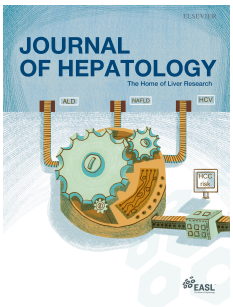

Urinary L-FABP is a promising prognostic biomarker of ACLF and mortality in patients with decompensated cirrhosis

Adrià Juanola, Isabel Graupera, Chiara Elia, Salvatore Piano, Cristina Solé, Marta Carol, Martina Pérez-Guasch, Octavi Bassegoda, Laia Escudé, Ana-Belén Rubio, Marta Cervera, Laura Napoleone, Emma Avitabile, Ann T. Ma, Núria Fabrellas, Elisa Pose, Manuel Morales-Ruiz, Wladimiro Jiménez, Ferran Torres, Gonzalo Crespo, Elsa Solà, Pere Ginès

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GRAPHICAL ABSTRACT

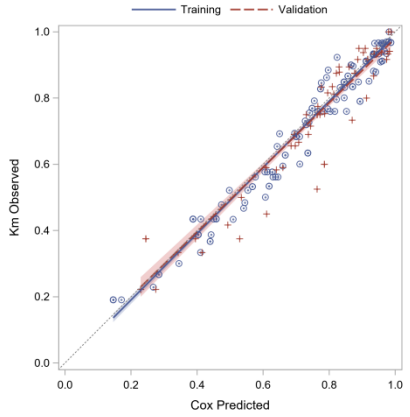
Study Cohort
(n = 305)

Validation Cohort
(n = 139)

Urinary L-FABP

Independent predictive factors associated with 3-month mortality

Variable	Units	HR (LL – UL)	p value
MELD Na	1	1.135 (1.106 - 1.165)	0.0001
uL-FABP	10	1.026 (1.011 – 1.041)	0.0006



Independent predictive factors associated with ACLF development

Variable	Units	HR (LL – UL)	p value
MELD Na	1	1.321 (1.194 - 1.462)	<0.0001
uL-FABP	10	1.044 (1.017 – 1.072)	0.0014

Urinary L-FABP is a promising prognostic biomarker of ACLF and mortality in patients with decompensated cirrhosis

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Author's contribution: The authors listed above have all contributed to this manuscript and approve the version of this submission. AJ, IG, CE, SP, ES and PG contributed to the conception and design of the study, acquisition of data, the analysis and interpretation of the data and drafting the manuscript; CS, MC, MPG, OB, LE, ABR, MC, LN, EA, ATM, NF, EP, MMR, WJ, FR and GC participated in the generation and collection of data, assembly of data, analyses of the results,

interpretation of data, and/or critical revision of the manuscript for important intellectual content.

Keywords: Liver Cirrhosis, Acute-On-Chronic Liver Failure, Organ Failure, Mortality, L-FABP, Fatty Acid-Binding Proteins.

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Lay Sumary

Increased values of liver fatty-acid binding protein (L-FABP), a protein related with lipid metabolism, has been associated with liver-related diseases. The present study analyzed urinary L-FABP (uL-FABP) levels in two independent groups of patients with decompensated cirrhosis (DC) and showed that higher uL-FABP levels correlated with increased mortality and risk of acute-on-chronic liver failure development. Therefore, uL-FABP levels could be useful as a new tool to predict complications in patients with DC.

ABSTRACT

Background/Aim: Decompensated cirrhosis (DC) is associated with high mortality, mainly due to development of acute-on-chronic liver failure (ACLF). There is need to identify patients with DC with high risk of mortality and ACLF development. Liver fatty acid-binding protein (L-FABP) is expressed in several organs and correlates with liver and systemic inflammation. Aim of study was to assess prognostic value of L-FABP in patients with DC.

Methods: Prospective series of 444 patients hospitalized for DC, divided in two cohorts: study cohort (305 patients) and validation cohort (139 patients). L-FABP was measured in urine and plasma samples collected at admission. NGAL was also measured in urine samples for comparison.

