremia represents an excess of water in relation to existing sodium stores, which can be decreased, essentially normal, or increased (4). Retention of water most commonly is related to the presence of conditions that impair renal excretion of water ; in a minority of cases, it is caused by excessive water intake, with a normal or nearly normal excretory capacity (Table 1). Conditions of impaired renal excretion of water are categorized according to the characteristics of the extracellular-fluid volume ; hypotonic hyponatremia may be hypovolemic, hypervolemic or euvolemic (4,15). With the exception of renal failure, these conditions are characterized by high plasma concentrations of AVP despite the presence of hypotonicity (4).

Physiology of AVP

To have information on AVP physiology the *Database for Annotation, Visualization, and Integrated Discovery* (*DAVID) 2008*, was used (http://david.abcc.ncifcrf.gov/home.jsp) (16). *DAVID2008* it is an online graph theory evidence-based method to agglomerate heterogeneous and widely distributed public databases (16). Information was also searched manually on PubMed. The gene *arginine vasopressin* (name aliases : "*antidiuretic hormone*", "*neurophysin II*", "*diabetes insipidus*", "*neurohypophyseal*" ; approved symbol *AVP*, aliases *ARVP*, *ADH*, *VP*) is located on the 20p13 region. This gene encodes a 164 amino acids precursor protein consisting of AVP and two associated proteins, neurophysin II and a glycopeptide, copeptin. AVP is a posterior pituitary hormone which is synthesized in the supraoptic nucleus and paraventricular nucleus of the hypothalamus. Along with its carrier protein, neurophysin II, it is packaged into neurosecretory vesicles and transported

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Table I. — **Examples of causes of hypotonic (dilutional) hyponatremia**

Impaired capacity of renal water excretion	
Decreased volume of extracellular fluid	*Normal volume of extracellular fluid*
Renal sodium loss	Thiazide diuretics
Diuretic agents	Hypothyroïdism
Osmotic diuresis (e.g., glucose)	Adrenal insufficiency
Adrenal insufficiency	Syndrome of inappropriate secretion of anti-diuretic hormone
Salt-wasting nephropathy	Cancer
Extrarenal sodium loss	e.g., pulmonary tumors
Diarrhea, vomiting	Central nervous system diorders
Blood loss	e.g., hemorrhoge
Bowel obstruction, peritonitis	Drugs
	Desmopressin, Nonsteroidal anti-inflammatory drugs
	Pulmonary conditions
	Infections, positive-pressure ventilation
Increased volume of extracellular fluid	
Cirrhosis	
Congestive heart failure	
Nephrotic syndrome	
Renal failure (acute or chronic)	
Pregnancy	
Excessive water intake	
Primary polydypsia	
Sodium-free irrigant solutions	
Multiple tap-water enemas	
Accidental intake of large amounts of water	

axonally to the nerve endings in the neurohypophysis where it is either stored or secreted into the bloodstream. The precursor is thought to be activated while it is being transported along the axon to the posterior pituitary. AVP is a peptide consisting of nine amino acids (nonapeptide) and its amino acid sequence is Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly, with the cysteine residues forming a sulfur bridge.

AVP is secreted from the posterior pituitary gland in response to reductions in plasma volume or increases in the plasma tonicity. Secretion in response to reduced plasma volume is activated by pressure receptors in the veins, atria, and carotids. Secretion in response to increases in plasma osmotic pressure is mediated by osmoreceptors in the hypothalamus (17). The main stimulus for secretion of arginine vasopressin is increased tonicity of plasma. Reduced volume of extracellular fluid is a less sensitive mechanism (17).

AVP has multiple endocrine functions such as the regulation of body fluid homeostasis (17). AVP actions are mediated by plasma membrane receptors, which belong to the G protein-coupled receptor family characterized by the presence of seven transmembrane helices connected by three extracellular and three intracellular loops. Three different subtypes of AVP receptors, V1a, V1b, and V2, have been cloned. V1a receptor expression has been described in smooth muscle and liver, with the V1b receptor in the anterior pituitary and the V2 receptor in the kidney (16-18). Since AVP V2 receptors are responsible for the anti-diuretic effect of AVP, information will be given now on these receptors.

