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CIRRHOSIS AND ITS COMPLICATIONS

Copeptin is an independent prognostic factor for transplant-free survival in cirrhosis

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Abstract

Background & Aims: Copeptin is a stable cleavage product of the arginine vasopressin (AVP) precursor and is equimolarly secreted with AVP. Copeptin is currently considered a reliable prognostic marker in a wide variety of diseases other than cirrhosis. We aimed to investigate the association between severity of cirrhosis and copeptin concentrations and to confirm whether copeptin is of prognostic significance in cirrhosis. *Methods:* One hundred and eighty-four cirrhotic patients hospitalized in two tertiary referral centres were studied. Serum copeptin was measured in samples obtained at hospital admission. Differences in serum copeptin between Child-Pugh classes were evaluated using the Kruskal–Wallis test. Cox proportional hazard regression and Kaplan–Meier analyses were performed to evaluate associations of copeptin and other possible prognostic factors with 6- and 12-month mortality. *Results:* Median serum copeptin (interquartile range) increased significantly through Child-Pugh classes A [5.4 (3.1–10.7) pmol/L], B [9.6 (6.0–17.3) pmol/L] and C [13.8 (5.8–34.1) pmol/L, $P < 0.01$]. Patients with serum copeptin >12.3 pmol/L displayed significantly higher mortality rates at 6 and 12 months as compared to those with serum copeptin ≤12.3 pmol/L (Log-rank test: $P < 0.01$). Serum copeptin >12.3 pmol/L was significantly associated with mortality, particularly at 6 months, independently of age, clinical parameters and Model for End stage Liver Disease (MELD), MELD-sodium and Child-Pugh score. *Conclusions:* Serum copeptin concentration increases significantly along with the severity of cirrhosis as defined by the Child-Pugh classification. A high serum copeptin concentration predicts survival, particularly at 6 months, independently of liver-specific scoring systems in a heterogeneous population of hospitalized cirrhotic patients.

Keywords
biomarker – cirrhosis – copeptin – prognosis

Advanced cirrhosis is characterized by haemodynamic impairment leading to the development of a hyperdynamic circulation defined as a decreased systemic vascular resistance and mean arterial blood pressure (MAP) and an increased cardiac output (1). The severity of circulatory derangement has been found to predict survival in cirrhosis (2). Currently, several liver-specific scoring systems are used to assess prognosis in cirrhosis, such as the Model for End stage Liver Disease (MELD), sodium MELD (MELD-Na) and Child-Pugh (CP) score. These scores do characterize the severity of the underlying liver disease, but do not take into account

Abbreviations
AVP, arginine vasopressin; CP, Child-Pugh; CRP, C-reactive protein; HRS, hepatorenal syndrome; INR, international normalized ratio; IQR, interquartile range; LT, liver transplantation; MAP, mean arterial blood pressure; MELD, Model for End stage Liver Disease; MELD-Na, sodium MELD; RF, renal failure; SD, standard deviation.

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Key points

- Serum copeptin concentration increases significantly along with the severity of the underlying liver disease, as defined by the Child-Pugh classification.
- Serum copeptin is significantly associated with 6- and 12-month mortality in a heterogeneous population of hospitalized cirrhotic patients.
- Serum copeptin predicts transplant-free survival independently of age, clinical parameters and MELD, MELD-sodium and Child-Pugh score, particularly at 6 months and to a lesser extent also at 12 months.
- Mortality rates in a population of hospitalized cirrhotic patients are significantly higher in patients with a high serum copeptin at admission, even when excluding patients with renal failure, severe infections or acute decompensation of cirrhosis.

the degree of circulatory derangement. Arginine vasopressin (AVP) is a key regulator in hemodynamic homeostasis and may therefore be interesting as a potential prognostic marker in cirrhosis. However, AVP measurements are not useful in clinical practice due to its instability in serum and its poor reproducibility (3). Copeptin is a stable cleavage product of the AVP precursor and is secreted together with AVP in equimolar amounts (4, 5). Serum copeptin concentration is increased in the event of systemic inflammation and is of prognostic significance in a wide variety of diseases (6–11). However, only a few studies have assessed the association between serum copeptin concentration and haemodynamic changes in cirrhotic patients (12, 13). So far, one study investigated the prognostic significance of copeptin in the setting of cirrhosis using a combined endpoint of death or liver transplantation (LT) (14). In the present study, we aim to investigate whether copeptin is of prognostic significance on transplant-free survival in cirrhosis, independently of clinical parameters and liver-specific prognostic scores.

Methods

Patients

This study was conducted in Liver Units of two tertiary referral centres, one in the Netherlands and one in France, with approval of the local ethics committee's (France: CCP Est-II (ref:11/634); the Netherlands: approval for the Liver Diseases Biobank by the Medical Ethics Committee (MDL 005NV/nv; 3.4120/09/FB/jr)). Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. A total of 184 hospitalized cirrhotic patients were studied. In the Netherlands, 61 cirrhotic patients hospitalized between October 1994 and April 2011 with a serum sample available for copeptin measurement were included. In France, 123 consecutive patients were recruited from September 2011 till June 2012. Details on this cohort have been recently reported (14). Serum samples for copeptin measurement were drawn at hospital admission for either elective screening for LT or for acute decompensation of cirrhosis. Demographics and clinical characteristics were collected at admission. The presence of renal failure (RF) was defined as a serum creatinine > 133 μmol/L. Severity of liver disease was assessed using MELD, MELD-Na and CP scores.