Results: Urine but not plasma L-FABP correlated with 3-month survival in univariate analysis. In multivariate analysis, uL-FABP and MELDNa were the only independent predictors of prognosis. Urine L-FABP levels were higher in patients with ACLF than in those without and also predicted the development of ACLF, together with MELD-Na, during follow-up. In patients with ACLF, uL-FABP correlated with liver, coagulation, and circulatory failure. Urine L-FABP levels were also increased in patients with AKI, particularly in those with acute tubular necrosis. The value of uL-FABP in predicting prognosis and ACLF development was confirmed in the validation cohort. Urine NGAL predicted prognosis in univariate but not in multivariate analysis.

Conclusions: uL-FABP levels are independently associated with 3-month clinical course in patients with DC, in terms of mortality and ACLF development. If confirmed in larger studies, urinary L-FABP appears to be a good biomarker candidate for use in prognosis prediction in DC, together with MELDNa score.

INTRODUCTION

Fatty Acid Binding Proteins (FABPs) are a group of intracellular chaperons that are involved in lipid-mediated processes. FABPs are thought to be critical mediators of metabolism and inflammatory pathways [1–3]. FABPS are 14-15 kDa proteins that bind hydrophobic ligands as fatty acids, among others. Different FABPs have been described, which have a specific tissue expression pattern, but there is no FABP exclusively expressed in a single tissue [2]. Liver FABP (L-FABP), also known as FABP1, is abundantly expressed in the liver, but also in other tissues such as the kidney, intestine, lungs and pancreas [2]. L-FABP function in the liver is not completely understood. It has been hypothesized that L-FABP participates in the intracellular storage and transport of fatty acids. L-FABP is also able to bind potentially toxic molecules besides fatty acids, such as heme group and others that may cause cytotoxicity [4].

In previous studies, increased L-FABP levels have been described in the setting of liver tissue injury in different conditions, including liver inflammation after surgical resection [5,6], acetaminophen-induced acute liver failure [7], liver transplant rejection[8], non-alcoholic fatty liver disease [9] and chronic hepatitis C (HCV) [10]. In this regard, the role of LFABP as biomarker in cirrhosis has been previously assessed but information is very limited [11,12]. Moreover, the potential role of L-FABP as a biomarker in the setting of ACLF has not been investigated.

On this background, we hypothesized that L-FABP could be a biomarker of prognosis and disease progression in cirrhosis, not only by reflecting liver injury but also multiorgan failure and lipid-related metabolic pathways potentially involved in the pathophysiology of ACLF [13]. Despite extensive research, the

number of good biomarkers in decompensated cirrhosis (DC) and ACLF remains limited [11,14–17]. Therefore, there is need for further research in this field. In this context, the aim of the present study was to investigate the usefulness of plasma and urinary L-FABP in the prediction of prognosis and ACLF development in patients with DC. Neutrophil gelatinase-associated lipocalin (NGAL), a previously reported biomarker of prognosis in cirrhosis and ACLF [15] , was also evaluated for comparison.

PATIENTS AND METHODS

Study population

The study was performed in a prospective series of 444 patients consecutively admitted for DC, divided in two cohorts: a cohort of 305 patients (study cohort) and another cohort of 139 patients (validation cohort). Exclusion criteria were: (1) hemodialysis before admission; (2) liver and/or kidney transplantation; (3) admission for elective diagnostic or therapeutic procedures; (4) advanced hepatocellular carcinoma beyond Milan criteria; and (5) severe extrahepatic diseases with poor short-term prognosis. All patients signed written informed consent and the protocol was approved by the Institutional Review Board of the Hospital Clínic of Barcelona.

Study design

Demographic and clinical data and standard liver and kidney function tests were collected at admission in all patients. Urine and plasma samples were also collected at the time of admission. Complications of cirrhosis were managed according to international guidelines [18]. Patients were followed-up for at least 3

months. Presence of ACLF at admission or its development during follow-up was carefully assessed in all patients.

