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The Vasopressin Biomarker Copeptin Is Linked to Systemic Inflammation and Refines Prognostication in Decompensated Cirrhosis

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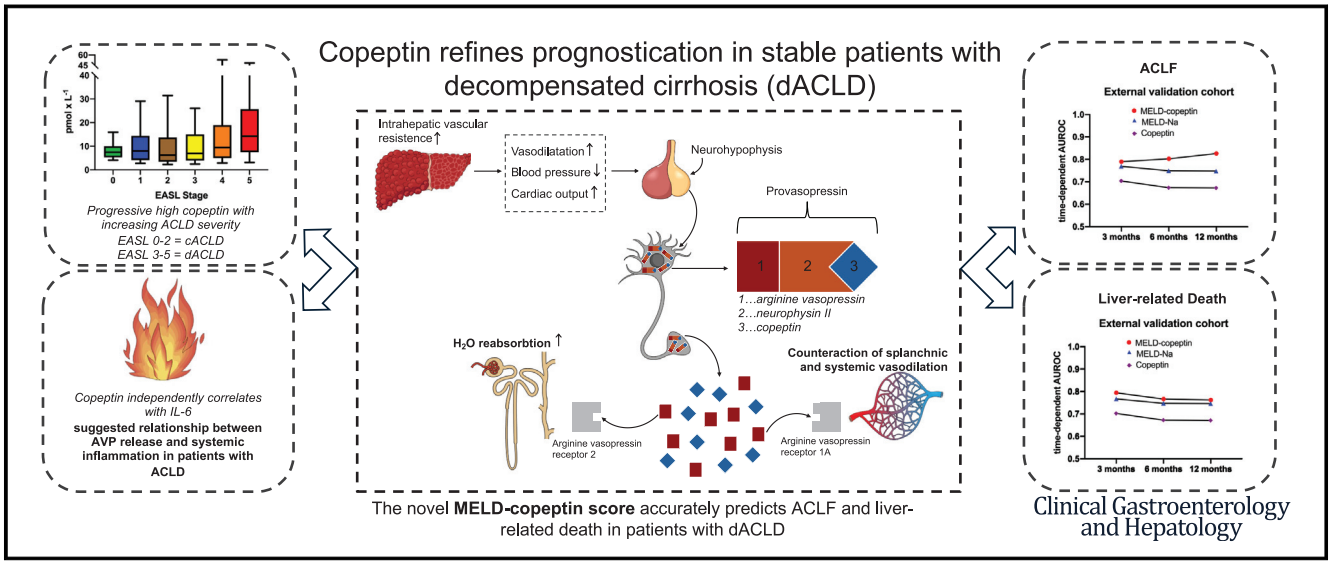

BACKGROUND & AIMS: **Copeptin, an arginine-vasopressin biomarker, may confer prognostic information in patients with advanced chronic liver disease (ACLD).**

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Abbreviations used in this paper: aB, adjusted Beta; ACLD, advanced chronic liver disease; ACLF, acute-on-chronic liver failure; asHR, adjusted subdistribution hazard ratio; AUROC, area under the receiver operating characteristic; AVP, arginine-vasopressin; CI, confidence interval; dACLD, decompensated advanced chronic liver disease; HVPG, hepatic venous pressure gradient; IL, interleukin; LRD, liver-related death; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MELD-copeptin, Model for End-Stage Liver Disease-Copeptin; MELD-Na, Model for End-Stage Liver Disease-Sodium; PH, portal hypertension.

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METHODS: **Patients with ACLD included in the Vienna Cirrhosis Study (NCT03267615) between January 2017 and April 2023 and available copeptin levels were prospectively recruited and classified into 6 predefined clinical ACLD stages from S0 (subclinical portal hypertension) to S5 (further decompensation). A prognostic score (MELD-copeptin score) in patients with decompensated ACLD (dACLD) was developed in a derivation cohort (n = 150) and validated in an internal (n = 148) and an external validation cohort (n = 771).**

RESULTS: **Among 475 patients with ACLD, 177 were compensated, whereas 298 were decompensated. Median levels of copeptin increased with progressive ACLD severity (S0, 7.5 pmol/L vs S5, 14.3 pmol/L; $P < .001$). Copeptin (adjusted Beta, 0.10; $P < .001$) was independently associated with interleukin-6 levels in dACLD. In dACLD, copeptin was linked to higher risk of further decompensation (adjusted subdistribution hazard ratio, 1.01; 95% confidence interval, 1.00–1.01; $P = .039$), acute-on-chronic liver failure (adjusted subdistribution hazard ratio, 1.01; 95% confidence interval, 1.01–1.02; $P < .001$), and liver-related death (adjusted subdistribution hazard ratio, 1.01; 95% confidence interval, 1.01–1.02; $P < .001$) independently of relevant cofactors. The MELD-copeptin score yielded higher area under the receiver operating characteristics (AUROCs) for liver-related events than the MELD-Na score in the internal validation cohort, accurately predicting liver-related death at 6 months (AUROC, 0.777 vs MELD-Na, 0.673), 1 year (AUROC, 0.784 vs MELD-Na, 0.661), and 2 years of follow-up (AUROC, 0.741 vs MELD-Na, 0.636). Similarly, the MELD-copeptin score consistently yielded higher AUROCS for the development of liver-related death and acute-on-chronic liver failure at 3, 6, and 12 months of follow-up in the external validation cohort.**

CONCLUSIONS: **In patients with dACLD, copeptin is independently linked to systemic inflammation. The MELD-copeptin score identifies patients with dACLD at risk for impaired clinical outcomes.**

Keywords: Arginine Vasopressin; Decompensation; Inflammation; ACLF.