Laboratory measurements

In both centres, serum copeptin measurements were performed in 50 μl samples using an immunoassay in the chemiluminescence-coated tube format (B.R.A.H.M.S., Kryptor, GmbH, Henningsdorf, Germany). The reference range of serum copeptin in healthy individuals is 1–12 pmol/L with median values of <5 pmol/L (15, 16).

Statistical analysis

Differences in baseline characteristics between centres were evaluated using the Mann–Whitney *U*-test, Student's *t*-test or Chi-square test when appropriate. The Kruskal–Wallis test was used to evaluate differences in serum copeptin concentration between CP-classes. Bonferroni's correction was applied for within-group comparison. Spearman's correlation analysis was performed to explore correlations between serum copeptin concentration and laboratory and clinical data. Optimal cut-off points of serum copeptin and C-reactive protein (CRP) concentration, MAP, MELD, MELD-Na and CP score in predicting mortality at 6 and 12 months, were determined using the Youden Index. Values exceeding these optimal cut-off points are hereinafter referred to as 'high' and values equal to or below these optimal cut-off points as 'low'. These factors were included in a univariate Cox proportional hazard regression analysis to determine their association with transplant-free survival at 6 and 12 months of follow-up. Parameters with a $P < 0.20$ in univariate analyses were entered into the multivariate analyses. Different models with a maximum of four predictor variables were fitted, a statistical requirement because of the limited number of events at both time points (17). MELD, MELD-Na and CP score were separately evaluated with age, serum copeptin, serum CRP, MAP or the presence of ascites in the multivariate models. Ascites was not included in the models with CP score, because ascites is already included in this score.

In order to evaluate whether serum copeptin concentration could give additional prognostic information next to the MELD, MELD-Na and CP score, survival analysis at 6 and 12 months stratified according to serum copeptin concentration and these liver-specific scores was performed using Kaplan–Meier analysis and compared using the Log-rank test. Patients were censored at time of LT or last hospital visit. Sensitivity anal-

yses were performed to investigate whether patients with a high serum copeptin concentration at admission predicted 6- and 12-month mortality when excluding patients with RF, a severe infection or patients admitted for acute decompensation of cirrhosis. Discrete variables are shown as counts (percentage) and continuous variables as mean ± standard deviation (SD). Skewed data are expressed as median [interquartile range (IQR)]. A *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

Baseline characteristics of the 184 cirrhotic patients hospitalized in the Netherlands and France are shown in Table 1. In 129 (70.1%) patients, there was a planned hospital admission either for screening for LT ($n = 55$) or routine liver examinations (ultrasonography, endoscopy or paracentesis; $n = 74$). In 51 (29.9%) patients, the cause of hospitalization was acute decompensation of cirrhosis (nine ascitic decompensation, four gastrointestinal haemorrhage, five encephalopathy and two type-1 hepatorenal syndrome) or severe infection (11 spontaneous bacterial peritonitis, 5 pneumonia, 2 urinary tract infections, 2 skin infections and 11 undetermined infections). Three other patients had severe acute alcoholic hepatitis and one patient had a flare-up of autoimmune hepatitis. No patient was lost to follow-up. Median follow-up time was 300 (161–450) days.

At 12 months, 33 (17.9%) patients had died and 43 (23.4%) had been transplanted. Deceased patients or those who underwent LT within 1 year of follow-up had significantly higher serum copeptin concentrations at admission as compared to those who survived without a LT [deceased: 17.5 (7.2–37.9) vs. LT: 11.2 (4.8–28.1) vs. survivors without LT: 7.9 (4.7–14.3) pmol/L, $P < 0.01$]. Serum copeptin concentration increased significantly through CP-classes A [5.4 (3.1–10.7) pmol/L], B [9.6 (6.0–17.3) pmol/L] and C [13.8 (5.8–34.1) pmol/L, $P < 0.01$, Fig. 1]. Within-group comparison showed

Table 1. Patient characteristics at hospital admission of the 184 cirrhotic patients