Definitions

Cirrhosis was diagnosed on the basis of a liver biopsy or by a combination of clinical, laboratory, and ultrasonographic findings, according to current guidelines [18]. ACLF was defined using criteria of the CANONIC study [19]. Acute kidney injury (AKI) was defined according to the current definition of the International Club of Ascites [20].

Samples and laboratory measurements

Plasma samples collected at admission were centrifuged at 2000 rpm for 10 minutes and the supernatant stored at -80°C until analysis. Urine samples were centrifuged at 1000 rpm for 10 minutes within the first 4 hours and stored at -80° until analysis.

L-FABP was measured using the Human L-FABP ELISA kit (Hycult Biotech). Coefficients of inter-assay and intra-assay variation for urine and plasma FABPs were lower than 10% and 15%, respectively. Urine L-FABP was expressed in µg/g creatinine. In addition to L-FABP, NGAL was also measured in urine samples of patients from the study cohort using ELISA, as previously reported [15,21].

Statistical analysis

Categorical variables are reported as absolute frequencies and percentages. Quantitative variables are reported as median and interquartile range, or

otherwise specified. There were <30% missingness for “CRP” (C-reactive protein) and “Albumin” in the training set which were handled by imputation using the Expectation-Maximization algorithm [22]. This method is valid under the reasonable missing at random assumption (i.e. missing data may be predicted from covariates) in this study where not missing not at random were not expected. No missing data were needed to be imputed for the rest of the data on the training or validation sets, and “CRP” and “Albumin” were not finally used in the predictive models.

Comparisons between variables were carried out using the Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. Survival function was described using the Kaplan-Meier method.

Factors associated with 90-day mortality were identified in a bivariate analysis. Transplanted patients (n=15, 5% of the study cohort; n=6, 4% of the validation cohort) were censored at the time of intervention. Factors showing statistically significant association in bivariate analysis were selected for the initial multivariate analysis. Cox regression models were used to select the best subset of predictors having assessed fitting characteristics. Continuous variables were fitted as continuous linear variables and categorical variables (using tertiles and the median cut-offs); deviations from linearity were explored by adding non-linear transformation terms to the model. The proportional hazards assumption was assessed by reviewing the survival function plots. The final model was fitted using a stepwise forward method based on the improvement in model likelihood ratios. Significance levels to enter and drop model variables were adopted as 5% and 10% respectively. All variables not selected for inclusion (p>=0.10) were checked against the final model in turn to determine whether their inclusion improved the

fit of the model, as evidenced by p <0.10 or a lower Akaike information criterion value.

The predictive model developed for the study cohort was applied to the validation cohort. The Cox coefficients from the study cohort analyses were fitted to the validation set.

Calibration and discrimination

Calibration describes how closely the predicted probabilities agree numerically with the actual outcomes [23]. Predicted probabilities from the Cox model were compared against the observed probabilities from the Kaplan-Meier method using the Brier score [24]. A calibration plot assessing whether the observed vs predicted regression slope was 1 and the intercept 0, as expected from a perfect fit, is shown for the study and validation sets.

Discrimination refers to the ability of the model to correctly distinguish between two classes of outcomes such as death and survival [23,25]. The Harrell concordance statistic (95%CI) [26] and area under the receiver operating characteristic curve (ROC-AUCs) [27] (7, 14, 28, 45, 60 and 90 days) were used to assess discrimination of the model. The predicted Cox and the observed probabilities of death are plotted in a survival plot and compared using the log-rank test.

Statistical analyses were performed using SAS (v9.4; SAS Institute Inc., Cary, NC). This article adheres to the “Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement“ (**Supplementary Materials**) [28].

RESULTS

Characteristics of the study population

Demographic and clinical characteristics of the study cohort are shown in **Table 1**. Most patients were male (65%) and the most common aetiology of cirrhosis was alcohol consumption (43%). Patients had moderate to severe impairment of liver function as reflected by a median MELD score of 17 and MELD Na score of 21. One hundred–and-eleven patients (36%) had ACLF at admission, with most patients with ACLF grade 1 (53 patients, 48% of patients with ACLF). Most patients (77%) had history of previous complications of cirrhosis before admission.