Although in early asymptomatic stage advanced chronic liver disease (ACLD) is considered compensated, patients progress to decompensated ACLD (dACLD) with the development of portal hypertension (PH)-related complications, specifically variceal bleeding, ascites, and hepatic encephalopathy.[1–3] Acute-on-chronic liver failure (ACLF), which may occur in patients with dACLD,[4,5] is characterized by hepatic and extrahepatic organ failures[6,7] and is associated with systemic inflammation.[8]

Development of PH is caused by an increase in intrahepatic vascular resistance and subsequentially aggravated by the development of hyperdynamic circulation with increased cardiac output, systemic vasodilation, and hypotension.[9,10] As a counterregulatory mechanism, the renin-angiotensin system is activated and the release of arginine-vasopressin (AVP) is upregulated.[11] As a result, increased levels of AVP have been documented in the circulation of patients with decompensated liver cirrhosis,[12] which leads to fluid overload[13,14] and may additionally impair the prognosis of patients with dACLD.

Copeptin is a cleavage product of an AVP precursor that is present in the circulation in amounts equimolar to AVP.[15] Because copeptin is more stable and can be easily measured, it has been proposed as an AVP biomarker.[15,16] Recently, a systematic review and meta-analysis presented copeptin as a promising marker for prognostication in patients with dACLD.[17] In this study, the ratio of means of copeptin for 90-day mortality in patients with dACLD even outperformed the Model for End-Stage Liver Disease (MELD) score.[17] Moreover, increased levels of copeptin have been reported in states of acute decompensation, such as spontaneous bacterial peritonitis.[18]

However, detailed data on copeptin in distinct stages of ACLD, and on its prognostic value for adverse outcomes in patients with dACLD, are still scarce and it is unclear whether copeptin represents an independent predictor of clinical outcomes in dACLD. Thus, this study aimed to (1) investigate the plasma levels of copeptin throughout the distinct clinical stages of ACLD,[5] (2) analyze parameters associated with copeptin levels in patients with dACLD, (3) evaluate whether copeptin >11.4 pmol/L (using the previously established cutoff) is linked to clinical outcomes in dACLD, and (4) investigate whether copeptin as a metric variable confers prognostic value in patients with dACLD on top of the established Model for End-Stage Liver Disease-Sodium (MELD-Na) score.

Patients and Methods

Study Design

This study (Vienna Cirrhosis Study, Clinical trial number NCT03267615) included consecutive clinically stable outpatients with ACLD with available plasma copeptin who underwent hepatic venous pressure gradient (HVPG) measurement at the Hepatic

Hemodynamic Lab of the Vienna General Hospital between January 2017 and April 2023 following a standardized operating procedure.[19]

Patients with vascular liver disease, portal vein thrombosis, hepatocellular carcinoma or other malignancy, a history of liver transplantation (LT), transjugular intrahepatic portosystemic shunt, congestive heart disease, active infection at the time of HVPG measurement, or insufficient available laboratory or clinical data were excluded.

Further information on the study design, definition of decompensation events, assessment of HVPG and liver stiffness measurement, and laboratory parameter analysis are given in the supplementary material.

Patient Cohorts

Details on baseline stratification of patients with ACLD are provided in the supplementary material. For the development and internal validation of the MELD-copeptin score, patients with dACLD were subdistributed into a derivation and a validation cohort of approximately the same size depending on the time point of the HVPG measurement (derivation cohort, January 2017–December 2019; internal validation cohort, December 2019–April 2023).

Moreover, we included an external validation cohort comprising hospitalized patients with dACLD from Besancon (included April 2008–June 2009; n = 125),[20] and patients without ACLF at baseline included in the CANONIC database (included March 2011–December 2011; n = 646).[21]

Statistical Analysis

Categorical variables were presented as number and proportion (%), whereas continuous data were reported as median with interquartile range. For comparison of continuous nonnormally distributed variables between 2 groups, Mann-Whitney *U* test was computed. Kruskal-Wallis test was performed for comparing continuous variables among 3 or more groups. Pearson chi-square test was used for group comparisons of categorical variables. Spearman Rho (ρ) was implemented to test for correlations. Linear regression analysis was conducted to investigate factors associated with plasma copeptin in patients with dACLD.

