Section A-Research paper

An Overview about Copeptin and liver cirrhosis

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Abstract

Background: Vasopressin (also known as antidiuretic hormone (ADH) or arginine vasopressin (AVP)) has been well described as an important hormone regulating fluid homeostasis and vascular tone. It is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus. Hypothalamic vasopressinergic magnocellular neurons project from the supraoptic nucleus to the posterior pituitary, utilising neurophysins. Vasopressin is then secreted into the circulation for the purpose of osmotic regulation via renal arginine vasopressin 2 (AVP2) receptors which lead to the membrane localization of aquaporin-2 (Aq2) channels in distal renal tubules enhancing water reabsorption from tubular fluid into the circulation. Vasopressin also contributes to vascular tone via arginine vasopressin 1a (AVP1a) receptors. In cirrhotic patients, intestinal bacterial translocation is responsible for overproduction of nitric oxide (NO) via activation of monocytes and lymphocytes and increase in circulating levels of proinflammatory cytokines. These properties make copeptin an interesting surrogate marker of AVP in clinical practice. Copeptin has been shown to be a reliable prognostic marker in decompensated congestive heart failure and a wide variety of other diseases. Limited data are available on its prognostic significance in patients with cirrhosis.

Keywords: copeptin, liver cirrhosis

Introduction

Vasopressin (also known as antidiuretic hormone (ADH) or arginine vasopressin (AVP)) has been well described as an important hormone regulating fluid homeostasis and vascular tone. It is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus. Hypothalamic vasopressinergic magnocellular neurons project from the supraoptic nucleus to the posterior pituitary, utilising neurophysins. Vasopressin is then secreted into the circulation for the purpose of osmotic regulation via renal arginine vasopressin 2 (AVP2) receptors which lead to the membrane localization of aquaporin-2 (Aq2) channels in distal renal tubules enhancing water reabsorption from tubular fluid into the circulation. Vasopressin also contributes to vascular tone via arginine vasopressin 1a (AVP1a) receptors **(1).**

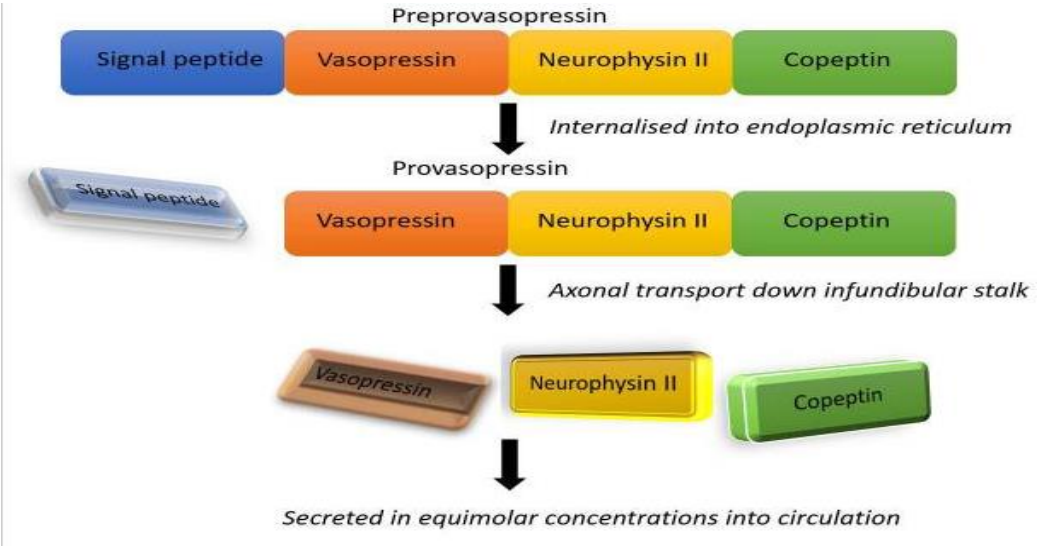
Parvocellular neurons in the paraventricular nucleus secrete vasopressin into the hypothalamo-hypophyseal portal circulation where it acts synergistically via arginine vasopressin 1b (AVP1b) receptors to stimulate pituitary adrenocorticotrophic hormone (ACTH) and ultimately adrenal cortisol secretion. Hence, vasopressin is secreted into the general and hypophyseal portal circulations in response to stress. Vasopressin also has a role in promoting platelet aggregation and hence haemostasis **(2).**