Relationship between urine L-FABP levels and mortality

During a 3-month follow-up period, 84 (27%) patients died, 15 (5%) were transplanted and the remaining 206 (68%) were alive at the end of follow-up. Univariate analysis of 3-month survival is shown in table 2. As expected, patients who died had more marked impairment of liver function as compared to those alive at the end of follow-up, as reflected by higher bilirubin levels, INR, MELD, and MELD-Na scores. In addition, although there were no significant differences in the frequency of bacterial infections at admission, patients who died had significantly higher leukocyte count compared to those who were alive at the end of follow-up. Moreover, the presence of AKI and ACLF was significantly more frequent in patients who died compared to those who survived. Finally, uNGAL and uL-FABP levels were significantly higher in patients who died compared to those of patients who survived. By contrast, there were no significant differences between groups in the plasma levels of L-FABP.

In the multivariate analysis, the best model that predicted 90-day mortality included uL-FABP levels together with MELD Na score [C-statistic: 0.810 (0.767 – 0.852)] **(**Table 3). uL-FABP was an independent predictive factor after adjustment for variables that could influence uL-FABP levels, such as presence of AKI or bacterial infections, leukocyte count or CRP levels. In contrast to uL-FABP, uNGAL levels were not associated with survival in multivariate analysis.

We next investigated the relationship between the probability of death and uL-FABP levels according to MELD-Na score values. uL-FABP levels modulated the 90-day prognostic value of MELD-Na. When patients where stratified according to median values of MELD Na and uL-FABP in the cohort, 90-day mortality was significantly different between groups, in such a way that for the same MELD-Na group, patients with higher uL-LFABP levels had significantly higher probability of mortality than those within the same MELD-Na group but with lower uL-FABP levels (**Figure 1**).

Validation cohort

To validate the role of uL-FABP we analyzed an independent cohort of 139 patients prospectively recruited within a subsequent 2-year period. The inclusion and exclusion criteria for the validation cohort were the same as those used for the study cohort. Comparison of baseline demographic, clinical, and laboratory characteristics of the study cohort and validation cohort are shown in Table 1. Patients from the validation cohort had similar baseline characteristics to those from the study cohort. There were only differences in etiology of cirrhosis, with a lower prevalence of HCV infection and higher prevalence of infections at admission in the validation vs study cohort. In the validation cohort, fifty-eight

(42%) patients had ACLF at admission and baseline MELD-Na score was 21 (15 – 28). Baseline median uL-FABP levels were similar between both cohorts.

Thirty-six (26%) patients of the validation cohort died during the 3-month follow-up period. Univariate analysis of survival is shown in Supplementary Table 1. Results from the multivariate analysis validated those obtained in the study cohort, showing that uL-FABP and MELD-Na score were independent predictive factors of 3-month mortality, and the model had a good discrimination performance as shown graphically in **Figure 2** (log-rank, p<0.0001) and confirmed by the C-statistic for the study [0.810 (0.768 – 0.852)] and the validation [0.819 (0.886 - 0.752)] cohort. The calibration plot showed a good fit between the observed and the predicted survival probabilities, and no statistical differences from a perfect fit (i.e intercept=0 and slope=1) were found for both the study and the validation cohorts (**Figure 3**).

Relationship between urine L-FABP levels and ACLF

We next sought to determine the relationship between uLFABP and the presence or development of ACLF. In the study cohort, 111 (36%) patients had ACLF at admission (Table 1). Patients with ACLF had significantly higher baseline uL-FABP levels compared to those of patients without ACLF (45 [18 – 89] vs 25 [14 – 60] µg/g of creatinine, p=0.005; respectively). Moreover, uL-FABP levels increased in parallel with ACLF severity. By contrast, there were no significant differences in plasma L-FABP levels according to the presence and severity of ACLF **(Figure 4)**. Similar findings were observed in the validation cohort: patients with ACLF also had higher levels of uL-FABP compared to those of patients who did not have ACLF at admission (54 [23 – 187] vs. 21 [9 – 39] µg/g of creatinine,