All clinical outcome analyses were performed exclusively on patients with dACLD. Clinical outcomes were assessed using cumulative incidence calculation at 0.5, 1, and 2 years of follow-up. Gray test, as previously described,[22] was assessed for cumulative incidence comparison. Fine and Gray competing risk regression models using the R package cmprsk[22,23] were computed to evaluate whether copeptin (as a continuous variable) was associated with the risk of clinical events of interest. Apart from copeptin, well-established risk factors for worse outcomes in ACLD (ie, age, MELD-Na score, albumin, and HVPG as a marker for PH) and sex and body mass index were evaluated by univariate and multivariate analysis. LT and non-liver-related death (LRD) were considered as competing risks for LRD, whereas LT and death were competing risks for ACLF in cumulative incidence comparisons and competing risk regression models. In both the linear regression models and the competing risk regression models, parameters that were associated with the parameter of interest in univariate analysis ($P \leq .100$) were included in the multivariate model. Moreover, copeptin as the main target parameter, and MELD-Na score and HVPG as established parameters of pathophysiological and prognostic relevance, were included in the multivariate models.

For estimating the hazard ratio function and 95% pointwise confidence band of plasma copeptin on liver-related mortality, a restricted cubic spline function was computed using the R package rms.[24] The MELD-copeptin score was developed with coefficients derived from a competing risk regression model of LRD containing both MELD-Na and plasma copeptin and considering LT as a competing event. The prognostic utility of copeptin for further decompensation, ACLF, and LRD was further investigated in the derivation cohort, the internal validation cohort, and the external validation cohort (data about ACLF were only available in the internal derivation cohort, the internal validation cohort, and the external cohort from the CANONIC database) by calculating areas under the time-dependent receiver-operating characteristic curve (AUROCs).

IBM SPSS 27.0 statistic software (IBM, Armonk, NY), R 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism 8 (GraphPad Software, La Jolla, CA) were used for

What You Need to Know

Background

Recently, the arginine-vasopressin (AVP) byproduct copeptin has been proposed as a marker linked to the prognosis of patients with decompensated advanced chronic liver disease (dACLD).

Findings

Plasma copeptin independently correlates with interleukin-6 in dACLD, linking AVP to systemic inflammation. The MELD-copeptin score predicts liver-related mortality with a high accuracy in patients with dACLD.

Implications for patient care

Copeptin refines prognostication in patients with dACLD. The MELD-copeptin score identifies patients at particularly high risk for adverse clinical outcomes, contributing to a more personalized management for patients with dACLD.

statistical analyses. A 2-sided P value of $< .05$ was considered statistically significant.

Ethics

The study was approved by the respective ethics committees and was performed in accordance with the current version of the Helsinki Declaration. All patients included in the Viennese cohorts are part of the prospective Vienna Cirrhosis Study (ClinicalTrials.gov, Number: NCT03267615). All patients included in the study gave their written informed consent before study inclusion.

Results

Patient Characteristics

In total, 475 patients with ACLD and a median MELD of 11 were included. The median age was 57.1 years and most included patients were male (72.6%). The patient flow chart is presented in Supplementary Figure 1 and baseline characteristics of patients with compensated ACLD and with dACLD are shown in Supplementary Table 1. The main etiology was alcohol-related liver disease (46.8%), of whom 74.8% (n = 166/222) were abstinent at the time of characterization. The study included 62.7% of patients with dACLD, most frequently caused by ascites (92.6%).

Plasma Copeptin Levels in Patients With Different Clinical Stages of Advanced Chronic Liver Disease

With progressive ACLD severity, patients exhibited significantly higher median plasma levels of copeptin (from S0: 7.5 pmol/L to S5: 14.3 pmol/L; $P < .001$) (Figure 1, Supplementary Table 2). Moreover, as depicted in Figure 1, the percentage of patients with copeptin >11.4 pmol/L significantly increased throughout the different clinical stages of ACLD from 18.4% (n = 9/49) of patients with ACLD stage S0 to 57.5% (n = 69/120) of patients with ACLD stage S5 ($P < .001$).

Follow-up and Clinical Outcomes in All Patients

The median follow-up period was 793 days. Overall, 32.8% of patients (n = 156) experienced at least 1 (further) decompensation event. Details on the rates of different decompensation events in the entire cohort, and among patients with compensated ACLD and dACLD are given in Supplementary Table 3. In the overall cohort, 16 patients (3.4%) developed hepatocellular carcinoma during follow-up. Transjugular intrahepatic portosystemic shunt implantation was conducted in 9.5% (n = 45) of patients and 37 patients (7.8%) underwent LT. A 25.1% (n = 119) of patients died, with 87 of these deaths (73.1%) being attributed to liver disease.

After adjustment for clinically relevant cofactors, copeptin was independently associated with higher risk of further decompensation (adjusted subdistribution hazard ratio [asHR], 1.01; 95% confidence interval [CI], 1.00–1.01; $P = .039$) (Table 1), ACLF (asHR, 1.01; 95% CI, 1.01–1.02; $P < .001$), and LRD (asHR, 1.01; 95% CI, 1.01–1.02; $P < .001$).

Correlations of Plasma Copeptin, Parameters of Liver Function, and Systemic Inflammation

Details on the correlation of copeptin with parameters of liver dysfunction, PH, endothelial dysfunction, and systemic inflammation in patients with dACLD are given in the supplementary material (Supplementary Table 4).