Copeptin is a 39-amino acid glycosylated peptide with a leucine-rich core. It is derived from pre-provasopressin together with (AVP) and neurophysin II. In contrast to vasopressin, the physiologic function of copeptin is not known. Copeptin was first described in 1972 by Holwerda and is co-synthesised in response to increasing osmolality with vasopressin and co-secreted in equimolar concentrations into the circulation. Vasopressin is a nonapeptide with a short half-life of approximately 24 min, and there are many limitations in direct vasopressin measurement assays including the rapid in vitro degradation of vasopressin and secretory pulsatility, complicating interpretation **(3).**

Fig. 1. Co-secretion of copeptin and vasopressin **(1).**

Copeptin's in vitro stability, stable serum levels due to its long circulating disappearance half-life by virtue of its glycosylation, and its length allowing more epitopes for raising antibodies for immunoassay development, make it an ideal surrogate biomarker for vasopressin release. In Australia, copeptin is measured with a chemiluminescence sandwich immunoassay (BRAHMS Copeptin proAVP) using two polyclonal antibodies to amino acids 132–164 of preprovasopressin **(4).**

For reasons that are not clear, men have higher plasma copeptin levels under normo-osmotic conditions but no sex difference was seen after hypertonic saline stimulation. Copeptin levels do not increase with age and do not display circadian variation. Stress, defined as a threat to homeostasis, stimulates



copeptin/vasopressin release, and this phenomenon allows copeptin to be used a stress biomarker **(5).**

Copeptin and diabetes insipidus:

Diabetes insipidus (DI) is a disorder characterized by polyuria and polydipsia. There are three types of DI: central DI where there is a deficiency in the secretion of vasopressin; nephrogenic DI where there is normal vasopressin secretion but renal resistance to its water retaining effect; and gestational DI due to the breakdown of endogenous vasopressin by placental vasopressinase. Determining the type of DI and distinguishing this condition from the differential diagnosis of primary polydipsia is crucial, as management of these conditions is different and an inappropriate management strategy may cause harm. Several tests have been proposed to evaluate polyuria and polydipsia **(1).**

Nephrogenic DI cases were excluded from this review but it is known that copeptin levels in nephrogenic DI are markedly elevated. Nephrogenic DI is much less common than central DI and studies on prevalence are limited but it is estimated that for X-linked nephrogenic diabetes, the prevalence is approximately 1 in 250,000 individuals.18 An underlying cause for nephrogenic DI is often clinically apparent, such as a family history of genetic nephrogenic DI, such as an X-linked AVP2 receptor mutation or rarer aquaporin-2

channel mutations in children.19 In adults, prolonged lithium administration, hypokalaemia, hypercalcaemia or the post-obstructive phenomenon after clearing a renal outflow tract blockage is generally readily apparent. Desmopressin is not used in treatment of nephrogenic DI **(1).**

Indirect Water Deprivation Test

The indirect water deprivation test measures the maximal urine concentration during a prolonged period of abstinence from oral liquids and serial measurements of urine concentration following administration of desmopressin – a synthetic form of arginine vasopressin which provides an indirect marker of vasopressin activity. This has been the diagnostic standard for over 50 years. Urine osmolality is measured hourly while fluids are withheld and once the urine osmolality becomes constant, blood is drawn to evaluate plasma osmolality and desmopressin or vasopressin is administered. Urinary osmolality is then re-assessed 60 min after. In some instances, this test may take up to 16–18 h to complete due to limited renal concentrating ability related to high urine output and reduced renal medullary tonicity limiting the response to circulating vasopressin **(4).**

Complete central DI is diagnosed in patients who have a maximal urine osmolality of less than 300 mOsm/kg and an increase in urine osmolality of more than 50% after administration of desmopressin. In partial central DI, the maximal urine osmolality is between 300 and 800 mOsm/kg and the increase in urine osmolality is between 9% and 50% after desmopressin. In primary polydipsia, the maximal urine osmolality is between 300 and 800 mOsm/kg and the increase in urine osmolality is less than 9% after desmopressin. The direct measurement of vasopressin following osmotic stimulation improved the diagnostic accuracy of the water deprivation test for central vs primary polydipsia but the lack of a reliable serum vasopressin assay severely limited its use **(4).**

