Received: 24 April 2023 | Accepted: 21 July 2023

DOI: 10.1002/ueg2.12472

ORIGINAL ARTICLE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

Toward a more precise prognostic stratification in acute decompensation of cirrhosis: The Padua model 2.0

Alberto Zanetto[1,2] | Filippo Pelizzaro[1,2] | Monica Maria Mion[3] | Marco Bucci[1,2] | Alberto Ferrarese[4] | Paolo Simioni[5] | Daniela Basso[3] | Patrizia Burra[1,2] | Marco Senzolo[1,2,6]

[1]Gastroenterology and Multivisceral Transplant Unit, Azienda Ospedale - Università Padova, Padova, Italy

[2]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy

[3]Department of Laboratory Medicine, Padova University Hospital, Padova, Italy

[4]Unit of Gastroenterology, Borgo Trento University Hospital of Verona, Verona, Italy

[5]General Internal Medicine and Thrombotic and Hemorrhagic Diseases Unit, Department of Medicine, Padova University Hospital, Padova, Italy

[6]Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-Liver), Padova University Hospital, Padova, Italy

Correspondence
Marco Senzolo, Gastroenterology and Multivisceral Transplant Unit, Azienda Ospedale - Università Padova, Padova, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy.
Email: marcosenzolo@hotmail.com

Funding information
Ministero dell'Università e della Ricerca

Abstract

Background: The clinical course of acutely decompensated cirrhosis (AD) is heterogeneous. Presepsin (PSP) is a plasmatic biomarker that reflects Toll-like receptor activity and systemic inflammation. We conducted a prospective study to: (1) measure PSP in AD and (2) assess whether PSP in AD can predict the development of acute-on-chronic liver failure (ACLF).

Methods: Patients with AD were prospectively recruited at admission and underwent determination of PSP. In study part 1, we compared PSP in AD versus controls (stable decompensated and compensated cirrhosis). In study part 2, we prospectively followed patients with AD for 1 year and evaluated predictors of ACLF.

Results: One hundred and seventy three patients with AD were included (median MELD: 18; CLIF-C AD score: 54). Compared with controls, patients with AD had higher levels of PSP (674 ng/L vs. 310 ng/L vs. 157 ng/L; $p < 0.001$). In patients with AD, Child–Pugh C and acute kidney injury were associated with higher levels of PSP. During the follow-up, 52 patients developed ACLF (median time from recruitment: 66 days). PSP, CLIF-C AD score, and Child–Pugh stage were independently associated with ACLF. A predictive model combining these variables (Padua model 2.0) accurately identified patients at higher risk of ACLF (AUROC 0.864; 95% CI 0.780–0.947; sensitivity 82.9%, specificity 76.7%). In patients at lower risk of ACLF based on a CLIF-C AD <50, a PSP >674 ng/L could discriminate between two groups at significantly different risk of ACLF. Finally, in patients who did not develop ACLF, baseline PSP was significantly higher in those who progressed toward unstable versus stable decompensated cirrhosis.

Conclusion: The Padua model 2.0 can be used to identify patients with AD at high risk of ACLF. If these results are validated by external cohorts, PSP could become a new biomarker to improve risk stratification in AD.

KEYWORDS
acute decompensation, acute on chronic liver failure, liver cirrhosis, presepsin

INTRODUCTION

Acute decompensation (AD) of cirrhosis has been defined as the acute development or worsening of ascites, hepatic encephalopathy, or variceal hemorrhage, which result in hospitalization.[1] There is a subgroup of patients with AD characterized by more severe systemic inflammation and development of organ failures. These are the hallmarks of "acute-on-chronic liver failure" (ACLF), a distinct clinical entity that is associated with a high risk of short-term mortality.[2]

Patients with AD without ACLF, however, constitute a heterogenous group of patients with a variable clinical course.[3] On the one hand, patients with "pre-ACLF," that is, patients who will progress from AD to ACLF and have a high risk of death. On the other hand, patients with unstable decompensated cirrhosis (UDC), who will experience further decompensation without developing ACLF and have an intermediate risk of death, and patients with stable decompensated cirrhosis (SDC), who will not experience any further decompensation and have a lower risk of 1-year mortality.[3]

Although our understanding of the pathophysiology of AD-ACLF syndrome has improved in the recent years,[4] leading to the "systemic inflammation hypothesis,"[5] prediction of the individual patient's trajectory after AD remains challenging.[6,7] However, better identification of patients with AD at higher risk of progression would improve patient management (i.e., identification of candidates for an expedite evaluation for liver transplantation and/or disease-modifying therapies currently under investigation).[8–10]

The cluster of differentiation 14 (CD14) is a glycoprotein expressed on the external membrane of monocytes and macrophages (i.e., innate immune system cells).[11] CD14 is a pattern recognition molecule that activates a proinflammatory signaling pathway responsible for the innate response to pathogens upon recognition of the complexes between lipopolysaccharide (LPS) and LPS-binding proteins.[11] During the inflammatory response, plasmatic proteases generate soluble fragments of CD14 (sCD14).[12] One of them, called sCD14 subtype (sCD14-ST), or presepsin (PSP), has been recently identified.[11] PSP is usually present in low concentrations in the serum of healthy individuals and its physiological role has not been fully understood yet; however, it may be involved in the regulation of phagocytosis and lysosomal cleavage of microorganisms.[11]

In patients without liver disease, the early rise in plasmatic levels of PSP in response to bacterial infections and bacteremia, before elevations in PCT or IL-6, makes it a potentially early sepsis biomarker.[12] In patients with decompensated cirrhosis and portal hypertension, there is an increased intestinal permeability and bacterial translocation.[13] In fact, levels of PSP are higher than in healthy individuals independently of infections,[14] and increase in parallel with the level of circulating LPS.[15] Therefore, in decompensated cirrhosis, PSP could be better used as a biomarker for systemic inflammation rather than for the diagnosis of bacterial infections.[16]

Per the recent "inflammatory hypothesis,"[5] episodic worsening of bacterial translocation and/or pro-inflammatory precipitants (mostly bacterial infections) would lead to an abrupt increase in systemic inflammation, leading to further decompensation and ACLF.[17] Therefore, it may be that the plasmatic level of PSP at the time of AD, which would reflect the severity of episodic worsening of bacterial translocation/systemic inflammation, could predict the risk of disease progression.