In multivariate linear regression analysis (Supplementary Table 5), copeptin was independently linked to interleukin (IL)-6 (per ng/dL; adjusted Beta [aB], 0.10; $P < .001$), Child-Turcotte-Pugh score (per point; aB, 1.52; $P < .001$), and creatinine (per mg/dL; aB, 9.13; $P < .001$) in patients with dACLD.

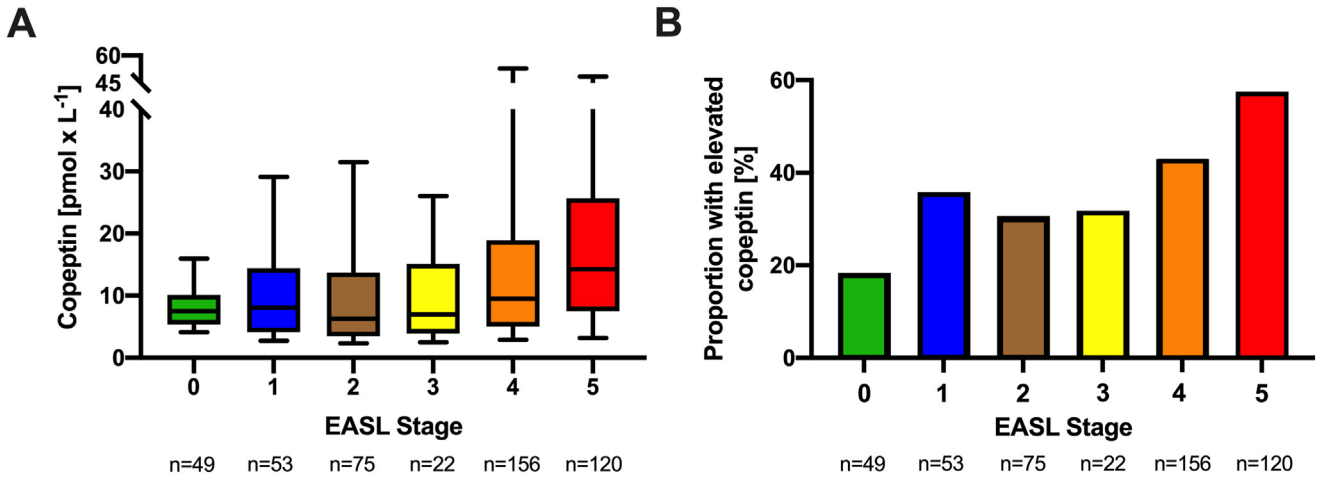

Figure 1. (*A*) Plasma levels of copeptin (pmol/L) and (*B*) the prevalence (%) of copeptin >11.4 pmol/L in patients with different stages of ACLD. Patients stratified by European Association for the Study of the Liver (EASL) clinical stages of cirrhosis.

Table 1. Impact of Copeptin on the Risk of Further Decompensation, ACLF, and Liver-Related Death in Patients With Decompensated Cirrhosis

	Univariate (unadjusted) analysis			Multivariate (adjusted) analysis		
Parameter of interest	sHR	95% CI	*P* value	asHR	95% CI	*P* value
Further decompensation						
Copeptin, *pmoL x L*$^{-1}$	1.01	1.00–1.01	**.039**	1.01	1.00–1.01	**.029**
Age, *y*	1.00	0.99–1.02	.650	—	—	—
Sex, male	1.03	0.69–1.54	.890	—	—	—
BMI, *kg/m*^{2}	0.98	0.94–1.01	.190	—	—	—
Child-Turcotte-Pugh score, points	1.17	1.07–1.28	**< .001**	1.13	1.02–1.25	**.018**
Creatinine, *mg x dL*$^{-1}$	0.99	0.85–1.15	.880	—	—	—
Sodium, *mmol x L*$^{-1}$	0.96	0.92–1.00	**.039**	0.99	0.95–1.03	.560
HVPG, *mm Hg*	1.03	1.00–1.06	**.025**	1.02	0.99–1.05	.190
ACLF						
Copeptin, *pmoL x L*$^{-1}$	1.01	1.01–1.02	**< .001**	1.01	1.00–1.01	**.014**
Age, *y*	1.03	1.01–1.05	**.003**	1.04	1.02–1.07	**< .001**
Sex, male	1.5	0.86–2.64	.160	—	—	—
BMI, *kg/m*^{2}	1.01	0.96–1.06	.650	—	—	—
Child-Turcotte-Pugh score, points	1.26	0.80–1.13	**< .001**	1.28	1.12–1.47	**< .001**
Creatinine, *mg x dL*$^{-1}$	1.13	0.98–1.30	.100	1.07	0.92–1.24	.390
Sodium, *mmol x L*$^{-1}$	0.93	0.89–0.98	**.004**	0.99	0.93–1.05	.760
HVPG, *mm Hg*	1.04	1.02–1.06	**< .001**	1.02	0.99–1.04	.140
Liver-related death						
Copeptin, *pmoL x L*$^{-1}$	1.01	1.01–1.02	**< .001**	1.01	1.00–1.01	**.006**
Age, *y*	1.03	1.01–1.06	**.002**	1.05	1.02–1.07	**< .001**
Sex, male	1.43	0.80–2.57	.230	—	—	—
BMI, *kg/m*^{2}	1.03	0.98–1.08	.300	—	—	—
Child-Turcotte-Pugh score, points	1.26	1.13–1.4	**< .001**	1.31	1.14–1.51	**< .001**
Creatinine, *mg x dL*$^{-1}$	1.12	0.97–1.29	.120	—	—	—
Sodium, *mmol x L*$^{-1}$	0.95	0.90–1.00	.068	1.01	0.95–1.08	.700
HVPG, *mm Hg*	1.04	1.02–1.06	**< .001**	1.02	0.99–1.04	.220