Copeptin as a Surrogate Marker of Vasopressin:

The measurement of copeptin in addition to the indirect water deprivation test was investigated. Patients with complete central DI had lower concentrations of plasma copeptin at the end of the study compared to patients with primary polydipsia as determined using the 'gold standard' of clinical assessment, review of investigations and evaluation of the response to a trial of desmopressin. This was the first study to investigate the use of plasma copeptin to diagnose patients presenting with polyuria and polydipsia and found that the ratio of the change in copeptin concentration for the duration of the test and serum sodium concentration at the end of the test, was accurate in distinguishing between partial central DI and primary polydipsia (sensitivity 86% and specificity 100%) using a specific index cut-off **(4).**

However, this approach was equally as time-consuming as the indirect water deprivation test so a follow up study evaluated the accuracy of a 'stimulated' copeptin concentration. Plasma copeptin concentration was measured after plasma sodium concentration increased to greater than 147 mmol/L either from water deprivation or in cases where water deprivation did not raise sodium concentrations to this threshold after 5 hours, a 3% saline infusion (hypertonic) at 0.1 mL/kg/min was administered until plasma sodium exceeded 147 mmol/L. Plasma copeptin concentrations measured when plasma sodium concentrations exceeded 147 mmol/L were greater in primary polydipsia compared with partial central DI with a sensitivity and specificity of 94% using a cut-off of >4.9 pmol/L **(6).**

Another method of stimulating copeptin included the use of arginine which compared a smaller cohort of 52 patients. Copeptin secretion was stimulated by 0.5 g/kg of intravenous L-arginine hydrochloride over 30 min and copeptin concentrations were measured at frequent intervals following the infusion for 120 min. Using a cut-off of 3.8 pmol/mmol at 60 min, diagnostic accuracy was reported to be 93% using pooled data from two cohorts **(1).**

Copeptin and Syndrome of Inappropriate Secretion of Anti-Diuretic Hormone:

Hyponatraemia is common in hospitalised patients and frequently a result of a condition known as syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). In response to stress, particularly nausea or pain, vasopressin is secreted into the general and hypophyseal portal circulations resulting in a combination of water retention and secondary sodium loss. **(1).**

Differentiating between SIADH and other causes of hyponatraemia can be challenging as concurrent disease or treatment can complicate the diagnostic work up. Therefore, the use of copeptin concentrations as a diagnostic aid has been explored **(1).**

In a prospective, multicentre, observational study of 298 patients with hyponatraemia and hypo-osmolarity, low plasma copeptin (<3.9 pmol/L) were predictive of primary polydipsia with high specificity (91%) and high plasma copeptin (>84 pmol/L) were predictive of hypovolaemic hyponatraemia with high specificity (90%). Sensitivity for both these associations was limited and apart from these specific conditions, copeptin had limited utility in differentiating between SIADH and other causes of hyponatraemia. The diagnostic utility of copeptin may be improved when combined with other parameters such as the urinary sodium concentration (U-Na) **(7).**

In a prospective, observational study of 106 patients, the copeptin to U-Na ratio was able to accurately differentiate between volume depleted and normovolaemic (e.g., SIADH) causes of hyponatraemia but unable to distinguish diuretic induced hyponatraemia. Given there are often multiple factors contributing to SIADH, the use of copeptin to subclassify SIADH and tailor management approaches is an interesting concept that needs to be evaluated further **(4).**

Copeptin and critical illness:

In the critical care setting, a prospective, observational study of 218 patients showed that high copeptin concentrations on admission to ICU was a predictor of short and long-term mortality. Inflammatory cytokines, key mediators of the stress response, such as IL-1, TNF-α stimulate vasopressin secretion and plasma copeptin is elevated in sepsis compared to patients with infections without systemic inflammation. **(8).**

Further supporting this relationship is a prospective, observational study of 50 critically ill patients that found an association between elevated plasma copeptin levels and advanced vasodilatory shock due to sepsis or systemic inflammatory response syndrome. These studies raise the possible use of copeptin for risk stratification of inpatients to determine who may need higher acuity care but further studies are needed to evaluate the effectiveness of this approach **(8).**