To test this hypothesis, we conducted a prospective cohort study to: (1) measure PSP in patients with AD and (2) assess whether PSP could predict the trajectories of AD, and specifically the development of ACLF during a 1-year follow-up.

Key summary

Summarize the established knowledge on this subject

- Acute decompensation of cirrhosis is associated with a variable course and prognosis (acute-on-chronic liver failure [ACLF] vs. unstable decompensation vs. stable decompensation).
- Severity of systemic inflammation is key in the progression from acute decompensation to ACLF.
- Prediction of individual patient trajectory is challenging.

What are the significant and/or new findings of this study?

- Presepsin (PSP), a plasmatic biomarker that reflects Toll-like receptor activity and systemic inflammation, is significantly increased in patients with acutely decompensated cirrhosis.
- In patients with AD, PSP, CLIF-C AD score, and Child–Pugh stage at the time of AD are independent predictors of ACLF during a 1-year follow-up.
- The Padua model 2.0 improves the identification of patients at higher risk of ACLF.
- In patients at lower risk of ACLF based on a CLIF-C AD score <50, a PSP >674 ng/L improved the identification of patients at risk of ACLF.

PATIENTS AND METHODS

Patient selection and study design

Consecutive patients at their first episode of AD[1] admitted to the Gastroenterology and Multivisceral Transplant Unit of Padova University Hospital between September 2018, 30 and January 2022 and 30 were prospectively screened to determine eligibility to participate in the study.

Assessment of PSP was performed within an ongoing prospective study investigating biomarkers of chronic gastrointestinal and liver diseases at Padova University Hospital (HIC protocol #0034435). This study requires baseline testing and prospective follow-up. The

study was conducted in compliance with the Declaration of Helsinki and all patients signed a consent to participate.

Patients with ACLF at time of screening[2]; patients transferred from other hospitals or intensive care units; patients with history or presence of hepatocellular carcinoma or extra-hepatic cancers, portal vein thrombosis, transjugular intrahepatic portosystemic shunt, chronic kidney disease, recent (within 30 days) surgery, and previous organ transplantation were not eligible.

Upon admission and having determined eligibility, all patients underwent a blood draw for the assessment of PSP. Peripheral blood was collected via venipuncture from an antecubital vein into vacutainer tubes (BD Vacutainer®, Becton, Dickinson and Company) containing EDTA, using a 21 g needle with a light tourniquet. All blood samples were obtained at fasting and sent to the local Laboratory Medicine for analysis, as previously reported.[14] The PSP concentration was determined using the PATHFASTTM analyzer (Mitsubishi Chemical Europe GmbH), using an analytical method based on the chemiluminescent enzyme immunoassay technique. The measuring range was between 20 and 20.000 ng/L; the imprecision was obtained by measuring for 20 non-consecutive days in duplicate four plasma samples that showed a mean value between 445 and 19.292 ng/L, with a coefficient of variation between 3.8% and 5.0%; the reference range was from 57 to 337 ng/L. See Supporting Information S1 for additional information regarding the assessment of PSP.

Two groups acted as controls for the assessment of PSP. The first group consisted of 56 outpatients with cirrhosis decompensated by ascites grade ≥2; the second group consisted of 52 outpatients with compensated cirrhosis.[18] These controls were prospectively recruited at the outpatient clinics for the management of cirrhosis and liver transplantation of the Gastroenterology/Multivisceral Transplant Unit. In both groups, individuals' medical records, past history, and laboratory data were reviewed to apply all the aforementioned exclusion criteria for patients with AD.

Data collection and definition of liver-related events during 1-year follow-up

Data collected from the medical record included causes for admission, patient demographics, laboratory data including liver and kidney function, C-reactive protein (CRP), procalcitonin (PCT), platelet count, international normalized ratio, presence of bacterial infections[19] and acute kidney injury (AKI).[20]

Child–Pugh stage, Model for End-stage Liver Disease (MELD) score, and CLIF-C AD score were calculated on the basis of clinical/biochemical data from the day of enrollment.

Patients with AD were prospectively followed for 1 year for the following trajectories: development of ACLF (primary outcome); rehospitalization due to complications of decompensated cirrhosis without ACLF (i.e., UDC); and no further decompensation or liver-related hospitalization (i.e., SDC). Liver transplant-free survival rates at 12 months were collected.

Statistical analysis

The primary objective of this study was to assess, in a prospective cohort of hospitalized patients with AD, the predictors of ACLF during a 1-year follow-up. In particular, we evaluated whether alterations of PSP at the time of AD could predict the development of ACLF. We hypothesized that a more marked increase in PSP could be associated with a higher risk of ACLF, independent of hepatic dysfunction.

Univariate and multivariate Cox regression analysis were used to identify the independent predictors of ACLF (backward elimination approach). The time of ACLF was calculated as the time (days) elapsed between patient recruitment (i.e., when assessment of PSP was performed) and development of ACLF. For the multivariate model, among the variables significantly associated with the onset of ACLF on univariate analysis, we selected those: (a) clinically and pathophysiologically relevant; (b) not collinear. Hazard ratios with 95% CIs were calculated. A multivariate Cox model based on multivariate analysis was used to create a prognostic model for ACLF risk stratification (see Supplementary materials for more information).

RESULTS

Baseline characteristics

One hundred seventy-three patients with AD were included (Figure 1); the median time from admission to the patient recruitment was 1 day (range: 1–2). Alcohol and chronic HCV infection were the most common etiologies of cirrhosis (46% and 25%, respectively). Ascites was the most common decompensating event (62%), followed by variceal hemorrhage (17%), and ascites with variceal hemorrhage (13%). Bacterial infections were the most common precipitant of AD (72%) (Table 1).

The median MELD score was 18 (14–23); 44% of patients were Child–Pugh B and 56% were Child–Pugh C. The median CLIF-C AD score was 54 (43–60). The median level of CRP was 21 mg/L (Table 1). Acute kidney injury was present in 23% of patients.

As controls, 56 outpatients with SDC (65% male, median age 63 years) and 52 outpatients with compensated cirrhosis (69% male, median age 61 years) were included. Median MELD was 14 (IQR: 11–17) and 7 (IQR: 5–9) in decompensated and compensated patients, respectively. Among decompensated patients, 21% were Child–Pugh A, 51% were Child–Pugh B, and 28% were Child–Pugh C; among compensated patients, 90% were Child–Pugh A and 10% were Child–Pugh B. Alcohol was the most common etiology of cirrhosis in both groups.