Variable	All patients ($n = 184$)	Dutch patients ($n = 61$)	French patients ($n = 123$)	*P*-value
Age, years (SD)	55.7 (10.9)	51.0 (11.6)	58.1 (9.8)	<0.001
Male gender, *n* (%)	130 (70.7)	46 (75.4)	84 (68.3)	0.32
Aetiology of cirrhosis, *n* (%)				<0.001
HBV or HCV	21 (11.4)	11 (18.0)	10 (8.1)	
Alcohol*	129 (70.1)	26 (42.6)	103 (83.7)	
Other	34 (18.5)	24 (39.3)	10 (8.1)	
Indication of hospitalization†, *n* (%)				<0.001
Elective	129 (70.1)	55 (90.2)	74 (60.2)	
Acute decompensation	20 (10.9)	5 (8.2)	15 (12.2)	
Severe infection	31 (16.8)	1 (1.6)	30 (24.4)	
Other	4 (2.2)	0 (0.0)	4 (3.3)	
Ascites, *n* (%)	105 (57.1)	41 (67.2)	64 (52.0)	0.47
HRS, *n* (%)	9 (4.9)	7 (11.5)	2 (1.6)	0.007
MAP (mmHg)	84.8 (75.0–93.3)	84.7 (80.0–93.3)	85.0 (73.3–93.3)	0.21
Copeptin (pmol/L)	9.6 (4.9–20.7)	11.0 (5.2–24.0)	8.9 (4.8–17.5)	0.30
Bilirubin (μmol/L)	43.5 (24.0–100.8)	45 (26.5–84.5)	43 (21–113)	0.65
Sodium (mmol/L)	137.1 (5.1)	138.2 (5.1)	136.6 (5.0)	0.05
Albumin (g/L)	29.8 (7.3)	31.5 (5.8)	28.7 (7.7)	0.021
Creatinine (μmol/L)	81 (65.3–100.8)	86 (68.5–109)	80 (64–96)	0.40
CRP (mg/L)	12 (5–37)	9 (5.5–29)	13 (5–43)	0.32
INR	1.5 (1.2–2.1)	1.3 (1.2–1.4)	1.6 (1.3–2.3)	<0.001
MELD score	15.0 (11.3–21.9)	13.5 (11.3–16.9)	17.0 (11.0–24.0)	0.031
MELD-Na score	17.3 (12.1–24.3)	14.9 (11.9–18.1)	18.7 (13.0–25.3)	0.008
Child-Pugh score	9.0 (7.0–10.0)	9.0 (7.0–10.0)	9.0 (6.0–11.0)	0.61
Child-Pugh classes, %				
A/B/C	23/38/39	15/54/31	27/30/43	0.006

*Six patients with alcoholic cirrhosis were infected with viral hepatitis C; these patients are included in the alcoholic group.

†'Elective' hospital admission is defined as either screening for liver transplantation or a routine liver examination. 'Acute decompensation' is defined as the acute development of a major complication of cirrhosis (i.e. ascites, hepatorenal syndrome, gastrointestinal bleeding or hepatic encephalopathy). Other causes of hospital admission were acute alcoholic hepatitis ($n = 3$) and a flare-up of autoimmune hepatitis ($n = 1$).

CRP, C-reactive protein; DBP, diastolic blood pressure; HBV, hepatitis B virus; HCV, hepatitis C virus; HRS, hepatorenal syndrome; INR, international normalized ratio, MAP, mean arterial pressure; MELD, Model for End stage Liver Disease; MELD-Na, sodium MELD; SBP, systolic blood pressure; SD, standard deviation.

Data are shown as counts (percentage), mean (standard deviation) or median (interquartile range).

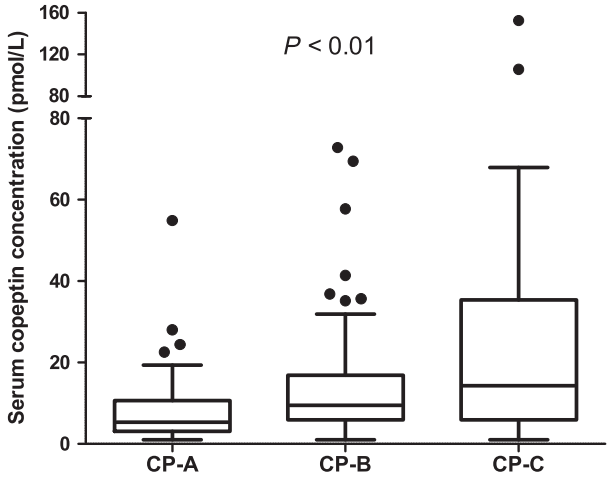

Fig. 1. Serum copeptin concentration in the three cirrhotic groups according to the Child-Pugh classification. Box plots represent serum copeptin concentrations in Child-Pugh classes A–C. Boxes are defined by interquartile ranges, and error bars represent the lowest and highest observed values within 1.5 times the length of the box. Data points outside this range are shown individually. Horizontal lines denote median values.

significant differences between serum copeptin concentration in CP-A and CP-B ($P < 0.01$) and between CP-A and CP-C ($P < 0.01$). Serum copeptin concentration did not differ significantly between CP-B and CP-C ($P = 0.35$). Patients admitted for acute decompensation of cirrhosis had more advanced stages of cirrhosis than electively admitted patients [CP-A/B/C: 0%/20% ($n = 11$)/80% ($n = 44$) vs. 32.6% ($n = 42$)/45.7% ($n = 59$)/21.7% ($n = 28$); $P < 0.01$] and had also higher serum copeptin concentrations [13.3 (5.9–34.1) vs. 8.5 (4.4–17.12) pmol/L, $P < 0.01$]. In patients with ascites at hospital admission ($n = 105$), a significantly higher serum copeptin concentration was measured as compared to patients without ascites [13.3 (6.9–31.8) vs. 6.1 (3.4–11.3) pmol/L, $P < 0.01$]. Serum copeptin concentration was also significantly higher in patients with RF ($n = 17$) at hospital admission as compared to patients without RF [36.8 (25.3–49.6) vs. 8.7 (4.6–16.7) pmol/L, $P < 0.01$]. Serum copeptin concentration was positively correlated with serum total bilirubin ($r = 0.26$, $P < 0.01$), CRP ($r = 0.34$, $P < 0.01$), creatinine concentration ($r = 0.39$, $P < 0.01$), INR ($r = 0.25$, $P < 0.01$) and MELD ($r = 0.38$, $P < 0.01$), MELD-Na ($r = 0.38$, $P < 0.01$) and CP ($r = 0.30$, $P < 0.01$) scores. No significant correlations with copeptin were found for MAP and serum sodium concentration.