NOTE. Univariate and multivariate competing risk regression models are shown. Liver transplantation and non-liver-related death were considered as competing risks, as appropriate. Bolded values mean that the value is statistically significant.
ACLF, acute-on-chronic liver failure; asHR, adjusted sHR; BMI, body mass index; CI, confidence interval; HVPG, hepatic venous pressure gradient; MELD-Na, Model for End-Stage Liver Disease–Sodium; sHR, subdistribution hazard ratio.

Impact of Copeptin >11.4 pmol/L on Clinical Outcomes in Patients With Decompensated Advanced Chronic Liver Disease

A detailed comparison of characteristics of patients with dACLD with and without copeptin >11.4 pmol/L is provided in the supplementary material and Supplementary Table 6.

Supplementary Table 7 exhibits the clinical outcomes of patients with dACLD with and without copeptin >11.4 pmol/L and details are given in the supplementary material. As depicted in Figure 2, Patients with dACLD and copeptin >11.4 pmol/L exhibited a higher cumulative incidence of further decompensation ($P = .002$) (Supplementary Table 8), ACLF ($P < .001$), and LRD ($P < .001$).

Development of a Prognostic Score in Decompensated Advanced Chronic Liver Disease Containing Copeptin (Derivation Cohort)

Because copeptin levels conferred prognostic information independently of the MELD-Na score, we developed a score containing copeptin (ie, MELD-copeptin score) in our derivation cohort of patients with dACLD (n = 150). This is described in detail in the supplementary material (Supplementary Figures 2 and 3) Characteristics and clinical outcomes of patients included in the derivation cohort, internal validation cohort, and external validation cohort are given in Table 2 and Supplementary Table 9.

In the derivation cohort, the MELD-copeptin score yielded higher AUROCs for liver-related events than the established MELD-Na score, accurately predicting not only liver-related 6-month mortality (AUROC 0.836 vs MELD-Na 0.803), but also ACLF (AUROC 0.828 vs MELD-Na 0.788) and further decompensation (AUROC 0.722 vs MELD-Na 0.671).

Prognostic Performance of the Model for End-Stage Liver Disease-Copeptin Score (Internal and External Validation Cohort)

Both in the internal (n = 148) and in the external validation cohort (n = 771), the MELD-copeptin score