Patients with AD had higher levels of PSP than controls with stable decompensated and compensated cirrhosis, particularly those with a more advanced liver dysfunction and severity of decompensation.

PSP was significantly increased in patients with AD (674 ng/L [308–1700]) versus controls with SDC (310 ng/L [190–458]) and compensated cirrhosis (157 ng/L [106–235]) (Figure 2). In AD, PSP was comparable between male and female individuals (699 ng/L

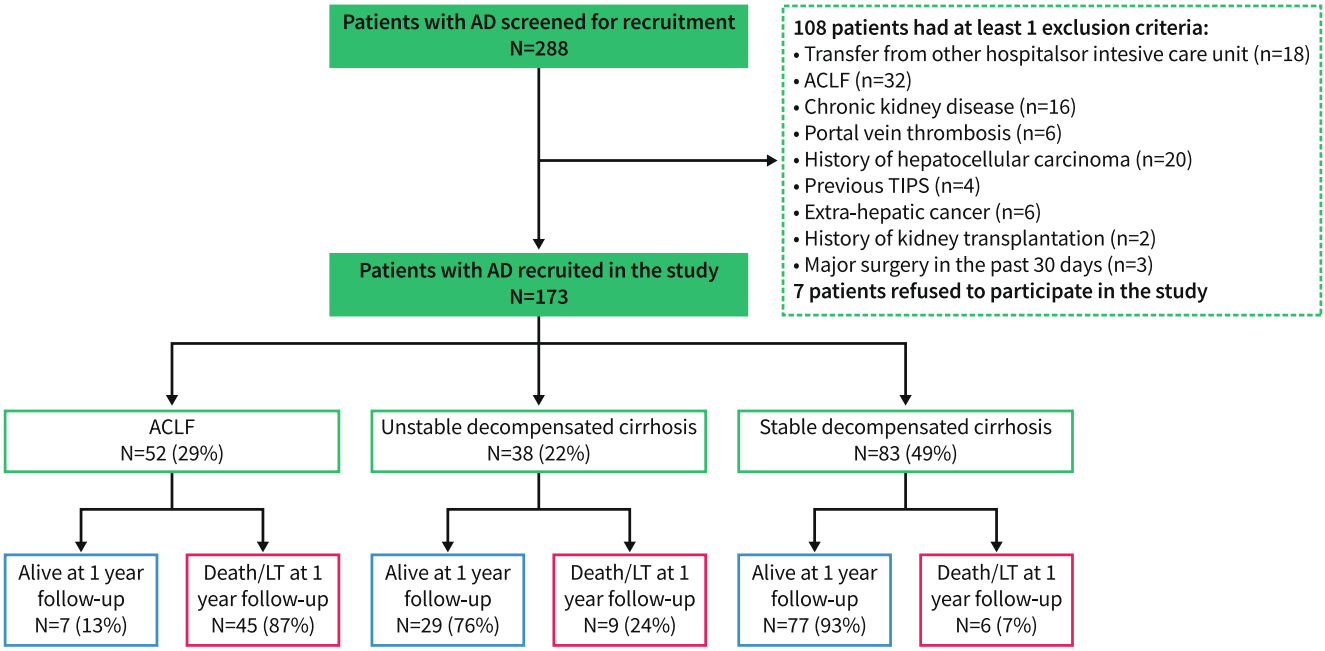


FIGURE 1 Flow chart of the study. AD, acute decompensation; ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt.

[271–1911] and 604 ng/L [310–1348], respectively; $p = 0.8$). The level of PSP was significantly higher in Child–Pugh C versus Child–Pugh B stage (1096 ng/L [360–1750]) versus 416 ng/L [246–1103]; $p = 0.04$) (Figure S1). Patients with AD precipitated by bacterial infections had higher levels of PSP than those with AD precipitated by other factors (1253 ng/L [524–2812] vs. 438 ng/L [253–1217]; $p = 0.001$). However, when comparing patients within the same Child–Pugh stage, PSP was higher in those with bacterial infections in Child–Pugh B (1700 ng/L [678–2860] vs. 455 ng/L [216–600] in patients without infections; $p = 0.001$) but not in Child–Pugh C (1253 ng/L [446–2400] ng/L vs. 920 ng/L [276–1553] in patients without infections; $p = 0.2$).

The level of PSP was significantly higher in patients with versus without AKI, independent of Child–Pugh stage (1481 ng/L [535–2685] vs. 432 ng/L [248–976] in Child–Pugh B, $p < 0.001$; 1253 ng/L [967–2500] vs. 557 ng/L [310–1470] in Child–Pugh C, $p < 0.001$).

Regarding the type of hepatic decompensation, patients with ascites had a higher level of PSP than those with variceal hemorrhage and hepatic encephalopathy (824 ng/L [328–2190] vs. 432 ng/L [235–1223] vs. 650 ng/L [286–1255]); however, the difference was not statistically significant (Figure S1). PSP was comparable between patients with multiple decompensating events (ascites plus variceal hemorrhage) and those with ascites as single decompensating event.

The severity of AD, as defined by a CLIF-C AD score ≥50,[21,22] was associated with a significantly higher level of PSP (1335 ng/L [450–2456] vs. 400 ng/L [251–1015] in patients with a CLIF-C AD score ≤50).

In AD, PSP was moderately correlated with both neutrophils and monocytes to lymphocytes ratios (rho: 0.4, $p = 0.03$; and rho: 0.5, $p = 0.02$), moderately correlated with CLIF-C AD score (rho = 0.4; $p = 0.001$), CRP (rho = 0.3; $p = 0.002$) and white blood cells (rho = 0.36; $p = 0.001$), and strongly correlated with procalcitonin (rho = 0.6; $p = 0.001$). PSP was not correlated with platelet counts.

PSP, CLIF-C AD score, and Child–Pugh stage at the time of AD were independent predictors of ACLF during follow-up.

Fifty-two (29%) patients developed ACLF during follow-up (Figure 1). Median time from inclusion to ACLF was 66 days (IQR: 28–120). Bacterial infections were the most common precipitant of ACLF ($n = 30$, 58%), followed by alcoholic hepatitis ($n = 7$, 13%), and gastrointestinal bleeding ($n = 3$, 5%). In 12 patients (24%), the precipitant of ACLF was not identified. The grade of ACLF was I in 36% of patients, II in 41%, and III in 23%.