The expression of V2 receptors has been described in the basolateral membrane of all of the principal and inner medullary collecting duct cells (16,17). AVP activates a V2 receptor/G_s protein/protein kinase A pathway to stimulate the production of cyclic AMP (cAMP), and eventually, through several mechanisms, the exocytic insertion of aquaporin-2 water channels into the apical plasma membrane. This dramatically increases water permeability (typically 8- to 10-fold) and allows the osmotically driven movement of solute-free water from the kidney tubule lumen into the kidney interstitium, promoting solute-free water retention and thereby lowering plasma osmolality. The V2 receptor is subject to internalization in response to binding of AVP (18). Internalization may also be involved in the vasopressin escape phenomenon, a physiological adaptation to prevent water intoxication with prolonged AVP action (18).

Pathophysiology of hypotonic (dilutional) hyponatremia in cirrhosis

Hypervolemic Hyponatremia

In the 'classical' scenario, splanchnic and systemic vasodilation plays a crucial role in the cascade of events leading to solute-free water retention and hyponatremia (13). The 'classical' model can be summarized as follows. In early cirrhosis, the development of portal hypertension is associated with arteriolar vasodilation in the splanchnic circulation due to the local production (in arterial walls) of nitric oxide and other vasorelaxant substances (19,20). As the disease progresses, splanchnic arterial vasodilation increases and the systemic circulation becomes hyperdynamic, i.e., characterized by high cardiac output and low systemic vascular resistance (21,22).

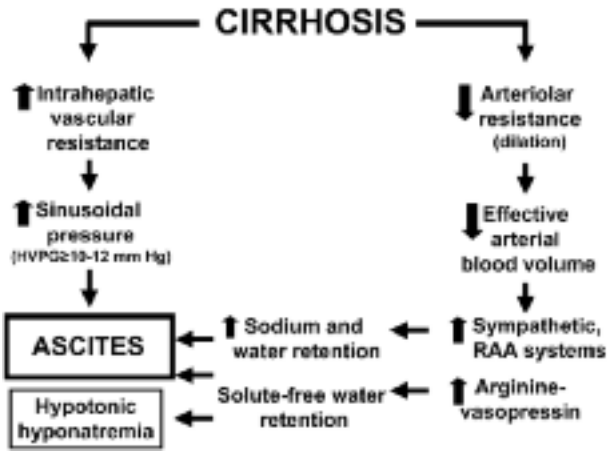

Fig. 1. — Mechanisms that are involved in sodium and water retention in cirrhosis. RAA, rennin-angiotensin-aldosterone system.

It should be noted that the decrease in splanchnic arterial tone plays a crucial role in the development of systemic vasodilation (22). Consequences of systemic vasodilation are decreases in effective arterial blood volume and arterial pressure (22). Arterial hypotension results in arterial baroreceptor unloading, reflex stimulation of the renin-angiotensin and sympathetic nervous systems (2,22-25), nonosmotic AVP secretion (1,2), sodium (26,27) and water retention (28) and the formation of ascites (Fig. 1). At this stage of decompensated cirrhosis, there is a marked neurohumoral hyperactivity and arterial pressure depends on arterial reactivity to the vasoconstrictor action of endogenous vasopressors, i.e., angiotensin-II, noradrenaline, and AVP (19). Since the splanchnic circulation is hyporeactive to the constrictor effect of pathophysiological concentrations of angiotensin-II, noradrenaline, and AVP, due to the local overproduction of vasorelaxant substances (19), the maintenance of arterial pressure is due to vasoconstriction in extra-splanchnic vascular territories including kidneys and brain (29). Some patients develop cardiac dysfunction (30) which may contribute to neurohumoral overactivation. Hepatorenal syndrome (HRS) is a complication of end-stage cirrhosis when there is extreme deterioration in effective arterial blood volume and marked arterial hypotension. In this syndrome, the homeostatic neurohumoral overactivity is very intense leading to marked renal (preglomerular) vasoconstriction and extreme decrease in renal blood flow (31).