Copeptin and diabetes mellitus:

A cross-sectional population study of 4742 patients found new onset diabetes mellitus to be associated with increasing plasma copeptin concentrations. Patients who subsequently developed diabetes mellitus over the 12.6 year follow up period had a 28% higher mean copeptin level. Women with polycystic ovary syndrome were found to have a 31% higher mean copeptin levels compared with healthy controls. The elevation in copeptin may be due to the low-grade chronic inflammation and elevated circulating inflammatory cytokines in metabolic syndrome **(9).**

Plasma copeptin levels have also been positively associated with major cardiovascular outcomes in type 2 diabetes mellitus as well as adverse renal outcomes. In a cohort study of 1328 patients, baseline copeptin levels were positively associated with an elevation in urinary albumin-creatinine ratio.38 Similarly, a higher baseline copeptin concentration was associated with a lower estimated glomerular filtration rate. Another retrospective study showed a significant association between baseline copeptin and progression to stage 3 chronic kidney disease in newly diagnosed diabetes. **(10).**

Whether more aggressive blood pressure, albuminuria or glycaemic targets could prevent progression to chronic kidney disease in patients with higher copeptin levels at diagnosis is an important question that needs prospective trials to evaluate. Therefore, there is emerging evidence that copeptin may have a role in predicting which patients may be predisposed to complications of diabetes mellitus **(10).**

Copeptin and stroke:

The usefulness of copeptin to differentiate between ischaemic stroke, transient ischaemic attack and stroke "mimics" such as delirium, complex migraine, epilepsy or vestibular neuronitis was explored in a pilot study of 45 adults. Median plasma copeptin concentration within 4.5 h of the onset of symptoms was approximately twice as high in patients with ischaemic stroke compared to transient ischaemic attacks. Using a plasma copeptin concentration cut-off of >16 pmol/L resulted in a sensitivity of 80% and specificity of 44% in confirming ischaemic stroke. Seven patients in this cohort had a diagnosis in the stroke mimic category which had a large interquartile range (7.57–255 pmol/L) and as such, the diagnostic utility of copeptin in distinguishing stroke from stroke mimics could not be determined from this study. Copeptin, however, may be useful in differentiating ischaemic stroke from transient ischaemic attacks particularly if combined with other risk stratification scores such as the ABCD2 score **(11).**

A higher plasma copeptin concentration also predicts stroke severity on admission, mortality and stroke recurrence. Poorer outcome among stroke patients with higher plasma copeptin may imply a role of vasopressin in brain oedema and neuronal injury. **(12).**

While the precise mechanism is not fully understood, blocking vasopressin receptors in mice models or using vasopressin deficient mice appears to attenuate brain oedema after ischaemia and trauma. Therefore, copeptin concentration has the potential to be used in stroke risk stratification but as it is elevated in a wide range of conditions, it will likely need to be used in combination with other parameters **(12).**

Copeptin and cardiovascular disease:

Most studies have shown that copeptin is positively associated with blood pressure. A suggested mechanism for this relationship is that activation of the renin-angiotensin-aldosterone system (RAAS) stimulates release of vasopressin. This mechanism may also be 'bi-directional' as vasoconstriction and tubular retention of sodium from vasopressin may contribute to blood pressure elevation **(1).**

Copeptin in combination with troponin measurements may increase the detection rate of acute coronary syndromes at admission and enable more accurate exclusion of acute myocardial infarction. It has also been shown that elevations in copeptin occur even before CK-MB and troponin T levels have risen. There have been suggestions that copeptin may have a role in rapid diagnosis, triaging of patients presenting with symptoms suggestive of acute coronary syndromes and determining whether invasive management is indicated. It has also been suggested that copeptin may help in the prediction of major adverse cardiovascular events in patients with symptomatic coronary artery disease **(13).**

However, non-specific stressors may limit the utility of copeptin in differentiating chest pain aetiologies. For example, although acute aortic syndromes have been associated with an elevated plasma copeptin concentration, this is similarly seen in important differential diagnoses such as acute coronary syndromes and pneumonia. **(14).**