Among patients who did not experience ACLF, 38 (22%) were re-hospitalized due to further complications of cirrhosis such as hepatic encephalopathy ($n = 7$), ascites/oedema ($n = 13$), variceal hemorrhage ($n = 2$), AKI ($n = 6$), portal vein thrombosis ($n = 5$), anemia/non-portal hypertensive bleeding ($n = 3$), and development of HCC ($n = 2$); 83 (49%) patients were not re-admitted (Figure 1).

Liver transplant-free survival at 12 months was lower in patients who developed ACLF than in those who were re-hospitalized for cirrhosis decompensation with no ACLF (i.e., UDC) and those who were not readmitted (i.e., SDC) (13% vs. 76% vs. 93%, respectively) (Figure 1).

Severity of liver dysfunction, presence of AKI, and degree of systemic inflammation were greater in patients who developed ACLF during follow-up than in those who did not (Table S1).

Univariate analysis showed that the MELD score, CLIF-C AD score, Child–Pugh stage C versus B, AKI, PSP, CRP, and procalcitonin at the time of AD were associated with the development of ACLF (Table 2). A multivariate model including CLIF-C AD, Child–Pugh, PSP, and CRP showed that PSP, CLIF-C AD score, and Child–Pugh stage were the only independent predictors of ACLF (Table 2).

TABLE 1 Baseline characteristics in patients with AD.

	Patients with AD (n = 173)
Age, years	61 (52–68)
Male, %	68
Etiology alcohol/HCV/NASH/other, %	46/25/16/13
Child-Pugh B/C, %	44/56
MELD score	18 (14–23)
CLIF-C AD score	54 (43–60)
Decompensating event, %	
Ascites grade ≥ 2	62
Ascites grade ≥ 2 + variceal hemorrhage	13
Variceal hemorrhage	17
Hepatic encephalopathy	8
Precipitant, %	
(Suspected) infections ± AKI	72
Alcohol consumption	15
Procedures/trauma	9
DILI	4
Platelet count, 10^9/L	90 (59–126)
C-reactive protein, mg/dL	21 (6–36)
Procalcitonin, ng/L	0.3 (0.2–01)

Note: Median values reported with 25th and 75th percentile values in parenthesis.

Abbreviations: AD, acute decompensation; ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; MELD, Model for End Stage Liver Disease; NASH, non-alcoholic steatohepatitis.

Alternative models including procalcitonin instead of CRP (Table S2) and CLIF-C AD, PSP, and CRP (Table S3) showed comparable results. A multivariate model including PSP, CRP, and CLIF-C-AD scores as continuous variables is shown in Table S4.

The hazard of developing ACLF was significantly greater in patients with high versus low PSP. One-year rate of ACLF was 64% versus 23%, respectively ($p < 0.0001$) (Figure S2). Notably, in patients who would be deemed at lower risk of ACLF based on a CLIF-C AD score <50, a level of PSP >674 ng/dL could still discriminate between two distinct populations at significantly different risk of ACLF (Figure S3).

The Padua model 2.0

Cox regression analysis identified three independent predictors of ACLF development: CLIF-C AD score, Child–Pugh class and PSP levels. Table 3 shows the values of the β regression coefficients and the corresponding hazard ratios for each independent predictor of ACLF. Based on the AUROC analysis (Figure 3a), the cut-off value of the multivariate score with the highest sensitivity and specificity in identifying patients at low and high-risk of developing ACLF was 2.47 (AUROC 0.864; 95% confidence interval [CI] 0.780–0.947; sensitivity 82.9%, specificity 76.7%). The AUROC curve of the Padua model 2.0 was higher than that of the single independent predictors of ACLF and the AUROC curve of the Padua model. The hazard of developing ACLF was statistically significantly greater in patients at high (score >2.47) compared with those at low (score ≤2.47) risk according to the established multivariate score (Figure 3b).

One-year ACLF development rates were 15.4% in patients with multivariate score ≤2.47 and 74.4% in patients with a multivariate score >2.47 ($p < 0.0001$). The fit between expected and observed probabilities of ACLF development was measured using the Hosmer–Lemeshow C test at a p value of 0.47.

In patients who did not experience ACLF, the level of PSP was higher in those who developed UDC than SDC.

In patients who did not experience ACLF during follow-up (n = 121), the baseline PSP was higher in those who progressed toward UDC (n = 38) than in those who did not experience further episodes of decompensation (767 ng/L [440–1228] vs. 328 ng/L [1238–499]; $p < 0.001$) (Figure 4). A level of PSP <680 ng/L accurately identified all the patients who did not progress toward UDC. However, 16/38 patients (42%) progressed to UDC despite having a baseline PSP <680 ng/L. Interestingly, we found that these patients had a more severe hepatic decompensation and a higher level of other markers of systemic inflammation than those who developed SDC (Table S5).

DISCUSSION

Predicting the course of AD, and particularly the development of ACLF, is challenging.[3] Given the recent advances in disease-modifying therapies of decompensated cirrhosis, refinements in risk stratification are increasingly important.[23] Furthermore, since progression to ACLF typically occurs early after AD,[3] early evaluation for liver transplantation may be indicated in selected patients at higher risk of progression.

Our prospective study shows that: (1) PSP is significantly higher in patients with AD than in controls with stable decompensated and compensated cirrhosis; (2) PSP, CLIF-C AD score, and Child–Pugh at the time of AD are independent predictors of ACLF; (3) a predictive model combining these variables (Padua model 2.0) can identify 2 distinct groups of patients at high versus low risk of ACLF; (4) in patients at lower risk based on a CLIF-C AD score <50, a PSP >674 ng/mL improves the identification of patients at risk of ACLF. Therefore, if our findings will be validated by external cohorts, PSP could become an easy-to-use biomarker for improving risk stratification in patients with AD.