Univariate analysis

Optimal cut-off points for serum copeptin and CRP concentration, MAP and MELD, MELD-Na and CP score in predicting mortality at 6 and 12 months are shown in Table 2A. Patients with a low serum copeptin concentration showed a significantly better transplant-free survival at both 6 and 12 months (Log-rank test: $P < 0.01$). Transplant-free survival at 6 months stratified according to serum copeptin concentration is shown in Fig. 2. In the univariate analyses, a high serum copeptin and CRP concentration and high MELD, MELD-Na and CP scores all showed a significant association with mortality at these time points. A significant association was also found with age, a low MAP (at 12 months) and the presence of ascites (Table 2A).

Patients with both a low serum copeptin concentration and high MELD, MELD-Na or CP score displayed the best transplant-free survival rates at 6 and 12 months as compared to (i) patients with both a high serum copeptin concentration and MELD, MELD-Na or CP score, (ii) patients with a low serum copeptin concentration and high MELD, MELD-Na or CP score and (iii) patients with a high serum copeptin concentration and low MELD, MELD-Na or CP score at time of hospital admission (Table 2A). Figure 3 shows transplant-free survival curves at 6 months, stratified according to both serum copeptin and MELD score. Figure S1A and S1B show transplant-free survival curves at 6 months, stratified according to serum copeptin and MELD-Na score and serum copeptin and CP score, respectively.

Multivariate analysis

Table 2B shows three multivariate Cox-regression models, in which copeptin is evaluated together with age, CRP and MELD (model 1), MELD-Na (model 2) or CP score (model 3), respectively. A high serum copeptin concentration at admission was found to be significantly associated with mortality at 6 and 12 months of follow-up, independently of age, high serum CRP and MELD, MELD-Na or CP score (Table 2B). Only at 12 months of follow-up, no significant association of high serum copeptin with mortality was found in the model with CP score. Separate multivariate Cox-regression models were fitted in order to evaluate the prognostic ability of high serum copeptin independently of the presence of ascites or a low MAP, in addition to age, high MELD or high MELD-Na score. A high serum copeptin concentration remained an independent predictor of mortality at 6 and 12 months of follow-up in these models. Ascites was not an independent prognostic factor at 6 or 12 months, whereas MAP only showed an independent association with mortality at 12 months (Table S1).

Sensitivity analysis

Sensitivity analyses were performed in order to assess the robustness of the prognostic value of copeptin in specific groups of cirrhotic patients. Survival analysis was performed in patients without RF, severe infections or acute decompensation of cirrhosis. When restricting survival analysis to patients without RF ($n = 167$), 6-

Table 2. Univariate (A) and multivariate (B) Cox regression analyses of factors influencing the 6- and 12-month transplant-free survival in 184 cirrhotic patients