p < 0.001, respectively]. Moreover, uL-FABP levels also increased with disease severity (**Supplementary Figure 1**). Interestingly, uL-FABP levels also correlated with the type of acute decompensation as defined by the classification of the Predict study[29], in such a way that patients with pre-ACLF had uL-FABP levels significantly higher compared to those of patients with stable or unstable DC [58 (35 – 106) in pre-ACLF vs 23 (12 - 56) and 19 (14 – 41) µg/g of creatinine in stable and unstable DC, respectively; p=0.027].

We also investigated the relationship between uL-FABP levels and the types of organ failures in patients with ACLF. Renal failure was the most common organ failure (77 patients, 25%), followed by liver failure (43 patients, 14%) and circulatory failure (41 patients, 13%). Notably, patients with liver failure, coagulation failure, and circulatory failure had significantly higher uLFABP levels than patients without these organ failures. By contrast, uL-FABP levels did not correlate with brain, renal, and respiratory failure (Table 4). Because L-FABP can be overexpressed in the kidneys in the setting of acute tubular injury and increased uL-FABP levels have been reported in patients with cirrhosis and AKI[30,31], we further investigated the potential relationship between uL-FABP and kidney failure. Interestingly, patients meeting the criteria of AKI (n=143) had significantly higher levels of uL-FABP compared to those of patients without AKI (n=162) [39 (15 – 87) vs 25 (13 – 60) µg/g of creatinine, respectively; p=0.01). Moreover, when the etiology of AKI was considered, patients with acute tubular necrosis (ATN) had significantly higher levels compared to those of patients with hepatorenal syndrome (HRS) [89 (30 – 149) vs 39 (14 – 66) µg/g of creatinine, respectively; p<0.001). Taken together, these findings suggest that uL-FABP levels are increased in the setting of AKI, particularly in the presence of ATN.

To further investigate the role of uL-FABP as biomarker in ACLF, we assessed whether uL-FABP levels were able to predict patients at risk of developing ACLF. Eighteen out of the 194 patients without ACLF at admission (9%) in the study cohort developed it during hospitalization or during the 3-month follow-up period [median time 7 (2 – 13) days]: 3 patients (17%) ACLF 1, 6 patients (33%) ACLF 2 and 9 patients (50%) ACLF 3. Patients who developed ACLF during follow-up had significantly worse liver and kidney function tests at admission compared to patients who did not develop ACLF, as assessed by higher MELD Na score, bilirubin or INR levels, and with the presence of AKI at admission (**Supplementary Table 2**). However, the presence of bacterial infections at admission was not different between patients who developed or did not develop ACLF. Patients who developed ACLF during follow-up had significantly higher uL-FABP levels at admission compared to those of patients who did not develop ACLF. In the multivariate analysis, again MELD-Na score and uL-FABP levels were the only independent factors associated with development of ACLF during follow-up [C-statistic 0.878 (0.808 - 0.948)] (Table 3). uNGAL levels showed a moderate correlation with uL-FABP levels ($r=0.335$, $p<0.001$) and were associated with development of ACLF in the univariate analysis but not in the multivariate analysis.

DISCUSSION

In the present study we investigated the role of uL-FABP as prognostic biomarker in patients with DC and in ACLF. The study has three major findings. First, uL-FABP levels are independently associated with 3-month mortality in hospitalized patients with DC, together with MELD Na score. Second, uL-FABP levels are associated with liver-related organ failures and with circulatory failure in patients with ACLF. Finally, uL-FABP levels are associated with the risk of developing ACLF during follow-up.