PSP is a 13 kDa N-terminal fragment, produced after the formation and subsequent proteolysis of the complex between LPS and its binding protein.[24] Previous studies from our[14] and other groups[25–27] demonstrated that PSP is higher in patients with cirrhosis than in healthy subjects and increases in parallel with disease severity.[14] The

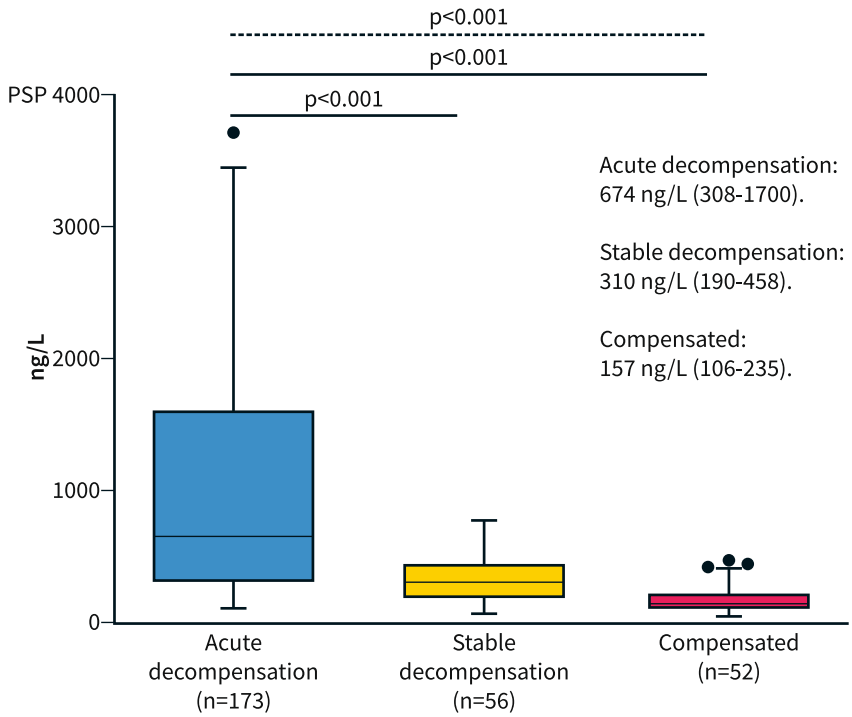


FIGURE 2 PSP was significantly increased in AD versus controls with stable decompensated cirrhosis and compensated cirrhosis. Dotted line indicates Kruskal-Wallis test. AD, acute decompensation; PSP, presepsin.

increased level of PSP in patients with decompensated cirrhosis would reflect the severity of bacterial translocation due to clinically significant portal hypertension; in fact, we found that PSP was higher in decompensated versus compensated cirrhosis. Here, we further show that patients with AD have a higher level of PSP than those with SDC, reflecting the episodic worsening of bacterial translocation and systemic inflammation due to acute precipitants.[5]

Patients with AD precipitated by bacterial infections had higher levels of PSP than those with AD precipitated by other factors; however, when the analysis was adjusted according to the underlying severity of cirrhosis, this effect was evident in Child–Pugh B and not in Child -Pugh C stage. This might reflect the positive association between the severity of portal hypertension and bacterial translocation/levels of circulating LPS,[15] which would mask the effect of infections on PSP levels in most advanced patients.[28]

In agreement with previous studies,[14,29] we confirm that AKI, a common complication of AD,[30,31] is associated with a higher level of PSP. Therefore, AKI and renal function should be considered when evaluating the level of PSP in AD.

Regarding the prognostic role of PSP in patients with cirrhosis, three retrospective studies found that PSP is independently associated with the risk of death.[25–27] However, these studies included heterogenous cohorts with variable durations of follow-up and outcomes. One prospective cohort by Ferrarese et al[14] confirmed the independent association between PSP and 28-day mortality in hospitalized patients with cirrhosis. However, this study mixed patients with AD and ACLF. Here, we included only patients with AD according to pre-defined exclusion criteria chosen to mitigate the effects of potential confounding factors.

We found that the increased level of PSP in patients with AD was associated with the development of ACLF during follow-up, independent of AKI, Child–Pugh, CRP, and CLIF-C AD score. A PSP >674 ng/L identified two distinct groups of patients with a significantly different risk of ACLF *early after the AD* (20% vs. 5% at 30 days, 34% vs. 8% at 60 days, and 55% vs. 13% at 90 days). This is clinically relevant as the development of ACLF mostly occurs within 3 months after AD.[3]

We previously developed a simple predictive model combining CRP, CLIF-C AD score, and Child–Pugh (i.e., Padua model) that can be used to identify patients with AD at risk of ACLF.[6] Interestingly, the predictive ability of the Padua model in this independent cohort was good (AUROC: 0.81 [CI: 0.72–0.89]), thus confirming its potential value in clinical practice. Based on our previous results and the current finding that PSP is also an independent predictor of ACLF, we propose a new predictive model that combines the severity of hepatic decompensation (CLIF-C score and Child-Pugh) and systemic inflammation (PSP) and would further improve the identification of patients at risk of ACLF (sensitivity 82.9% and specificity 76.7%). Notably, the predictive ability of the Padua model 2.0 was slightly higher than that of the Padua model (AUROC: 0.864 vs. 0.815, respectively), suggesting that the inclusion of PSP instead of CRP may improve prognostic stratification in AD of cirrhosis.

TABLE 2 Parameters associated with the development of ACLF at univariate and multivariate analyses.

Variables	aHR (95% CI)	*p*
Univariate		
MELD score (>18)	3.1 (1.5–6.0)	0.002
CLIF-C AD score (>54)	4.8 (2.3–10.1)	<0.001
Child-Pugh stage C versus B	5.7 (2.4–13.7)	<0.001
AKI (YES vs. NO)	3.9 (2.1–7.8)	<0.001
Infection (YES vs. NO)	1.8 (0.93–3.45)	0.08
Presepsin, ng/L (>674)	3.9 (1.9–8.5)	<0.001
C-reactive protein, mg/dL (>21)	3.4 (1.6–7.1)	0.001
Procalcitonin, ng/mL (>0.5)	2 (1.1–3.9)	0.03
Multivariate		
Presepsin, ng/L		
≤674	1	-
>674	3.28 (1.52–7.06)	0.002
CLIF-C AD score		
≤50	1	-
>50	4.20 (1.73–10.18)	0.001
Child-Pugh stage		
B	1	-
C	3.18 (1.23–8.28)	0.02

Note: The model included PSP, C-reactive protein, CLIF-C AD score, and Child-Pugh stage. C-reactive protein was not associated with ACLF in phase 1 (aHR [95% CI]: 1.51 [0.68–3.31]; $p = 0.3$), and was therefore eliminated (backward eliminating procedure).

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver disease; PSP, presepsin.

TABLE 3 The Padua model 2.0: independent predictors of ACLF based on multivariate analysis.