	6-month mortality		12-month mortality	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
A. Univariate				
Age	1.06 (1.02–1.10)	0.004	1.06 (1.02–1.10)	0.001
Ascites	3.06 (1.23–7.63)	0.016	2.95 (1.32–6.57)	0.008
MAP				
Cut-off point (mmHg)	83		78	
High MAP	0.47 (0.21–1.05)	0.065	0.38 (0.19–0.76)	0.006
CRP				
Cut-off point (mg/L)	16.5		16.5	
High CRP	6.89 (2.59–18.29)	<0.001	4.72 (2.19–10.18)	<0.001
Copeptin				
Cut-off point (pmol/L)	12.3		12.3	
High copeptin	6.21 (2.49–15.48)	<0.001	3.90 (1.89–8.05)	<0.001
MELD score				
Cut-off point	18		24	
High MELD score	4.47 (1.99–10.04)	<0.001	6.55 (3.27–13.12)	<0.001
MELD-Na score				
Cut-off point	17		17	
High MELD-Na score	12.76 (3.02–54.04)	0.001	6.40 (2.47–16.61)	<0.001
Child-Pugh score				
Cut-off point	10		9	
High Child-Pugh score	3.82 (1.77–8.25)	0.001	5.72 (2.47–13.24)	<0.001
Copeptin and MELD score*				
Low copeptin + high MELD	0.68 (0.08–5.86)	0.72	5.00 (1.48–16.57)	0.009
High copeptin + low MELD	2.11 (0.57–7.84)	0.27	2.34 (0.88–6.25)	0.09
High copeptin + high MELD	10.41 (3.79–28.57)	<0.001	13.79 (5.70–33.36)	<0.001
Copeptin and MELD-Na score†				
Low copeptin + high MELD-Na	8.26 (0.99–68.61)	0.051	4.90 (1.35–17.81)	0.024
High copeptin + low MELD-Na	2.91 (0.18–46.56)	0.45	1.97 (0.33–11.82)	0.16
High copeptin + high MELD-Na	33.77 (4.50–253.50)	0.001	13.27 (3.91–45.04)	0.001
Copeptin and CP score‡				
Low copeptin + high Child-Pugh	0.00 (0.00–0.00)	0.98	2.86 (0.92–8.88)	0.07
High copeptin + low Child-Pugh	2.62 (0.88–7.80)	0.08	1.30 (0.33–5.20)	0.71
High copeptin + high Child-Pugh	11.53 (4.35–30.54)	<0.001	10.68 (4.23–27.00)	<0.001
B. Multivariate				
Model 1				
Age	1.05 (1.01–1.10)	0.010	1.06 (1.02–1.10)	0.002
High CRP	3.81 (1.37–10.62)	0.010	2.56 (1.11–5.89)	0.027
High copeptin	3.36 (1.26–8.98)	0.016	2.20 (1.00–4.82)	0.050
High MELD score	2.72 (1.12–6.59)	0.027	4.38 (2.03–9.47)	<0.001
Model 2				
Age	1.04 (1.00–1.09)	0.030	1.05 (1.01–1.09)	0.008
High CRP	2.88 (1.02–8.12)	0.046	2.49 (1.08–5.74)	0.033
High copeptin	3.59 (1.39–9.31)	0.009	2.47 (1.14–5.31)	0.021
High MELD-Na score	5.86 (1.30–26.30)	0.021	3.61 (1.31–9.97)	0.013
Model 3				
Age	1.05 (1.01–1.09)	0.017	1.07 (1.03–1.12)	<0.001
High CRP	4.14 (1.50–11.45)	0.006	3.11 (1.39–6.96)	0.006
High copeptin	3.65 (1.38–9.67)	0.009	1.84 (0.82–4.12)	0.14
High Child-Pugh score	2.16 (0.95–4.92)	0.066	5.26 (2.22–12.47)	<0.001

'Low' and 'high' refers to values below and above the optimal cut-off point as defined using the Youden index respectively. *,†,‡The reference groups were patients with low serum copeptin and *low MELD score, †low MELD-Na score, and ‡low Child-Pugh score.

CI, confidence interval; CP, Child-Pugh; CRP, C-reactive protein; HR, hazard ratio; MAP, mean arterial blood pressure; MELD, Model for End stage Liver Disease; MELD-Na, sodium MELD.

and 12-month survival rate was significantly lower in patients with a high serum copeptin concentration ($n = 57$) as compared to patients with a low serum copeptin concentration ($n = 110$; 6 months: 70.2% vs. 94.5%, $P < 0.01$; 12 months: 68.4% vs. 90.0%, $P < 0.01$). In patients without severe infections

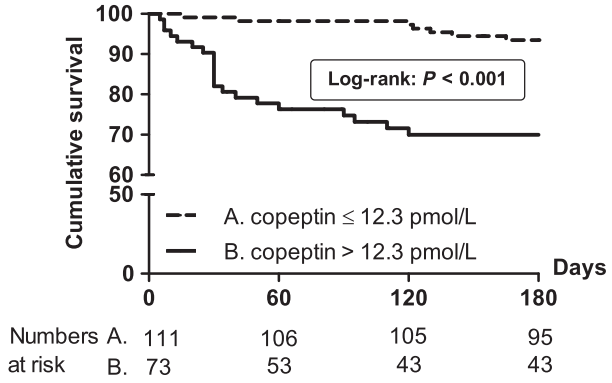

Fig. 2. Transplant-free survival at 6 months of follow-up of 184 hospitalized cirrhotic patients stratified according to serum copeptin concentration. Patients are censored at time of liver transplantation or last hospital visit.

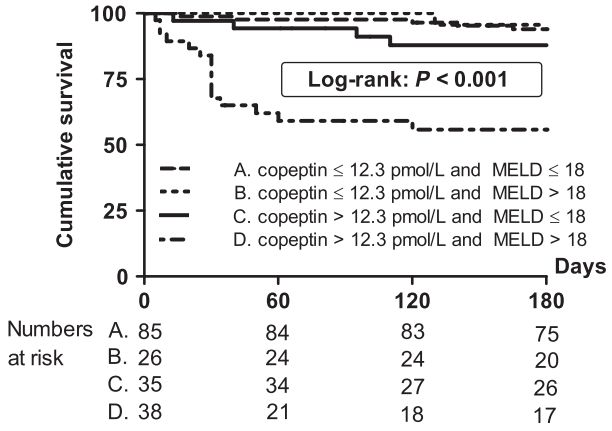

Fig. 3. Transplant-free survival at 6 months of follow-up of 184 hospitalized cirrhotic patients stratified according to serum copeptin concentration and Model for End stage Liver Disease (MELD) score. Patients are censored at time of liver transplantation or last hospital visit.