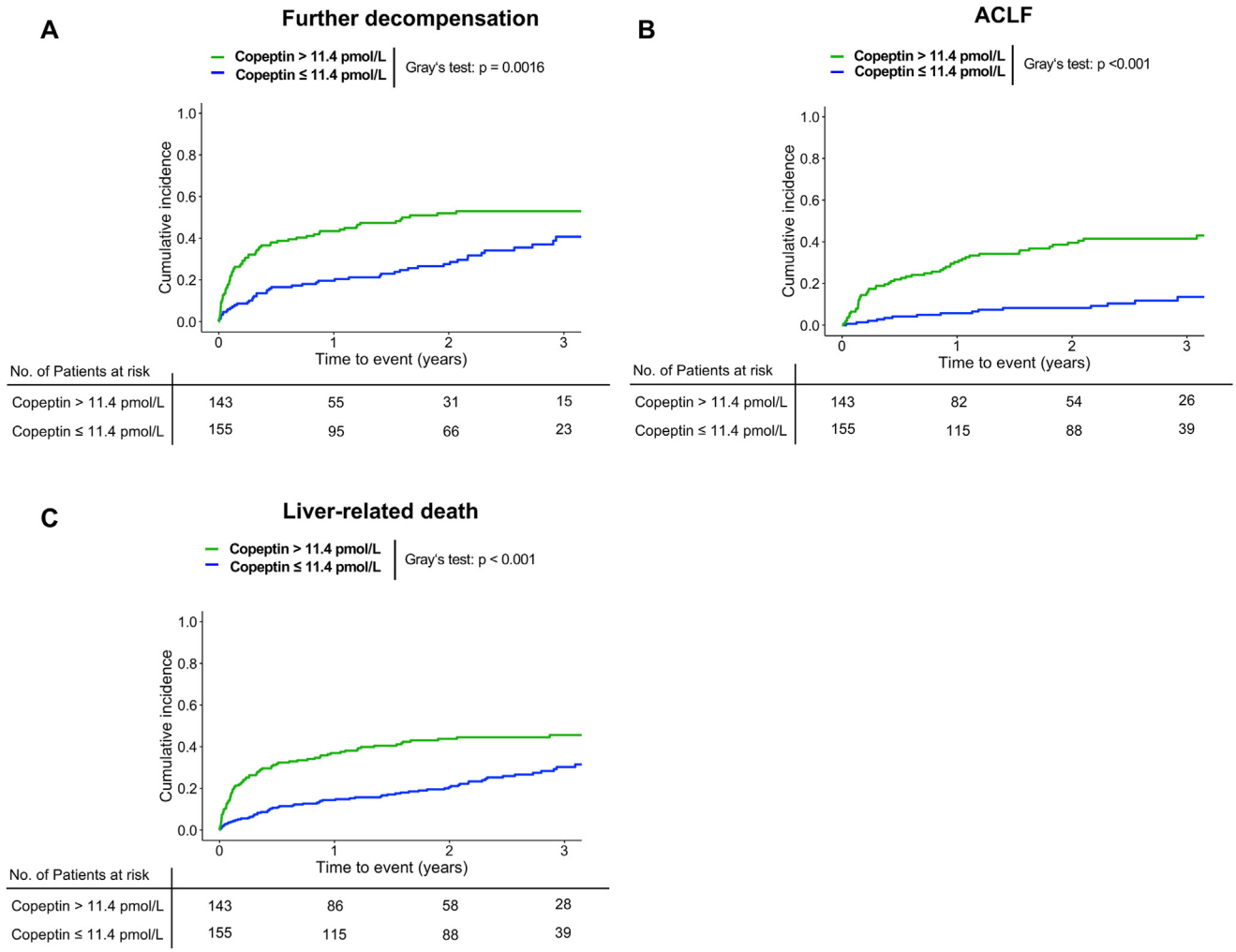

Figure 2. Cumulative incidence of (*A*) further hepatic decompensation, (*B*) ACLF, and (*C*) liver-related death stratified by copeptin >11.4 pmol/L. Liver transplantation and non-liver-related death were considered as competing risks. Cumulative incidences were compared via Gray test.

achieved excellent time-dependent AUROCs for LRD at different time points during follow-up (Figure 3) (Internal validation cohort: 6 months, AUROC 0.777; 12 months, AUROC 0.784; 24 months, AUROC 0.741. External validation cohort: 3 months, AUROC 0.793; 6 months, AUROC 0.765; 12 months, AUROC 0.761), which were consistently higher than the AUROCs of the MELD-Na score (Internal validation cohort: 6 months, AUROC 0.673; 12 months, AUROC 0.661; 24 months, AUROC 0.636. External validation cohort: 3 months, AUROC 0.768; 6 months, AUROC 0.748; 12 months, AUROC 0.747).

Moreover, as detailed in Supplementary Tables 10 and 11, the MELD-copeptin score also accurately predicted ACLF in the internal and the external validation cohort (n = 771), consistently yielding the highest AUROCs at different time points during follow-up.

Discussion

In this prospective study, by thoroughly assessing plasma levels of copeptin in clinically stable outpatients with ACLD, we demonstrate that copeptin levels are elevated with increased disease severity of ACLD. Notably, plasma copeptin levels were independently linked to IL6, indicating that systemic inflammation is a driver for AVP increase in dACLD. Importantly, we found that copeptin represents an independent risk factor for further decompensation, ACLF, and LRD in dACLD. Finally, the MELD-copeptin score exhibited high accuracy for the prediction of liver-related events in an internal and an external validation cohort, indicating that copeptin refines the prognostic information of MELD-Na in patients with dACLD.

AVP is a potent vasoconstrictor that, together with the sympathetic nervous system and the renin-angiotensin system, counteracts systemic vasodilation in patients with dACLD, maintaining normal or near-normal blood pressure.[14] In addition, AVP induces reabsorption of free water and thus impairs the renal capacity for fluid and sodium excretion and causes volume overload.[14] Moreover, these alterations cause a decrease in glomerular filtration rate and distal tubular filtration.[25] Indeed, the prevalence of acute kidney

Table 2. Patient Characteristics of the Patients With dACLD in the Derivation Cohort, Internal Validation Cohort, and External Validation Cohort