While the specificity of copeptin concentrations may be insufficient to accurately 'rule in' acute coronary syndromes, it may be able to more effectively 'rule out' acute coronary syndromes when used in combination with troponin concentration measurements. Combined copeptin and troponin concentration measurements compared with measurement of troponin concentration alone has a 98% negative predictive value (vs 96%) and 92% sensitivity (vs 81%) but lower specificity **(14).**

Copeptin has also been investigated for its role in prognosticating heart failure. Copeptin is a strong biomarker for mortality and morbidity in patients with heart failure after acute myocardial infarction and the predictive value of copeptin is even stronger than BNP or NT-proBNP. A possible factor for copeptin's potential utility is that unlike BNP, copeptin does not vary with age **(1).**

Copeptin and respiratory disease:

Pulmonary disease has long been associated with hyponatraemia and elevated vasopressin of central origin or ectopic production from neuroendocrine tumours, such as small cell lung cancer. Elevated plasma copeptin on admission have been associated with increased severity and mortality of community acquired pneumonia. Multiple studies have also shown that elevated copeptin levels has been associated with increased severity of ventilator-associated pneumonia and is an independent predictor of mortality **(15).**

Plasma copeptin concentrations have been incorporated into a risk index that predicts mortality in chronic obstructive pulmonary disease. In a small study with 28 paediatric cystic fibrosis patients, higher plasma copeptin concentrations was associated with worsening symptoms of severity and more significant radiologic changes during pulmonary exacerbations of cystic fibrosis. **(16).**

Raised copeptin in severe respiratory disease may be due to inflammatory cytokines, the known effect of hypoxia and hypercapnia on vasopressin secretion, or other lung-central vasopressin release pathways **(16).**

Copeptin and kidney disease:

Copeptin has a negative correlation with glomerular filtration rate (GFR) and a positive correlation with albuminuria. The exact mechanisms are not known but there are two hypotheses. Firstly, given copeptin is cleared by renal excretion, a decrease in renal function will result with an increase in copeptin levels. Secondly, as renal function declines, there may be a loss of the ability to concentrate water, disruption of water homeostasis and activation of the renin-angiotensin-aldosterone system. Arguments against these hypotheses include the observation that copeptin levels increase before estimated GFR decreases and a study that showed no change in copeptin levels following a reduction in GFR from the donation of a kidney in healthy donors. Therefore, it is likely that GFR alone is not the only determinant of copeptin levels. Cross-sectional analysis has shown a correlation between copeptin and disease severity in autosomal-dominant polycystic kidney disease (ADPKD). The vasopressin antagonist Tolvaptan has been shown to have a renoprotective effect in ADPKD and further studies are needed to determine if copeptin may be a marker of treatment efficacy **(17).**

Copeptin and liver cirrhosis:

In cirrhotic patients, intestinal bacterial translocation is responsible for overproduction of nitric oxide (NO) via activation of monocytes and lymphocytes and increase in circulating levels of proinflammatory cytokines. NO increases splanchnic vasodilation that stimulates compensatory systems to restore adequate blood volume: sympathetic nervous system, renin-angiotensin-aldosterone system and arginine vasopressin (AVP, also called antidiuretic hormone). It has been shown that AVP concentrations increase with deterioration of liver function and this biological marker may thus have a prognostic value. However, its measurement is difficult and not routinely available **(18).**

Copeptin, the pre-pro-AVP C terminal fragment, is released into the serum in equimolar quantities than AVP. Hence, copeptin concentrations closely reflect the production of AVP, either in healthy subjects or in stressful situations such as sepsis. The main interest of copeptin is its serum stability, conversely to AVP. Copeptin is thus easy to measure. Moreover, its concentration increases much more than cortisol in the event of stress. The prognostic value of copeptin was recently mentioned in several diseases: high concentrations of copeptin were associated with unfavorable outcomes in patients with chronic heart failure, pulmonary infections, and in patients with transient ischemic stroke **(19).**