MELD-Na has been shown to improve the prognostic accuracy of MELD score and is able to reclassify patients who despite low MELD score have higher risk of mortality [32,33]. In this regard, MELD-Na is the most widely used method for liver allocation in patients awaiting liver transplantation because it provides a good prognostic stratification of patients with DC. Nonetheless, there are still limitations when using MELD-Na. In fact, data from a recent study in a large cohort of patients with cirrhosis show that patients with persistently low MELD-Na score values still have significantly high rate of liver-related mortality [32]. Therefore, there is need to improve prognosis stratification in patients with DC. Findings from the present study clearly show that uL-FABP levels represent and independent predictor of 3-month mortality together with MELD-Na score.

L-FABP has been described to be increased in the context of liver injury in different conditions [5–10]. In addition, LFABP has also been involved in inflammatory processes and lipid metabolism [34,35]. It is well known that DC is associated with chronic systemic inflammation that correlates with disease severity and clinical outcomes [36–38]. Therefore, we hypothesize that the

current findings of uL-FABP as biomarker in cirrhosis may be explained, at least in part, by two major reasons. First, uL-FABP levels may reflect not only liver injury, but also multiorgan dysfunction of patients with DC. Second, uL-FABP levels may reflect the systemic inflammatory milieu occurring in DC, which is not captured by MELD-Na score variables.

To date, several scores have been reported to predict mortality in patients with ACLF [39–42]. However, there is no widely validated method or biomarker to predict patients at risk of developing ACLF. Considering its dismal short-term prognosis, identifying methods that help predicting the development of ACLF is an unmet need. In the present study we showed, that uL-FABP is significantly higher in patients with ACLF and that it correlates with some organ failures, particularly liver, circulation and coagulation. Moreover, uL-FABP levels also correlated with the existence of renal failure, specifically with the presence of ATN. The discrepancy between differences in uL-FABP levels according to the definition of renal failure used, either the ACLF definition or the AKI definition, likely depends on different diagnostic criteria of these two definitions (>2 mg/dL of serum creatinine in ACLF and AKI standard criteria, respectively) [19,20]. In addition, interestingly, our results showed that uL-FABP levels are higher in patients without ACLF who will develop ACLF during follow-up. Therefore, uL-FABP could be useful as biomarker to identify patients at risk of ACLF. Nevertheless, this finding should be interpreted with caution because of the reduced number of patients developing ACLF during follow-up in the current series.

L-FABP plays a role in fatty acid trafficking and metabolism, and in the conversion of fatty acids to eicosanoid intermediates and in the stabilization of leukotrienes

[2]. Recent data suggest that patients with ACLF have impairment in fatty acid beta oxidation [43] similar to that of inflammatory conditions such as sepsis. In addition, it has been reported that patients with ACLF display a specific lipid profile that correlates with the stage of the disease and prognosis [13]. High levels of leukotriene 4 (LTE_4) have been associated with the presence of ACLF and its severity. Moreover, differences in lipid profile were found in patients with liver, coagulation or circulatory failure, despite the lack of differences in lipid profile in patients with renal, brain or respiratory failure [13]. Our findings are consistent with these results and taken together we can hypothesize that increased uL-FABP levels may reflect the activation of inflammatory pathways through lipid mediators occurring in ACLF, where FABPs, and particularly L-FABP may play an important role. The reason why urine but not plasma levels of L-FABP are predictive of prognosis is intriguing and could not be unraveled from the results of the current study. It is possible that an increased renal production of the peptide could explain the relationship between uL-FABP levels and prognosis in some patients, particularly in those with associated ATN. However, further studies should be performed to investigate this issue.

The current study has some strengths and limitations that should be mentioned. First, the study includes a large prospectively collected cohort of patients with DC. In addition, results were validated in an independent cohort of patients. However, this is a single-center study and, therefore, results should be validated in multicenter studies. Finally, the design of our study does not allow drawing mechanistic conclusions about the role of L-FABP in the pathophysiology of ACLF. However, our results suggest a mechanistic hypothesis that will need to be investigated in future studies.

In conclusion, our study shows that urinary L-FABP is a promising biomarker to predict mortality in patients with DC. In addition, L-FABP is a good biomarker of ACLF and may reflect the inflammation and impaired lipid metabolism is involved in the pathophysiology of the syndrome.