Hypovolemic Hyponatremia

Little is known on mechanisms of this type of hyponatremia. Since it is triggered by diuretic overuse (32,33), and since diuretics are known to stimulate AVP release (see ref. 4 and Table 1), this mechanism may play a role in the reduction in serum sodium levels.

Prevalence of hyponatremia in cirrhosis

The prevalence of hyponatremia has been prospectively investigated in a large, multicenter, international study conducted in 997 patients with cirrhosis (1). The prevalence of low serum sodium concentration as defined by a serum sodium level $\leq$ 135 mmol/L, $\leq$ 130 mmol/L, $\leq$ 125 mmol/L was 49.4%, 21.6%, and 5.7%, respectively. Recently, a 2-year study investigated 13,940 patients on the waiting list for liver transplantation and showed that 31% of the patients had serum sodium levels < 135 mmol/L, including 2.5% of patients with serum sodium levels < 125 mmol/L (34).

It should be noted that in the survey of 997 patients, almost all patients had ascites and 84% of the patients received at least one diuretic and 60% spironolactone plus furosemide (1). Moreover, 42% of the patients were treated with large-volume paracentesis and 7% with transjugular intrahepatic portosystemic shunts (1). Therefore, this study probably included patients with true hypervolemic hyponatremia and also patients with hypovolemic hyponatremia

Preliminary results of a prospective study have shown that hypervolemic hyponatremia occurred in 90% of the patients and hypovolemic hyponatremia in the remaining 10% (35). Serum sodium concentrations were significantly lower in patients with hypovolemic hyponatremia than in those with the hypervolemic form (121 ± 5 mmol/L vs. 125 ± 4 mmol/L, respectively). Hypovolemic hyponatremia was found to occur in patients with previous hypervolemic hyponatremia (35).

Prognostic value of hyponatremia

Hyponatremia is Associated with the Severity of Cirrhosis

There is a clear correlation between the frequency of hyponatremia and the severity of the underlying liver disease. The above-mentioned large survey (1) has shown that the incidence of hyponatremia (defined as serum sodium concentrations $\leq$ 135 mmol/L) significantly differed between Child-Pugh grade C and grade A patients (62% vs. 23%, respectively). Interestingly, the incidence of hyponatremia was intermediate (41%) in grade B patients. Similarly, the incidence of hyponatremia (defined as serum sodium concentrations $\leq$130 mmol/L) significantly differed according to the Model for End-Stage Liver Disease (MELD) score (8,9) ; for example, it was ~34% in patients with MELD score $\geq$ 21, 8.7% with MELD score 14-21, and 4% with MELD score < 14 (9).

It should be emphasized that some patients develop hyponatremia while they have only moderate liver insufficiency as assessed by Child-Pugh class or the MELD score (6-9). Therefore, the 'classical' scenario in which the development of hyponatremia depends on the severity of cirrhosis and the existence of marked alterations in

the splanchnic and systemic hemodynamics (see above and figure 1) does not explain all cases of hyponatremia in patients with cirrhosis. Studies are needed in this field.

Serum sodium concentration is a predictor of death in cirrhosis

Several studies have shown that serum sodium concentration is an independent predictor of death in patients with cirrhosis (5-12,34). Interestingly, the prognostic value of hypovolemic hyponatremia seems to be similar to that of hypervolemic hyponatremia (35).