They studied this marker in a cohort of 125 cirrhotic patients including 34 Child-Pugh A, 29 Child-Pugh B, 32 Child-Pugh C and 30 infected patients with Child-Pugh score > B8[29]. Copeptin concentrations were higher in infected patients (18.81 pmol/L vs 6.64 pmol/L in patients without infection, P = 0.0007), patients with ascites (13.27 pmol/L vs 6.06 pmol/L in others, P < 0.0001) and patients with renal impairment (44.67 pmol/L vs 8.40 pmol/L in patients with normal renal function, P = 0.0018). Copeptin concentrations were positively correlated with Child-Pugh, MELD scores (r = 0.43, P < 0.0001) and CRP levels (r = 0.49, P < 0.0001). After a median follow-up of 12 mo, 8 patients were transplanted and 28 (24%) patients had died. **(20).**

In univariate analysis, patients who died or were transplanted had higher baseline copeptin concentrations compared with others (15.02 pmol/L vs 6.68 pmol/L; P = 0.0006), and nearly three quarters of patients who had died belonged to the two highest quintiles regarding copeptin concentrations. Survival analysis showed excess mortality in patients with copeptin values > 13 pmol/L. In multivariate analysis, high value (> 13 pmol/L) of copeptin kept its detrimental impact on prognosis after adjustment on CRP and MELD score. This study suggests that copeptin could be a good marker of stress during cirrhosis. Its impact on survival warrants confirmation by larger studies **(20).**

Portal hypertension may develop in patients with liver cirrhosis, as a result of an increased intrahepatic vascular resistance, reduced systemic vascular resistance and increased portal inflow. In early stages of cirrhosis, decreases in systemic vascular resistance are compensated by an increase in cardiac output. In more advanced stages, there is a marked reduction of systemic vascular resistance which cannot be compensated by additional increases in cardiac output, leading to a decreased effective arterial blood volume **(21).**

This triggers the activation of counter regulatory systems, such as the renin-angiotensin-aldosterone (RAAS) system, sympathetic nervous system and non-osmotic release of arginine vasopressin (AVP). Activation of these vasoconstrictor systems helps to restore the effective arterial blood volume, but has negative effects on kidney function, particularly due to renal sodium and solute-free water retention, which is associated with the development of ascites, edema and hyponatremia. Ultimately, intrarenal vasoconstriction and hypoperfusion may lead to the development of a hepatorenal syndrome, which is associated with a poor prognosis. **(22).**

The Model of End stage Liver Disease (MELD) score is widely used as a prognostic score and a tool for organ allocation in patients eligible for liver transplantation (LT**) (22).**

However, this liver specific score falls short on assessing the severity of circulatory dysfunction. The accuracy of the estimation of prognosis based on information included in liver specific scoring systems, such as the MELD and MELD-sodium (MELD-Na) score, may be improved by adding information on circulatory dysfunction. Because of its key role in circulatory homeostasis and its systemic vasoconstrictor effects, AVP might be particularly interesting as a marker of circulatory dysfunction and prognosis in cirrhosis. However, AVP has a relatively short half-life time of approximately 20 minutes and more than 90% of AVP is bound to platelets in the circulation **(23).**

Therefore, AVP is not useful as a biomarker in clinical practice. Copeptin has been first described in 1972 and is a cleavage product of the C-terminal part of the AVP precursor, pre-pro-vasopressin, which is secreted by the posterior pituitary in response to hypotension and hyperosmolality. The actual function of copeptin is unknown. In contrast to AVP, copeptin is a stable molecule that does not bind to platelets in the circulation. Moreover, copeptin is secreted together with AVP in equimolar amounts and has a strong correlation with AVP over a wide range of osmolalities **(24).**