Abbreviations: Acute kidney injury (AKI), acute-on-chronic liver failure (ACLF), area under the receiver operating characteristic curve (ROC-AUCs), C-reactive protein (CRP), decompensated cirrhosis (DC), Fatty Acid Binding Proteins (FABPs), hepatitis C (HCV), liver fatty acid-binding protein (L-FABP), leukotriene 4 (LTE_4), Model for End-stage Liver Disease (MELD), Model for End-stage Liver Disease Sodium (MELD Na), ROC AUC, Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD), urinary liver fatty acid-binding protein (uL-FABP), urinary neutrophile gelatinase-associated lipocalin (u-NGAL).

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FIGURE LEGENDS

Figure 1.- 90-day survival according to median MELD Na and median uL-FABP. Kaplan-Meier survival curves grouped per median MELD Na and median uL-FABP levels in the study cohort. Units of uL-FABP are µg/gr creatinine. Level of significance: $p < 0.001$ (log-rank test).

Figure 2.- Survival plot with the observed (step lines) and predicted (marks) probabilities of death stratified per tertiles from the Kaplan-Meier and Cox model for the study (TRN) and validation (VLD) cohorts. Level of significance: $p<0.0001$ (log-rank test).

Figure 3. Calibration plot comparing the observed and predicted probabilities of death from the Kaplan-Meier and Cox model for the training and validation cohorts. The estimated intercept [95%CI] and slope [95%CI] for the study set were -0.01 [-0.025 to 0.006] and 1.001 [0.981 to 1.02], respectively, and for the validation set 0.006 [-0.035 to 0.047] and 0.974 [0.922 to 1.026], respectively. No statistical significance was found when testing whether the intercept was different from 0 ($p=0.212$ and $p=0.765$ for the study and validation sets, respectively), and when testing whether the slope was different from 1 ($p=0.936$ and $p=0.326$ for the study and validation sets, respectively). The Bier score [95%CI] for the study and validation sets were 0.216 [0.182-0.250] and 0.206 [0.159-0.252], respectively.

Figure 4 – Urinary and plasma L-FABP levels according to the presence and severity of ACLF. Level of significance: $p = 0.005$ and $p = 0.099$, respectively. (Kruskal-Wallis test).

Table 1.- Baseline demographic and clinical characteristics of patients included in the validation cohort compared to the study cohort.

Variable	Study Cohort (n=305)	Validation Cohort (n=139)	p value
Age (years)	59 (52 - 68)	60 (52 – 65)	0.586
Female gender	108 (35)	44 (32)	0.439
Etiology			
Alcohol related	131 (43)	86 (62)	
Alcohol related + HCV	36 (12)	12 (9)	**< 0.001**
HCV	95 (31)	19 (14)	
Other	43 (14)	22 (15)	
Presence of ascites	204 (67)	91 (66)	0.769
Presence of hepatic encephalopathy	101 (33)	51 (37)	0.462
Albumin (g/L)	28 (25 - 32)	29 (25 – 34)	0.169
Bilirubin (mg/dL)	2.4 (1.3 – 5.2)	2.5 (1.2 – 7.6)	0.796
INR	1.55 (1.32 – 1.88)	1.54 (1.30 – 1.95)	0.944
Serum Creatinine (mg/dL)	1.2 (0.8 – 1.9)	1.1 (0.6 – 1.9)	0.063
Serum Sodium (mEq/L)	135 (131 – 138)	136 (133 - 139)	**0.015**
Leucocyte count ($x10^9/mm^3$)	5.7 (3.9 – 8.8)	6.4 (4.3 – 9.8)	0.136
C-reactive protein (mg/dL)	2.2 (0.9 – 5.1)	2.6 (0.9 – 5.1)	0.0504
MELD Sodium score	21 (16 - 28)	21 (15 – 28)	0.579
AKI	143 (47)	74 (53)	0.214
Bacterial infections	117 (38)	78 (56)	**0.001**
ACLF	111 (36)	58 (42)	
Grade 1	53 (48)	31 (54)	0.225
Grade 2	34 (30)	17 (29)	
Grade 3	24 (22)	10 (17)	
u-NGAL (μg/gr creatinine)	46 (23 - 125)	NA	-
Plasma L-FABP (ng/mL)	25 (17 - 39)	NA	-
uL-FABP (μg/gr creatinine)	30 (15 – 69)	30 (13 – 66)	0.812