(n = 154), survival rates at 6 and 12 months were significantly lower in patients with a high serum copeptin concentration (n = 54) as compared to patients with a low serum copeptin concentration (n = 100; 6 months: 79.6% vs. 95.0%, $P < 0.01$; 12 months: 77.8% vs. 90.0%, $P = 0.04$). When restricting survival analysis to patients who were electively admitted (n = 129), patients with a high serum copeptin concentration (n = 84), showed significantly lower survival rates at 6 months as compared to patients with a low serum copeptin concentration (n = 45; 6 months: 84.4% vs. 95.2%, $P = 0.04$; 12 months: 82.2% vs. 89.3%, $P = 0.26$).

Discussion

In this study, we show that serum copeptin concentration is elevated in a large population of hospitalized, cirrhotic patients with varying degrees of disease severity. The highest serum copeptin concentrations were observed in patients with CP-C as compared to CP-A and CP-B patients, which is in accordance with previous recent findings (12–14). Patients who died or who received a LT within 1 year of follow-up had a significantly higher serum copeptin concentration at admission as compared to those who survived without a LT. Moreover, we show that serum copeptin is a predictor of short-term (6 months) and long-term (12 months) mortality, independently of age, serum CRP, MAP (at 12 months), the presence of ascites and liver-specific prognostic scores.

An increased intrahepatic vascular resistance and portal inflow and a decreased systemic vascular resistance contribute to the development of portal hypertension in cirrhosis. In advanced stages of cirrhosis, further reduction of systemic vascular resistance cannot be compensated by additional increases in cardiac output, leading to the activation of counter regulatory systems, such as the renin-angiotensin-aldosterone system, sympathetic nervous system and to the release of AVP by the posterior pituitary gland. The release of AVP into the blood stream leads to vasoconstriction and renal water retention (18). Because of the key role of AVP in haemodynamic homeostasis, exploration of AVP as a potential biomarker of haemodynamic derangement and prognosis in cirrhosis may be relevant. However, AVP molecules have a short half-life and more than 90% is bound to platelets in the circulation. Therefore, AVP measurements are not useful in clinical practice (3). Copeptin, a stable cleavage product of the C-terminal part of the AVP precursor, is secreted together with AVP in equimolar proportions and is not bound to platelets in the circulation (5). Serum copeptin is therefore a surrogate marker of AVP and is a promising prognostic marker in cirrhosis, as haemodynamic derangement is reported to be related to the severity of hepatic dysfunction and survival (2). Recent studies have shown associations between high serum copeptin levels and systemic haemodynamic changes, such as portal hypertension, a hepatic venous pressure gradient >12 mmHg and a decreased cardiac output (12, 13). It has also been reported that high serum copeptin concentrations are associated with the presence of ascites in cirrhosis (13). Currently, copeptin is considered a reliable prognostic factor in a wide variety of diseases, such as diabetes, heart failure, sepsis and lower respiratory tract infection (6–11). To date, one study has investigated the prognostic value of copeptin in the setting of cirrhosis (14). However, in that study, the combined endpoint 'mortality or LT' was used. The current study is the first one to evaluate copeptin as a potential marker of increased risk of mortality without LT in cirrhosis and the results corroborate that copeptin could serve as an independent prognostic marker in cirrhosis. In addition, we found that copeptin might give additional prognostic information next to the widely used MELD score and MELD-Na score.

In cirrhosis, pro-inflammatory cytokines have been found to be elevated and are related to circulatory derangement (19, 20). Patients with cirrhosis have an increased risk of developing systemic inflammation as a result of increased intestinal permeability and bacterial translocation (21). CRP is a well-known marker of inflammation and has recently demonstrated its prognostic significance in predicting short-term mortality in cirrhotic patients (22, 23). It has also been found that serum CRP and copeptin concentrations are both associated with disease severity and prognosis in non-cirrhotic patients with sepsis (11, 24). The results of the present study confirm the prognostic value of CRP in cirrhotic patients. We have also found a significant positive correlation between serum copeptin and CRP, indicating that copeptin is more than a potential biomarker of haemodynamic derangement. This might be explained by the fact that the release of AVP, and thus of copeptin, may also be triggered by exposure to stress, such as severe bacterial infection and sepsis. Another explanation may be that elevation of both serum CRP and copeptin is induced by common precipitating events, as exposure to bacteria and their endotoxins may exacerbate circulatory derangements and thus lead to an increase in serum copeptin concentration (12, 13, 25). In the current study, serum copeptin predicted mortality in hospitalized cirrhotic patients independently of CRP, also when restricting survival analysis to patients without severe infections at hospital admission.

A strength of our study is that the study population consisted of a heterogeneous group of cirrhotic patients, with a wide variety of disease severity and different indications of admission. The differences observed in baseline characteristics between the Dutch and French cohort, as indicated in Table 1, are also likely to be related to differences in these specific indications of hospital admission between the two centres. In the Dutch cohort, a vast majority of the patients were electively admitted for screening for LT, whereas in the French cohort a relatively large number of the cirrhotic patients were admitted for acute decompensation or a severe infection. In addition, there were evident differences in the aetiological background of cirrhosis between the two centres. The release of AVP, and thus of copeptin, is triggered under several conditions, such as pain, bleeding, nausea, infection, hypoxia and hypovolaemia (26). These factors are more likely to be present in patients suffering from acute decompensation of cirrhosis or sepsis than in electively admitted patients. Despite the heterogeneity of the study population, serum copeptin concentration independently predicted mortality, even when restricting survival analysis to the electively admitted patients. This finding shows the generalizability of the prognostic value of copeptin in cirrhosis.