A study performed in patients on the waiting list for liver transplantation found that the risk of death at 90 days significantly increased by 21% per unit increase in the MELD score (34). In this study, a Cox model, adjusted for the MELD score, showed an increase in the risk of death of 5% per unit decrease in the serum sodium concentration when the serum sodium concentration was between 125 and 140 mmol/L (34). A significant interaction was found between the MELD score and the serum sodium concentration as predictors of death : the effect of hyponatremia gradually diminished as the MELD score increased (34). In other words, in patients with moderate MELD scores and hyponatremia, the risk of death is underestimated by the MELD score (6,9,34). Whether the association existing between hyponatremia and mortality is attributable to hyponatremia itself or reflects the fact that patients with hyponatremia tend to be ill in general remains to be determined.

Does chronic hyponatremia per se play a role in brain dysfunction ?

Studies have shown that a previous history of hepatic encephalopathy was more frequent in patients with low serum sodium concentrations than in those without (1,5). However, these studies did not provide information on the chronology of the two events.

Patients with cirrhosis and chronic decreases in serum sodium levels were found to have marked reductions in brain organic osmolytes that probably reflect compensatory osmoregulatory mechanisms against cell swelling triggered by a combination of high intracellular glutamine and low extracellular tonicity (36). These findings may be relevant to the pathogenesis of encephalopathy in patients with hyponatremia.

There are data suggesting that chronic hyponatremia may have consequences on brain function. Mild chronic hyponatremia has been shown to be associated with a high incidence of falls possibly as the result of marked gait and attention impairments (37). A randomized trial of tolvaptan (a drug that increases serum sodium levels by blocking AVP action, see below) in patients with hyponatremia, has shown that increase in serum sodium with tolvaptan was associated with improved cognitive functions (14). In addition, preliminary results of a randomized clinical trial suggest that satavaptan (another drug able to increase serum sodium levels, see below) decreases the incidence of hepatic encephalopathy (38). Therefore, in patients with cirrhosis, chronic hyponatremia may induce brain dysfunction and play a role in poor outcome.

Treatment of hyponatremia

In general, there is no urgency to treat chronic hyponatremia (15). If the correction of hyponatremia is too rapid, patients may develop central pontine myelinosis (15).

Hypovolemic hyponatremia

There are no results of randomized trials to guide therapy. The opinion of international experts on diuretic-induced hypovolemic hyponatremia can be summarized as follows (32,33) :

- For patients with serum sodium levels of 126-135 mmol/L and normal serum creatinine levels, diuretics can be continued and water restriction is not needed ;
- For patients with serum sodium levels of 121-125 mmol/L and normal serum creatinine levels, diuretics can be continued ;
- For patients with serum sodium levels of 121-125 mmol/L and serum creatinine levels > 150 μmol/L, diuretics should be stopped and fluid replacement therapy given ;
- Diuretic therapy should be stopped in patients with serum sodium levels < 120 mmol/L.

Hypervolemic hyponatremia

Fluid restriction remains the usual approach. Other treatment options are demeclocycline, urea, and aquaretics (15). Difficulty in use coupled with toxicity make the first two options unattractive (15). Aquaretic drugs are under evaluation. Aquaretics are drugs that increase solute-free water excretion by antagonizing the antidiuretic action of AVP. This effect can be achieved either by using niravoline (RU515599), an agonist of central k-opioid receptor which inhibits AVP synthesis/secretion by the hypothalamo-neurohypophysial system ; or by using a drug of the vaptan family which blocks AVP from biding to the V2 receptors of the distal nephron.

The proof-of-concept that AVP inhibition results in increases in solute-free water excretion and serum sodium levels has been provided by a pilot study using short-term niravoline administration in a small series of patients with cirrhosis (28). However, these effects have not been confirmed in larger studies because the development of this drug has been stopped.