Variable	B coefficient	HR (95% CI)	*p* value
Presepsin			
≤674	0	1	-
>674	1.186	3.28 (1.52–7.06)	0.002
Child-Pugh			
B	0	1	-
C	1.435	4.20 (1.73–10.18)	0.001
CLIF-C AD score			
≤50	0	1	-
>50	1.158	3.18 (1.23–8.28)	0.02

Note: The cumulative score is calculated by adding the B coefficient obtained for each variable. A cut-off value of 2.47 differentiates between individuals at high versus low risk of ACLF.

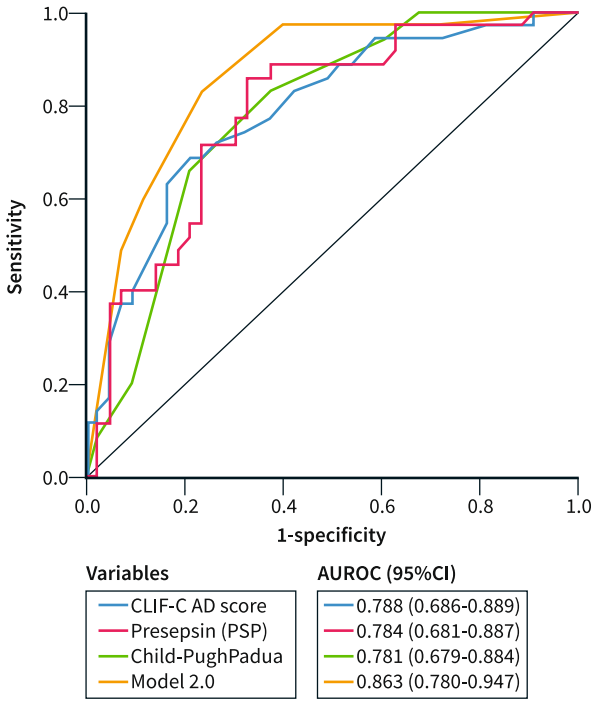
Abbreviation: ACLF, acute-on-chronic liver failure.

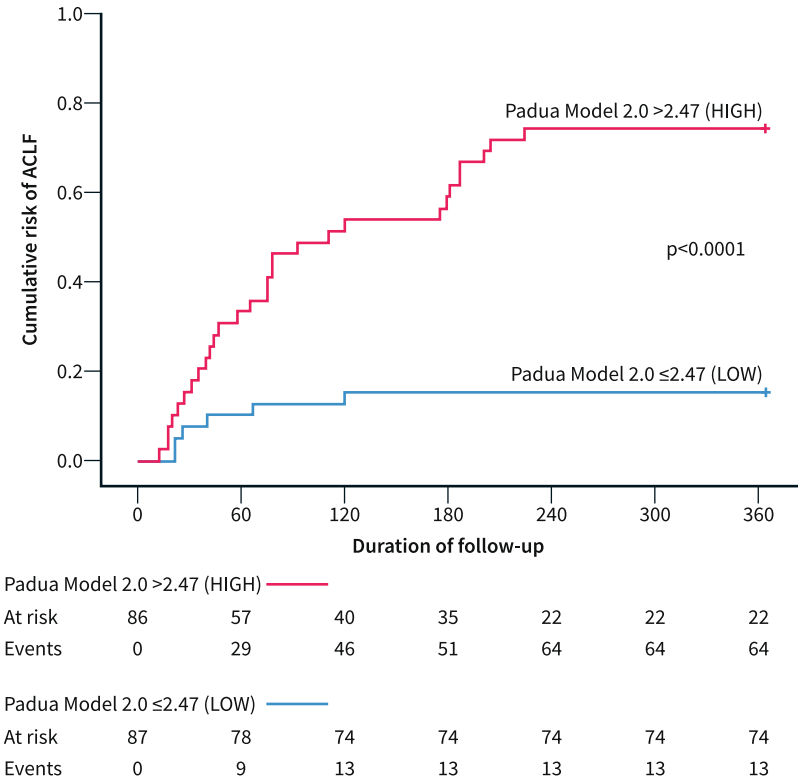
The independent association between an increased level of PSP at the time of AD and the risk of ACLF during follow-up is further proof that systemic inflammation is a major, independent driver for progression from AD to ACLF.[3] Interestingly, we found that CRP was not independently associated with ACLF when PSP was included in the same model. PSP is directly released by the innate immune system cells upon stimulation by LPS and bacterial products,[11] whereas CRP is mostly an acute phase reactant synthesized by the hepatocytes in response to interleukins 1 and 6. Therefore, in hospitalized patients with AD, PSP could be a relatively more direct and sensitive biomarker for the worsening degree of systemic inflammation than CRP. Larger studies assessing the relationship between PSP and CRP in AD/ACLF are needed to test this hypothesis and confirm our results.

We also found that PSP may be used as a single independent biomarker to identify, among the subgroups of patients with a CLIF-C AD score <50, those at higher risk of ACLF. It could be that PSP as a single biomarker could be beneficial in patients with AD without a strong inflammatory response/severe hepatic decompensation, as assessed by the Padua score or plasmatic level of CRP (which is the most important determinant of the Padua score), in whom nonetheless the increased bacterial translocation/circulation driven by acute precipitants would ultimately result in innate immune activation, worsening of systemic inflammation, and development of ACLF. However, this was a single-center study and the first to assess the potential prognostic value of PSP in patients with AD. Thus, larger external cohorts are required to validate our findings and better understand how the integration of clinical and laboratory data reflecting the underlying pathophysiology of AD/ACLF can be used to improve the clinical management of these patients.

In patients who did not develop ACLF during follow-up, 1-year liver transplant-free survival was lower in those who progressed to UDC versus SDC (76% vs. 93%). Thus, we retrospectively evaluated whether PSP could improve discrimination between these two trajectories. We found that patients who progressed to UDC had significantly higher levels of PSP than those who did not, and that a PSP <680 ng/L also accurately identified the patients who developed SDC. However, 42% of patients who progressed to UDC had baseline PSP <680 ng/L, which indicates that a single determination of PSP at time of AD cannot discriminate between these two trajectories. Interestingly, severity of AD and systemic inflammation in patients who progressed to UDC despite having a lower level of PSP were significantly higher than in those who developed SDC. Therefore, we suggest that further studies should evaluated whether the combination of PSP, CLIF-C AD score, and levels of CRP or procalcitonin may improve risk stratification in AD.