Patient characteristics	Derivation cohort (n = 150)	Internal validation cohort (n = 148)	External validation cohort (n = 771)	*P* value
Sex, male/female (% male)	117/33 (78.0)	96/52 (64.9)	508/263 (65.9)	**.012**
Age, *y* (IQR)	57.1 (49.7–66.5)	56.7 (49.0–65.7)	57.7 (50–65.4)	.872
Ethnicity, n (%)				**< .001**
White	138 (92.0)	135 (91.2)	754 (97.8)	
Black	2 (1.3)	6 (4.1)	3 (0.4)	
Asian	10 (6.7)	7 (4.7)	4 (0.5)	
Other	0 (0.0)	0 (0.0)	10 (1.3)	
Etiology, n (%)				**< .001**
ALD	83 (55.3)	94 (63.5)	478 (62.0)	
Viral hepatitis	13 (8.7)	8 (5.4)	164 (21.3)	
ALD + viral hepatitis	14 (9.3)	10 (6.8)	6 (0.8)	
MASH	9 (6.0)	5 (3.4)	15 (1.9)	
Cholestatic	2 (1.3)	9 (6.1)	23 (3.0)	
AIH	4 (2.7)	4 (2.7)	0 (0.0)	
Cryptogenic	13 (8.7)	10 (6.8)	1 (0.1)	
Other	12 (8.0)	7 (4.7)	84 (10.9)	
MELD-Na, points (IQR)	15 (12–19)	15 (12–20)	18 (14–23)	**< .001**
CTP score, points (IQR)	7 (6–9)	8 (6–10)	9 (8–11)	**< .001**
CTP stage, n (%)				**< .001**
A	41 (27.3)	38 (25.7)	79 (10.2)	
B	76 (50.7)	72 (48.6)	302 (39.2)	
C	33 (22.0)	38 (25.7)	283 (36.7)	
Bilirubin, *mg x dL*$^{-1}$ (IQR)	1.4 (0.9–2.4)	1.6 (0.9–2.7)	2.7 (1.5–5.6)	**< .001**
Albumin, *g x dL*$^{-1}$ (IQR)	34.7 (29.9–38.4)	34.1 (31.0–37.8)	29.0 (25.0–33.0)	**< .001**
INR, *U* (IQR)	1.5 (1.3–1.6)	1.4 (1.2–1.6)	1.5 (1.3–1.8)	.066
Sodium, *mmol x L*$^{-1}$ (IQR)	1370. (125.0–140.0)	137.0 (134.0–139.0)	136.0 (133.0–139.0)	.178
Copeptin, *pmoL x L*$^{-1}$ (IQR)	11.9 (6.6–22.2)	10.3 (5.1–19.4)	10.6 (4.3–26.1)	.456
WBC, *G x L*$^{-1}$ (IQR)	4.7 (3.3–6.4)	4.9 (3.4–6.6)	5.7 (4.1–8.3)	**.001**
CRP, *mg x dL*$^{-1}$ (IQR)	0.5 (0.2–1.2)	0.5 (0.2–1.5)	0.9 (0.1–2.9)	**< .001**

NOTE. Bolded values mean that the value is statistically significant.
ACLD, advanced chronic liver disease; AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; dACLD, decompensated advanced chronic liver disease; INR, international normalized ratio; IQR, interquartile range; MASH, metabolic dysfunction-associated steatohepatitis; MELD-Na, Model for End-Stage Liver Disease–Sodium; WBC, white blood cell count.

injury during follow-up in our cohort was significantly higher among patients with copeptin >11.4 pmol/L and higher copeptin was independently linked to creatinine in linear regression analysis, indicating that antidiuretic hormone–mediated arterial vasoconstriction within the kidney[14] might trigger acute kidney injury in these patients. Of note, we want to emphasize that this study investigated clinically stable outpatients with dACLD without acute states of decompensation, infection, and renal failure. Indeed, in case of hepatorenal syndrome (ie, hepatorenal syndrome/acute kidney injury), the AVP analogue terlipressin has been shown to actually exert beneficial effects on renal function in patients with dACLD.[26,27]

Investigating the entire spectrum of ACLD, we were able to demonstrate that a significant increase of plasma copeptin occurs in the stage of dACLD.[5] Therefore, we only included patients with dACLD in our follow-up analyses. Interestingly, in dACLD, copeptin showed a considerable correlation with IL6 as a parameter of systemic inflammation[3] and in linear regression analysis, these 2 parameters were associated independently of hepatic dysfunction and HVPG. This suggests that systemic inflammation may be a relevant driver of AVP release in patients with dACLD. Supporting this, 1 study in rats found that AVP release is promoted on administration of lipopolysaccharide,[28] representing an AVP response to inflammation.[29] Moreover, it has been demonstrated that plasma copeptin is up-regulated in sepsis[30] and lower respiratory tract infections.[31] In fact, copeptin has been proposed as a prognostic marker in patients with community-acquired pneumonia.[32–34] Further studies are required to determine whether there is a mechanistic link between AVP release and inflammation in ACLD.