Several non-peptide AVP receptor antagonists are under clinical investigation for hyponatremia : lixivaptan (VPA-985), tolvaptan (OPC-41061), satavaptan (SR-121463), and RMJ-351647, and conivaptan (YM-087) (Table 2). All are selective for V2 receptors except

Table 2. — **Antagonists of Arginine Vasopressin (AVP) receptor**

Antagonist	*Target (AVP Receptor(s))*	*Development*
Oral		
Lixivaptan (VPA-985)	V2	: Phase 2
Tolvaptan (OPC-41061)	V2	: Phase 2
Satavaptan (SR-121463)	V2	: Phase 3
Mozavaptan (OPC-31260)	V2	: SIAHD* (Japan)
RMJ-351647	V2	: Phase 1
Intravenous		
Conivaptan (YM-087)	V1a/V2	: SIAHD* (USA)

*SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

conivaptan which blocks both V2 and V1a receptors (Table 2). Conivaptan is used intravenously while the other compounds are used orally. Little is known on the effects of RMJ-351647 or conivaptan in patients with cirrhosis while there are studies investigating the effects of the three other drugs. These studies are summarized below.

Lixivaptan. Two randomized, multicenter studies of lixivaptan in humans have been reported (39,40). The first was an unblinded, placebo-controlled study of hospitalized patients with stable hyponatremia (< 130 mmol/L for 3 consecutive days) ; of the 44 patients enrolled, 33 had cirrhosis, 6 had congestive heart failure, and 5 had the syndrome of inappropriate secretion of antidiueretic hormone (SIADH) (39). The patients were randomized to receive one of three doses of oral lixivaptan or placebo twice daily for 7 days. The study found a significant increase in free water clearance with the 125-mg and 250-mg twice-daily doses of lixivaptan compared with placebo. The 250-mg twice-daily dose was associated with significant increases in serum sodium levels compared with placebo. There were no significant changes in orthostatic blood pressure, serum creatinine levels, or urinary sodium excretion in the lixivaptan groups compared with the placebo group. The 250-mg twice-daily dose was associated with reports of excessive thirst and dehydration manifested by marked increases in serum sodium levels, often requiring one or more doses to be withheld (39).

The second published study of lixivaptan was a double-blind trial in 60 patients with cirrhosis and hyponatremia (defined as serum sodium concentrations between 112-132 mmol/L) (40). Patients were randomized to receive 100 or 200 mg/day of oral lixivaptan or placebo for 7 days or until serum sodium was normalized. Fluid intake was restricted to 1,000 mL/day. The primary end point was normalization of serum sodium level (serum sodium $\geq$ 136 mmol/L). Serum sodium levels were normalized in 27% of patients receiving lixivaptan 100 mg/day and 50% of patients receiving 200 mg/day compared with 0% placebo recipients. The 200-mg dose also was associated with significant reductions in urine osmolality and body weight. Thirst sensation increased significantly in the 200-mg dose group but not in the 100-mg or placebo groups. Rates of serious adverse events leading to treatment discontinuation were similar among the three groups. No patient developed neurologic abnormalities, and lixivaptan had no significant effects on blood pressure or heart rate (40).

Tolvaptan. One multicenter, randomized, double-blind, placebo-contolled trial of tolvaptan has been published (14). In two multicenter, randomized, double-blind, placebo-controlled trials, the efficacy of tolvaptan was evaluated in 448 patients with hyponatremia (due to cirrhosis in 120, chronic heart failure in 138, SIADH and other in 190). Patients were randomly assigned to receive oral placebo (223 patients) or oral tolvaptan (225 patients) at a dose of 15 mg daily. The dose of tolvaptan was increased to 30 mg daily and then to 60 mg daily, if necessary, on the basis of serum sodium concentrations. The two primary end points for all patients were the change in the average daily area under the curve for the serum sodium concentration from baseline to day 4 and the change from baseline to day 30. Serum sodium concentrations increased significantly more in the tolvaptan group than in the placebo group during the first 4 days and after the full 30 days of therapy. Side effects associated with tolvaptan included increased thirst, dry mouth, and increased urination. There was significant improvement from baseline to day 30 in the tolvaptan group according to scores on the Mental Component of the Medical Outcomes Study 12-item Short-Form General Health Survey (14).