Our study has some limitations. Firstly, this is a single center study and our results require external validation. The threshold of PSP associated with ACLF, however, was comparable to the ones proposed by previous independent investigators,[25–27] which suggests that a PSP >600–700 ng/mL should be considered with caution in hospitalized patients with decompensated cirrhosis. Secondly, decompensated cirrhosis is a highly dynamic condition; therefore, a serial assessment of (dynamics) of PSP in response to treatments would likely provide a





Padua Model 2.0 >2.47 (HIGH)							
At risk	86	57	40	35	22	22	22
Events	0	29	46	51	64	64	64
Padua Model 2.0 ≤2.47 (LOW)							
At risk	87	78	74	74	74	74	74
Events	0	9	13	13	13	13	13

FIGURE 3 AUROC curves (left) and cumulative hazard of ACLF according to the Padua model 2.0 (right). ACLF, acute-on-chronic liver failure; AD, acute decompensation.

more thorough assessment, reflecting response to therapies and controls of precipitants, and may have a greater prognostic value than a single determination. Thirdly, we mostly included patients with alcohol and viral-related cirrhosis, in whom AD was precipitated by bacterial infections. Therefore, the use of PSP in different categories of patients requires further investigation.

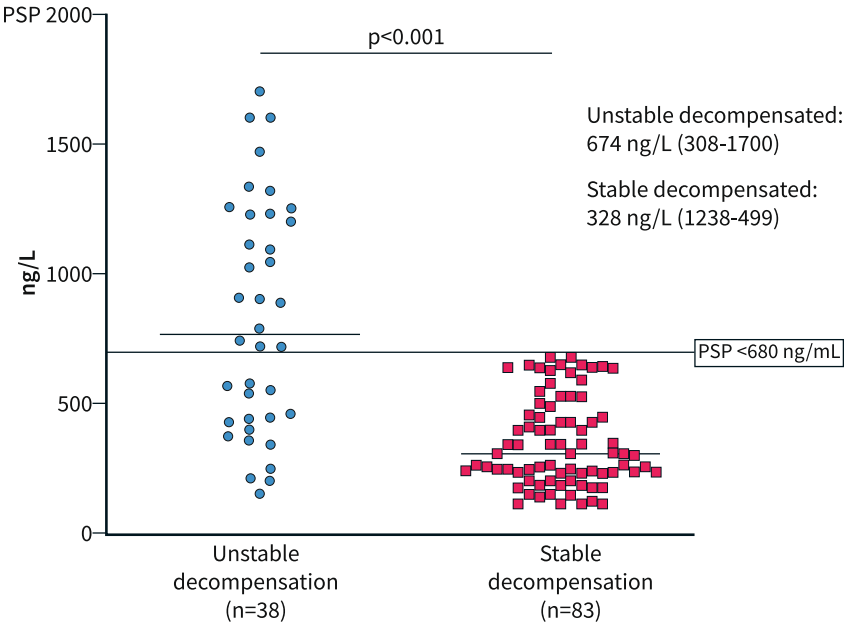


FIGURE 4 In patients who did not experience ACLF, the baseline PSP was higher in those who developed unstable versus stable decompensated cirrhosis. ACLF, acute-on-chronic liver failure; AD, acute decompensation; PSP, presepsin.

In conclusion, hospitalized patients with AD of cirrhosis have a significantly increased level of PSP. Increased PSP, CLIF-C AD score, and Child–Pugh at the time of AD are independently associated with the development of ACLF. The Padua model 2.0, which combines these variables, can identify patients with AD at risk of ACLF. If our findings will be confirmed, PSP could become an independent, easy-to-use biomarker to improve prognostic stratification in patients with AD.

AUTHOR CONTRIBUTIONS

Alberto Zanetto: research design, performance of the research (patients' enrollment), interpretation of the data, and writing of the manuscript. Filippo Pelizzaro: data analysis, creation of the Padua model 2.0, and critical revision of the manuscript. Monica Maria Mion: laboratory work. Marco Bucci: acquisition and interpretation of the data. Alberto Ferrarese: acquisition and interpretation of the data. Paolo Simioni: acquisition of the data and critical revision of the manuscript. Daniela Basso: laboratory work. Patrizia Burra: acquisition of the data and critical revision of the manuscript. Marco Senzolo: research design, interpretation of the data, critical revision for important intellectual content, and final approval of the manuscript.

ACKNOWLEDGMENTS

The authors wish to thank all the nurses of the Gastroenterology and Multivisceral Transplant Unit of Padova University Hospital for their assistance with the collection of blood samples.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data are available from the first author (Dr. Alberto Zanetto; alberto.zanetto@unipd.it) upon reasonable request.

ETHICS APPROVAL

This study was approved by the Padova University Hospital (HIC protocol #0034435-08/06/20) and was conducted in compliance with the principles of the Declaration of Helsinki. All patients signed a consent to participate.

TRIAL REGISTRATION NUMBER

NA.

ORCID

Alberto Zanetto https://orcid.org/0000-0002-6734-7178
Patrizia Burra https://orcid.org/0000-0002-8791-191X

REFERENCES

1. D'Amico G, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. J Hepatol. 2022;76(1):202–7. https://doi.org/10.1016/j.jhep.2021.06.018
2. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–37; 37 e1-9. https://doi.org/10.1053/j.gastro.2013.02.042
3. Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol. 2020;73(4):842–54. https://doi.org/10.1016/j.jhep.2020.06.013
4. Weiss E, de la Pena-Ramirez C, Aguilar F, Lozano JJ, Sanchez-Garrido C, Sierra P, et al. Sympathetic nervous activation,