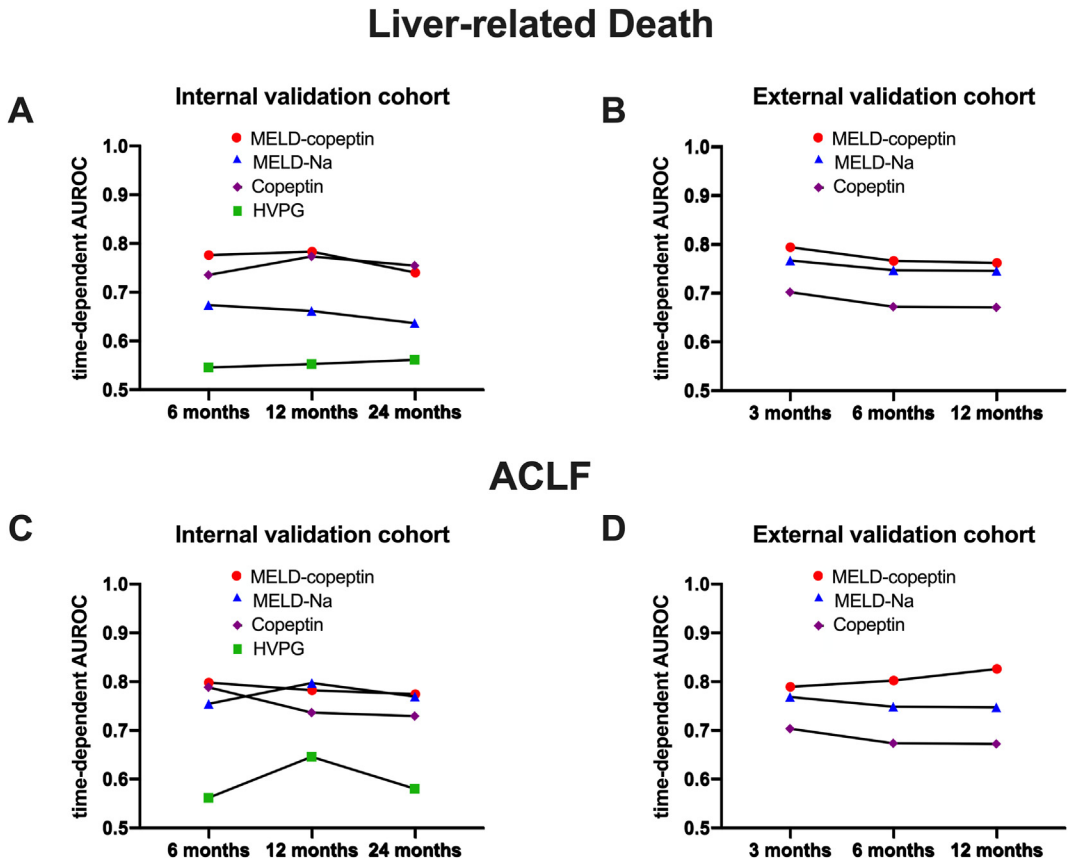

Figure 3. Time-dependent AUROCs of (*A-D*) the MELD-copeptin score, plasma copeptin, MELD-Na score, and (*A, C*) HVPG for the development of clinical outcomes at (*A, C*) 6 months, 12 months, and 24 months of follow-up in the internal validation cohort and (*B, D*) at 3 months, 6 months, and 12 months of follow-up in the external validation cohort.

Importantly, our study demonstrates that copeptin carries significant prognostic value in patients with dACLD. In our cohorts of 298 patients with dACLD, we could demonstrate that copeptin is a predictor of further decompensation, ACLF, and liver-related mortality independent of liver dysfunction and PH (assessed by the HVPG). This confirms and extends the findings of a previous study of our group, which showed similar results, but was limited by the small sample size (n = 77 with dACLD and available copeptin levels).[16] Although another study also independently linked increased levels of copeptin to decreased 6-month transplant-free survival,[20] our study is the first that identifies copeptin as an independent risk factor for liver-related mortality implementing competing risk regression analysis. Importantly, copeptin represents an independent risk factor not only for LRD, but also for further decompensation and ACLF, which underscores the detrimental role of AVP in ACLD, because it links increased levels of copeptin to disease progression and the development of organ failures. Although 1 study demonstrated that elevated copeptin in inpatients with ACLD with hospital admission caused by acute decompensation independently predicts ACLF,[21] our data indicate that this is also the case in clinically stable outpatients with dACLD without acute decompensation.

Most notably, we propose a novel MELD-copeptin score for risk stratification in patients with dACLD. MELD-copeptin exhibited excellent prognostic accuracy in terms of LRD and ACLF in both the internal and the external validation cohort. This underscores the prognostic value of plasma copeptin on top of the well-established MELD-Na and goes beyond the data of a recent meta-analysis, which reported that copeptin is a prognostic biomarker for 90-day mortality in patients with dACLD.[17]

Our study also has limitations. First, regarding the MELD-copeptin score, the Viennese cohorts and the external validation cohort differed in some regards. Most importantly, the Viennese cohorts included clinically stable outpatients with dACLD, whereas the external validation cohort included hospitalized patients. To account for this limitation, we stratified the Viennese patients with dACLD into a derivation and a validation cohort depending on the time of HVPG measurement. Thus, we were able to demonstrate the prognostic accuracy of the MELD-copeptin score in an independent cohort of outpatients, and in an external cohort of inpatients with dACLD. Second, because of the design of our study, we cannot comment on a possible mechanistic relationship between copeptin levels and systemic inflammation. Further studies are required in this regard.

In conclusion, our prospective observational study showed that copeptin was independently linked to IL6, suggesting a relationship between AVP release and systemic inflammation in dACLD. Importantly, the MELD-copeptin score predicts LRD with a high accuracy, facilitating a refined prognostication in dACLD. Based on our study results, assessment of plasma copeptin should be implemented for risk stratification in patients with dACLD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.04.030.

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Conflicts of interest
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