This study has a number of limitations. Firstly, blood samples for serum copeptin measurements were only drawn at admission. After 12 months of follow-up, the independent predictive value of copeptin disappeared when adjusting for the MELD and CP score. This might be explained by changes in the course of liver disease progression over time. Prospectively conducted studies providing serial copeptin measurements are needed to evaluate potential effects of variation in serum copeptin concentration over time on survival. Secondly, we did not extensively investigate the relationship between renal function and serum copeptin concentration. Several studies have shown an inverse correlation between copeptin concentrations and renal function (15, 27, 28). In the current study, this inverse relationship between copeptin concentration and renal function was confirmed by a strong positive correlation between copeptin and creatinine concentration and the fact that serum copeptin was significantly higher in patients with RF as compared to patients without RF. The interpretation of serum copeptin concentration in cirrhotic patients should take into account renal function, but further research is needed to investigate whether a high serum copeptin concentration is causally related to renal impairment. Nevertheless, when restricting survival analysis to patients without RF at hospital admission, patients with a high serum copeptin concentration still displayed significantly higher mortality rates as compared to patients with a low serum copeptin concentration. Finally, we were not able to define the presence of acute-on-chronic liver failure (ACLF) in patients admitted for acute decompensation of cirrhosis in our present study cohort. ACLF is the most common cause of death in patients with decompensated cirrhosis (29) and it would be interesting to investigate whether there is an association between copeptin levels and the risk of development of ACLF. Because of the systemic vasoconstrictor effects of AVP, which are thought to contribute to the development of organ failures, copeptin levels might also be a potential predictor of the development of ACLF and survival in these patients.

In conclusion, serum copeptin concentration, as an indirect marker of circulatory dysfunction, increases significantly along with the severity of cirrhosis. More importantly, copeptin appears to predict 6-month and 12-month survival, independently of liver-specific scoring systems in a large and heterogeneous population of hospitalized cirrhotic patients.

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Supporting information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1111/liv.12992/suppinfo

Supplementary material

COPEPTIN IS AN INDEPENDENT PROGNOSTIC FACTOR FOR TRANSPLANT-FREE SURVIVAL IN LIVER CIRRHOSIS

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1) **Table S1**: **Multivariate Cox regression models of copeptin and other potential prognostic factors for 6- and 12-month transplant-free survival in 184 cirrhotic patients, including ascites (models 1 and 2) and mean arterial blood pressure (models 3 to 5).**

Variables	6 month- mortality		12 month- mortality	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1				
Age	1.07 (1.03-1.12)	0.002	1.07 (1.03-1.11)	< 0.001
Ascites	1.44 (0.55-3.77)	0.455	1.47 (0.62-3.51)	0.382
High copeptin	3.74 (1.41-9.93)	0.008	2.06 (0.93-4.57)	0.076
High MELD score	3.38 (1.42-8.09)	0.006	6.16 (2.83-13.41)	< 0.001
Model 2				
Age	1.06 (1.02-1.10)	0.006	1.06 (1.02-1.10)	0.003
Ascites	1.14 (0.44-2.96)	0.781	1.38 (0.59-3.22)	0.461
High copeptin	4.02 (1.57-10.29)	0.004	2.46 (1.15-5.25)	0.020
High MELD-Na score	8.49 (1.93-37.37)	0.005	5.85 (1.97-17.35)	0.001
Model 3				
Age	1.06 (1.02-1.11)	0.003	1.09 (1.05-1.13)	< 0.001
Low MAP	0.53 (0.23-1.20)	0.127	0.32 (0.15-0.68)	0.003
High copeptin	4.00 (1.52-10.53)	0.005	2.69 (1.22-5.94)	0.014
High MELD score	3.56 (1.49-8.52)	0.004	5.42 (2.50-11.75)	< 0.001
Model 4				
Age	1.06 (1.02-1.10)	0.004	1.08 (1.03-1.12)	< 0.001
Low MAP	0.48 (0.21-10.8)	0.076	0.36 (0.17-0.76)	0.007
High copeptin	4.54 (1.79-11.50)	0.001	3.32 (1.56-7.07)	0.002
MELD-Na score	9.21 (2.15-39.83)	0.003	4.15 (1.53-11.28)	< 0.001
Model 5				
Age	1.06 (1.02-1.10)	0.003	1.09 (1.05-1.14)	< 0.001
Low MAP	0.49 (0.22-1.10)	0.082	0.36 (0.17-0.75)	0.006
High copeptin	4.53 (1.75-11.74)	0.002	2.54 (1.15-5.61)	0.021
High CP score	3.01 (1.34-6.77)	0.008	5.24 (2.18-12.58)	< 0.001