Satavaptan. One multicenter, randomized, double-blind, placebo-controlled study of satavaptan has been published (41). A total of 110 patients with cirrhosis, ascites, and hyponatremia (serum sodium < 130 mmol/L) were randomly assigned to receive either fixed doses of satavaptan (5 mg, 12.5 mg, or 25 mg once daily) or placebo. Duration of treatment was 14 days and all patients received spironolactone at 100 mg/day. Satavaptan treatment was associated with improved control of ascites, as indicated by a reduction in body weight and a parallel reduction in abdominal girth. This beneficial effect on ascites was associated with improvements in serum sodium concentrations. Thirst was significantly more common in patients treated with satavaptan compared to those treated with placebo, whereas the frequency of other adverse events was similar among groups.

What about long-term effects of satavaptan in patients with cirrhosis ? We now have preliminary results of a multicenter, randomized, single-blind study of satavaptan (38). One hundred thirty-nine patients with cirrhosis, ascites and history of hyponatremia (serum sodium $\leq$ 130 mmol/L) were randomized to receive in a 2:1 ratio either a flexible dose-regimen of satavaptan (5-50 mg once daily) or placebo. Diuretics and paracentesis

were used as required. Planned duration of treatment was up to 52 weeks. Ninety-two were randomized to satavaptan and 47 to placebo. The estimated number of normonatremic days (serum sodium ≥ 135 mmol/L) over 1 year was significantly longer with satavaptan than placebo (208 days vs. 93 days, respectively).The estimated mean number of paracenteses/patient over 1 year was tended to be lower with satavaptan (4.3 for vs. 6.1, respectively). Median time to first hospitalization for any cause was significantly longer for satavaptan (32 weeks vs. 10 weeks, respectively). The Kaplan-Meier 52-week estimated probability of serum potassium ≥ 5.5 mmol/l was 45.3% for satavaptan and 31.5% for placebo, and for serum creatinine increase (≥ 50% from baseline and > 1.5 mg/dL) was 32.5% for satavaptan and 27.4% for placebo. Interestingly, Kaplan-Meier 52-week estimated probabilities of hepatic encephalopathy and variceal bleeding were significantly lower with satavaptan than with placebo. No significant effects of satavaptan on mortality or SBP were found (39).

Summary on vaptans. There is no doubt that short-term vaptan therapy is effective to treat hypervolemic hyponatremia in patients with cirrhosis. However, there is no information on the long-term effects of lixivaptan and tolvaptan. Preliminary results of long-term effects of satavaptan are encouraging ; however, to date there is no full-paper reporting results in terms of long-term efficacy and safety.

Hyponatremia and Liver Transplantation

Liver transplantation is the only treatment that can cure decompensated cirrhosis. Under the current liver-transplantation policy followed, donor organs are offered to patients with the highest risk of death. The risk of death is evaluated by using the MELD score (42, 43). However, as discussed earlier (see above and refs. 6,9,34), the MELD score may not accurately reflect the risk of death in patients with moderate MELD scores and hyponatremia. The use of the new MELDNa score might improve organ allocation in patients on the waiting list. The formula for the MELNa is MELDNa = MELD − Na − [0.025 × MELD × (140 − Na)] + 140 (where the serum concentration is bound between 125 and 140 mmol/L) (34). It should be emphasized that the range of 125-140 mmol/L for serum sodium levels may be clinically pertinent because it does not favor patients with marked hyponatremia (i.e., serum sodium concentration < 125 mmol/L). Hyponatremia at the time of liver transplantation has been associated with increased morbidity (e.g., due to central pontine myelinolysis (44-46)) and mortality in the early post-transplantation period (47,48). Thus, an allocation system that excessively favors patients with marked hyponatremia may diminish the overall outcome after liver transplantation. Future studies should elucidate the place of the value of serum sodium concentrations in the setting of allocation of organs for liver transplantation.

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