These properties make copeptin an interesting surrogate marker of AVP in clinical practice. Copeptin has been shown to be a reliable prognostic marker in decompensated congestive heart failure and a wide variety of other diseases. Limited data are available on its prognostic significance in patients with cirrhosis **(21).**
No relationship between copeptin and portal pressure or mesenteric blood flow was found in these cirrhotic animals. It has previously been shown that copeptin is extracted in the kidneys in cirrhotic humans and several previous studies have shown an inverse correlation between copeptin concentration and renal function **(25).**
Their findings were confirmed by a significant inverse correlation of serum copeptin with creatinine, but the study design of the present and previous studies was not appropriate to define whether an increase in serum copeptin is causally related to renal impairment. The results of the animal study add to these data that serum copeptin concentration is elevated in cirrhotic rats with portal hypertension and circulatory dysfunction, even in the absence of kidney failure, ascites and the use of medication **(21).**
In cirrhotic humans, previous studies have been performed to test the association of copeptin with circulatory dysfunction. It has been shown that copeptin is positively correlated with portal pressure and inversely correlated with cardiac output in cirrhosis. As copeptin has been found to be a potential marker of development of cardiac dysfunction, which is associated with poor prognosis in cirrhosis, Others hypothesized that copeptin might also give prognostic information in cirrhosis**.** The prognostic potential of copeptin as a surrogate marker of circulatory dysfunction has already been demonstrated in the setting of acute myocardial infarction and congestive heart failure **(26).**
To date, two studies evaluated the prognostic significance of copeptin in the setting of liver cirrhosis. Moreno et al showed that copeptin independently predicted 1-year mortality or LT in cirrhotic patients **(20).** In contrast, **Wiese et al (34).** did not find copeptin to be related to long-term survival. There are no studies specifically assessing the prognostic value of copeptin in a population of cirrhotic patients registered at the waiting list for LT. Currently, the MELD-score is widely used as an organ allocation tool in patients registered at the waiting list for LT and as a prognostic tool in patients undergoing therapy such as transjugular intrahepatic portosystemic shunt (TIPS) procedure. The MELD score characterizes the severity of the underlying liver disease and kidney function, but falls short on assessing the severity of portal hypertension associated with circulatory dysfunction. The MELD-Na score has also been proposed as a marker for organ allocation. In this score, serum sodium is accounting for hemodynamic deregulations associated with end-stage cirrhosis. Incorporation of sodium in the MELD score has been shown to improve its prognostic accuracy. However, a limitation of the MELD-Na score is that marked changes in serum sodium may result from several factors, such as administration of diuretics and hypotonic fluids. Several studies have shown that parameters estimating systemic hemodynamics have a better prognostic ability in predicting survival in cirrhosis than those assessing liver function **(27).**

Therefore, they hypothesized that markers of hemodynamic dysfunction would be predictors of transplant-free survival in cirrhosis, independently of widely used liver specific prognostic scoring systems. However, the assessment of the presence and impact of hemodynamic dysfunction in cirrhosis is complicated, due to the instability and poor reproducibility of potential biomarkers such as plasma norepinephrine, renin activity and AVP concentration. AVP is particularly interesting as a marker of circulatory dysfunction and prognosis in cirrhosis as it is not only a potential biomarker, but is also involved in the pathogenesis of the development of complications of cirrhosis, due to its systemic vasoconstrictor effects. Copeptin, the surrogate marker of AVP, is easily applicable in clinical practice and therefore interesting as a marker of hemodynamic derangement and prognosis in cirrhosis **(21).**