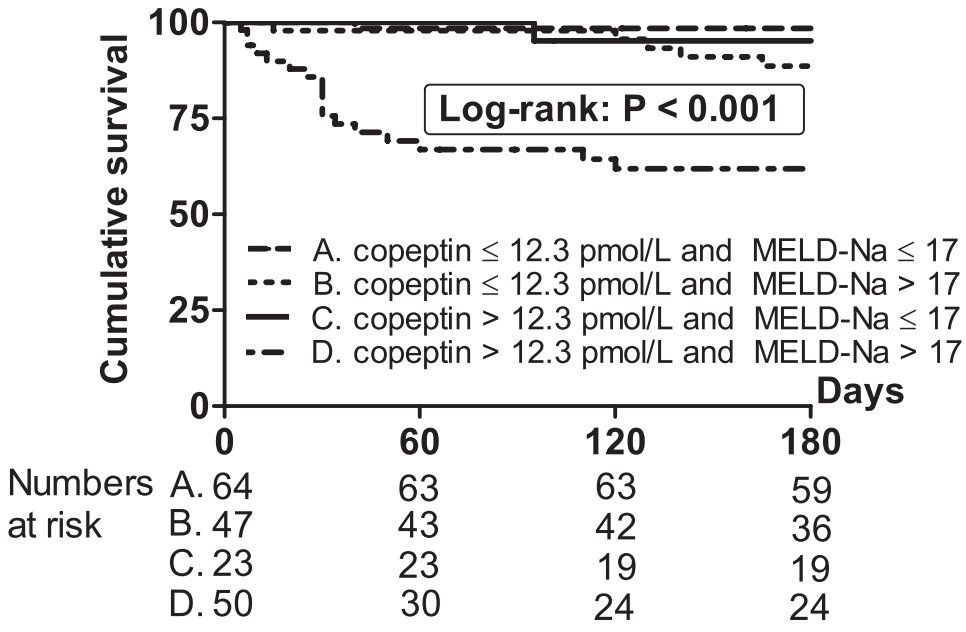
CI, confidence interval; CP, Child Pugh; CRP, C-reactive protein; HR, hazard ratio; MAP, mean arterial blood pressure; MELD, Model of End stage Liver Disease; MELD-Na, sodium MELD.

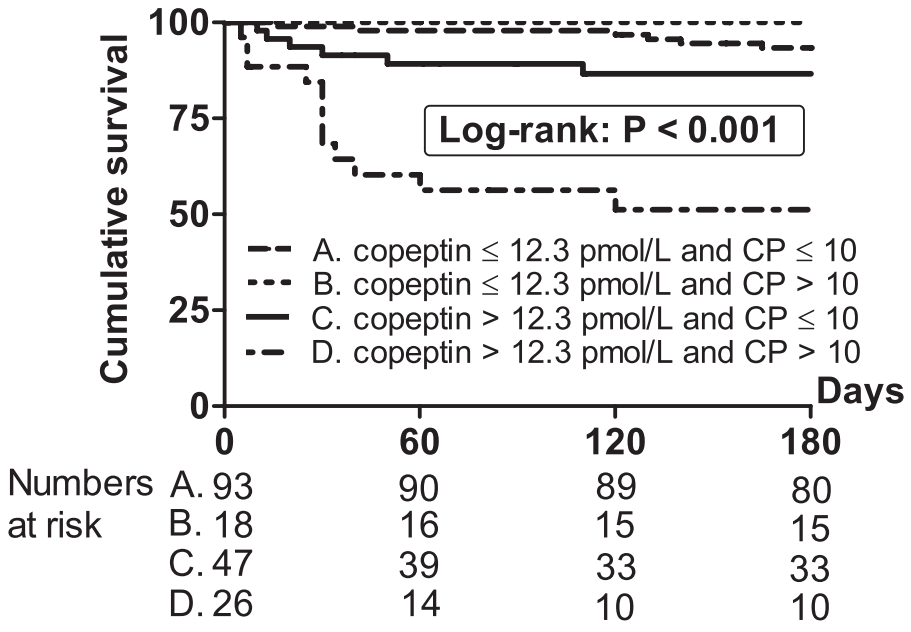
“Low” and “high” values refers to values below and above the optimal cut-off point as defined using the Youden index, respectively.

2) Figure legend of supplementary figure 1.

Supplementary figure S1. Transplant-free survival at 6 months of follow-up of 184 hospitalized cirrhotic patients stratified according to serum copeptin concentration and MELD-Na (A) and serum copeptin and Child-Pugh score (B).

Patients are censored at time of liver transplantation or last hospital visit.


Cumulative survival
100
75
50
25
0
Log-rank: P < 0.001
A. copeptin ≤ 12.3 pmol/L and MELD-Na ≤ 17
B. copeptin ≤ 12.3 pmol/L and MELD-Na > 17
C. copeptin > 12.3 pmol/L and MELD-Na ≤ 17
D. copeptin > 12.3 pmol/L and MELD-Na > 17
Days
0
60
120
180
Numbers at risk
A. 64 63 63 59
B. 47 43 42 36
C. 23 23 19 19
D. 50 30 24 24


Cumulative survival
100
75
50
25
0
Log-rank: P < 0.001
A. copeptin ≤ 12.3 pmol/L and CP ≤ 10
B. copeptin ≤ 12.3 pmol/L and CP > 10
C. copeptin > 12.3 pmol/L and CP ≤ 10
D. copeptin > 12.3 pmol/L and CP > 10
Days
0
60
120
180
Numbers at risk
A. 93 90 89 80
B. 18 16 15 15
C. 47 39 33 33
D. 26 14 10 10