mitochondrial dysfunction and outcome in acutely decompensated cirrhosis: the metabolomic prognostic models (CLIF-C MET). Gut. 2023;72(8):1581–91. https://doi.org/10.1136/gutjnl-2022-328708
5. Arroyo V, Angeli P, Moreau R, Jalan R, Claria J, Trebicka J, et al. The systemic inflammation hypothesis: towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol. 2021;74(3):670–85. https://doi.org/10.1016/j.jhep.2020.11.048
6. Zanetto A, Pelizzaro F, Campello E, Bulato C, Balcar L, Gu W, et al. Severity of systemic inflammation is the main predictor of ACLF and bleeding in individuals with acutely decompensated cirrhosis. J Hepatol. 2023;78(2):301–11. https://doi.org/10.1016/j.jhep.2022.09.005
7. Balcar L, Semmler G, Pomej K, Simbrunner B, Bauer D, Hartl L, et al. Patterns of acute decompensation in hospitalized patients with cirrhosis and course of acute-on-chronic liver failure. United Eur Gastroenterol J. 2021;9(4):427–37. https://doi.org/10.1002/ueg2.12089
8. Zanetto A, Campello E, Bulato C, Gavasso S, Farinati F, Russo FP, et al. Increased platelet aggregation in patients with decompensated cirrhosis indicates higher risk of further decompensation and death. J Hepatol. 2022;77(3):660–9. https://doi.org/10.1016/j.jhep.2022.03.009
9. Zaccherini G, Tufoni M, Bernardi M, Caraceni P. Prevention of cirrhosis complications: looking for potential disease modifying agents. J Clin Med. 2021;10(19):4590. https://doi.org/10.3390/jcm10194590
10. Deltenre P, Zanetto A, Saltini D, Moreno C, Schepis F. The role of transjugular intrahepatic portosystemic shunt in patients with cirrhosis and ascites: recent evolution and open questions. Hepatology. 2023;77(2):640–58. https://doi.org/10.1002/hep.32596
11. Memar MY, Baghi HB. Presepsin: a promising biomarker for the detection of bacterial infections. Biomed Pharmacother. 2019;111:649–56. https://doi.org/10.1016/j.biopha.2018.12.124
12. Yaegashi Y, Shirakawa K, Sato N, Suzuki Y, Kojika M, Imai S, et al. Evaluation of a newly identified soluble CD14 subtype as a marker for sepsis. J Infect Chemother. 2005;11(5):234–8. https://doi.org/10.1007/s10156-005-0400-4
13. Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol. 2013;58(5):911–21. https://doi.org/10.1016/j.jhep.2012.12.011
14. Ferrarese A, Frigo AC, Mion MM, Plebani M, Russo FP, Germani G, et al. Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection. Clin Chem Lab Med. 2021;59(4):775–82. https://doi.org/10.1515/cclm-2020-1212
15. Albillos A, de la Hera A, Gonzalez M, Moya JL, Calleja JL, Monserrat J, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. Hepatology. 2003;37(1):208–17. https://doi.org/10.1053/jhep.2003.50038
16. Ferrarese A, Plebani M, Frigo AC, Burra P, Senzolo M. Presepsin as a biomarker of inflammation and prognosis in decompensated liver disease. J Hepatol. 2021;75(1):232–4. https://doi.org/10.1016/j.jhep.2021.01.016
17. Zanetto A, Northup P, Roberts L, Senzolo M. Haemostasis in cirrhosis: understanding destabilising factors during acute decompensation. J Hepatol. 2023;78(5):1037–47. https://doi.org/10.1016/j.jhep.2023.01.010
18. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VIIF, et al. Baveno VII - renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959–74. https://doi.org/10.1016/j.jhep.2021.12.022
19. Zanetto A, Campello E, Bulato C, Gavasso S, Saggiorato G, Shalaby S, et al. Global hemostatic profiling in patients with decompensated cirrhosis and bacterial infections. JHEP Rep. 2022;4(7):100493. https://doi.org/10.1016/j.jhepr.2022.100493
20. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015;64(4):531–7. https://doi.org/10.1136/gutjnl-2014-308874
21. Arroyo V, Fernandez J, Moreau R. Reply to: "Systemic inflammation and disorders of hemostasis in the AD-ACLF syndrome". J Hepatol. 2021;74(5):1265–7. https://doi.org/10.1016/j.jhep.2021.02.021
22. Gambino C, Piano S. Identifying the four shades of acute decompensation of cirrhosis. United Eur Gastroenterol J. 2021;9(4):421–2. https://doi.org/10.1002/ueg2.12074
23. Zanetto A, Campello E, Senzolo M, Simioni P. The evolving knowledge on primary hemostatis in patients with cirrhosis: a comprehensive review. Hepatology. 2023 Feb 27. https://doi.org/10.1097/HEP.0000000000000349
24. Chenevier-Gobeaux C, Borderie D, Weiss N, Mallet-Coste T, Claessens YE. Presepsin (sCD14-ST), an innate immune response marker in sepsis. Clin Chim Acta. 2015;450:97–103. https://doi.org/10.1016/j.cca.2015.06.026
25. Papp M, Tornai T, Vitalis Z, Tornai I, Tornai D, Dinya T, et al. Presepsin teardown - pitfalls of biomarkers in the diagnosis and prognosis of bacterial infection in cirrhosis. World J Gastroenterol. 2016;22(41):9172–85. https://doi.org/10.3748/wjg.v22.i41.9172
26. Fischer P, Grigoras C, Bugariu A, Nicoara-Farcau O, Stefanescu H, Benea A, et al. Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis? Dig Liver Dis. 2019;51(12):1685–91. https://doi.org/10.1016/j.dld.2019.05.025
27. Elefsiniotis I, Tsakiris SA, Barla G, Tasovasili A, Vrachatis D, Mavrogiannis C. Presepsin levels in cirrhotic patients with bacterial infections and/or portal hypertension-related bleeding, presenting with or without acute kidney injury. Ann Gastroenterol. 2018;31(5):604–12.
28. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60(6):1310–24. https://doi.org/10.1016/j.jhep.2014.01.024
29. Nagata T, Yasuda Y, Ando M, Abe T, Katsuno T, Kato S, et al. Clinical impact of kidney function on presepsin levels. PLoS One. 2015;10(6):e0129159. https://doi.org/10.1371/journal.pone.0129159
30. Zanetto A, Rinder HM, Campello E, Saggiorato G, Deng Y, Ciarleglio M, et al. Acute kidney injury in decompensated cirrhosis is associated with both hypo-coagulable and hyper-coagulable features. Hepatology. 2020;72(4):1327–40. https://doi.org/10.1002/hep.31443
31. Campello E, Zanetto A, Radu CM, Bulato C, Truma A, Spiezia L, et al. Acute kidney injury is associated with increased levels of circulating microvesicles in patients with decompensated cirrhosis. Dig Liver Dis. 2021;53(7):879–88. https://doi.org/10.1016/j.dld.2020.12.118

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zanetto A, Pelizzaro F, Mion MM, Bucci M, Ferrarese A, Simioni P, et al. Toward a more precise prognostic stratification in acute decompensation of cirrhosis: the Padua model 2.0. United European Gastroenterol J. 2023;11(9):815–24. https://doi.org/10.1002/ueg2.12472