Recent trials have also found a strong correlation between copeptin and the degree of liver disease **(20).**
Tawfik et al. study found that copeptin was significantly elevated in liver cell failure group **(28).**
This was in accordance with Morgenthaler et al,19 who found that AVP concentrations increased with worsening of liver function, and this biological marker may thus have a prognostic function. Copeptin, the pre-pro-AVP C-terminal fragment, is secreted into the serum in equimolar quantities to AVP **(19).**
Copeptin was also significantly elevated in GI hemorrhage, HRS, and liver cell failure groups vs compensated cirrhosis group. This is in accordance with Kimer et al, who found that patients with Child A cirrhosis had significantly lower concentrations of copeptin compared with Child C cirrhosis **(29).**
There was a significant positive correlation between the level of copeptin and serum creatinine. This is in accordance with Moreno et al. **(20).**
There was also a significant negative correlation between the copeptin level and serum Na+ and albumin **(28).** This is in accordance with Solà et al, who found that AVP release from the neurohypophysis increases in parallel with the progression of cirrhosis and with circulatory dysfunction **(30).**
Moreover, they have also suggested the important role of AVP in the development of hyponatremia **(28).**
Also, this accords with Ball, who found in hypervolemic hyponatremia as in cirrhosis that the stimulation of AVP secretion was due to a secondary hemodynamic stimulus that showed a moderate increase of AVP. Importantly, hyponatremia in cirrhosis is a frequent event well reflecting the severity of portal hypertension and independently associated with poor quality of life and mortality **(31).**
In Tawfik et al. study, copeptin showed a significant positive correlation with Child score **(28).** This was in accordance with Moreno et al, who found that the copeptin concentrations were positively correlated with Child–Pugh score **(20).**
Tawfik et al. study found no correlation between the level of copeptin and bilirubin **(28).** This is in accordance with Kerbert et al, who found that copeptin was not correlated with bilirubin concentration or INR **(21).**
There was a significant positive correlation in the level of copeptin with INR. This is not in accordance with Kerbert et al, who found that copeptin was not correlated with the use of diuretics, bilirubin concentration, or INR **(21).** This may be due to their study done on cases of cirrhosis in general and not on specific complication of cirrhosis **(28).**
Copeptin predicted liver disease at a cutoff value 7 pmol/L with different sensitivity and specificity figures according to each group. The compensated cirrhosis group exhibited 78% sensitivity and 85% specificity. In GI hemorrhage group, 94% sensitivity and 97% specificity were observed. The HRS group exhibited 88% sensitivity and 90% specificity. The liver cell failure group showed 82% sensitivity and 83% specificity. They detected that copeptin exhibited higher specificity and sensitivity in GI hemorrhage group and HRS group, indicating that it is a sensitive measure of hemodynamics **(28).**
Therefore, copeptin can be regarded as a novel prognostic marker of liver cirrhosis. There is a significant association between serum level of copeptin and complications of liver cirrhosis. Copeptin could be a marker for liver disease progression and follow-up. Being a marker for AVP, copeptin mirrors the hypovolemic changes due to liver failure. Copeptin concentrations increase along with the severity of liver disease as well as some of its complication **(28).**
Sequential serum samples for copeptin measurement were available for 421 out of 779 patients included in the study; 179 patients had a sample available at both days 0–2 and 3–7, and 85 patients had samples available at days 0–2, 3–7, and 8–14. Overall serum copeptin concentration decreased in the first week of follow-up **(21).**

Delta serum copeptin in the first week after hospital admission (i.e., serum copeptin at days 3–7 minus serum copeptin at days 0–2) was –3 (–29 to 9) pmol/L. Median serum copeptin at days 3–7 was found to be significantly higher in ACLF patients with a worsening or steady disease course (n = 48) during the follow-up period of 28 days compared with patients with improvement of the ACLF course (n = 52; 43 (21–70) vs. 22 (10–36) pmol/L; p = 0.003) **(32).**

In contrast, median serum copeptin at days 0–2 and delta copeptin did not significantly differ between these groups. However, in the whole study population, median serum copeptin at days 0–2 was significantly more elevated in ACLF patients with a worsening or steady disease course (n = 68) compared with those showing improvement of the disease (n = 71) during follow-up (41 (18–91) vs. 30 (13–53) pmol/L; p = 0.030) **(21).**

The ideal prognostic biomarker for predicting short-term ACLF development and mortality in patients with AD is one that is elevated at the time of onset of AD, is involved in the pathophysiology of disease progression, and can therefore help in directing and monitoring therapy. Markers reflecting hemodynamic systemic changes in cirrhotic patients, such as the hepatic venous pressure gradient (HVPG) and MAP, are well known to be associated with the presence of organ failure and prognosis in cirrhosis **(33).**

In clinical practice, a prognostic biomarker reflecting the degree of circulatory derangement may therefore be of importance since it may help to distinguish between patients who are at a higher risk of developing organ failure and short-term mortality. **(34).**

It may also add prognostic information to conventional prognostic scoring systems in cirrhosis, such as the MELD and Child-Pugh score, which take into account indirect, nonspecific, or subjective markers of hemodynamic derangement such as ascites and creatinine concentration. Recent studies have shown an association **(34).** of high serum copeptin levels with hemodynamics, such as portal hypertension (HVPG > 12 mmHg) and a decreased cardiac output

The role of copeptin in hemodynamic homeostasis was shown by the finding of a weak, but significant inverse correlation between MAP and DBP with copeptin. The weakness of this association may be explained by the fact that, besides peripheral vasodilation, copeptin levels may also be influenced by a number of other stimuli, such as hyperosmolarity, physiological and psychological stress, and medication (i.e., diuretics, beta blockers and vasopressors) **(21).**

Conflicts of Interest: The authors declare no conflict of interest.

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