Values are numbers or medians and percentages or interquartile ranges (in brackets)

HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease; ACLF, acute-on-chronic liver failure; AKI, acute kidney inury; u-NGAL, urinary Neutrophil gelatinase-associated lipocalin; uL-FABP, urinary Liver fatty acid-binding protein.

NA, not available: plasma L-FABP and u-NGAL were not available in patients from the validation cohort.

Table 2.- Baseline characteristics of patients from study cohort according to 3-month survival.

Variable	Alive # (n=221)	Dead (n=84)	HR (95% IC)	p value
Age (years)	58 (51 – 66)	56 (49 – 65)	0.998 (0.979 - 1.017)	0.8038
Gender (Female)	82 (37)	26 (31)	0.773 (0.486 - 1.227)	0.2744
Etiology				
Alcohol	93 (42)	39 (45)	Ref	
Alcohol + HCV	27 (12)	9 (11)	0.849 (0.411 - 1.756)	
HCV	70 (32)	25 (30)	0.906 (0.547 - 1.500)	0.9655
Other	31 (14)	12 (14)	0.939 (0.490 - 1.796)	
Presence of ascites	134 (61)	70 (83)	2.834 (1.596 - 5.032)	**0.0004**
Presence of hepatic encephalopathy	54 (24)	47 (56)	3.331 (2.163 - 5.129)	**<.0001**
Albumin (g/L)	28 (25 – 31)	28 (25 – 32)	0.988 (0.948 - 1.029)	0.5613
Bilirubin (mg/dL)	2.2 (1.2 – 3.9)	5.5 (2.3 – 22.9)	1.078 (1.061 - 1.096)	**<.0001**
INR	1.5 (1.4 – 1.8)	1.9 (1.6 – 2.8)	2.450 (2.015 - 2.978)	**<.0001**
Serum Creatinine (mg/dL)	1.1 (0.8 – 1.8)	2.0 (1.1 – 2.9)	1.663 (1.448 - 1.909)	**<.0001**
Serum Sodium (mEq/L)	136 (132 – 138)	131 (126 – 136)	0.901 (0.872 - 0.930)	**<.0001**
Leucocyte count ($x10^9/mm^3$)	5.2 (3.7 – 7.8)	7.5 (5.4 – 12.0)	1.128 (1.083 - 1.175)	**<.0001**
C-reactive protein (mg/dL)	2.2 (0.8 – 5.0)	2.4 (1.6 – 5.9)	1.013 (0.966 - 1.062)	0.5861
MELD score	17 (13 – 22)	29 (22 – 35)	1.118 (1.094 - 1.142)	**<.0001**
MELD Sodium score	21 (15 – 26)	31 (25 – 36)	1.140 (1.111 - 1.170)	**<.0001**
AKI	83 (38)	60 (71)	3.727 (2.318 - 5.993)	**<.0001**
Bacterial infections	81 (37)	36 (43)	1.280 (0.831 - 1.972)	0.281
ACLF at inclusion	57 (26)	54 (64)		
Grade 1	36 (16)	17 (20)	4.445 (2.836 - 6.967)	**<.0001**
Grade 2	15 (7)	19 (23)		
Grade 3	6 (3)	18 (21)		
u-NGAL (μg/gr creatinine)	39 (18 – 106)	84 (37 – 263)	1.001 (1.000 - 1.001)	**<.0001**
Plasma L-FABP (ng/mL)	24 (16 - 37)	26 (18-46)	1.001 (0.997 - 1.005)	0.6018
uL-FABP (μg/gr creatinine)	27 (12 – 64)	52 (23 – 117)	1.010 (1.003 - 1.016)#	**0.006**

Values are numbers or medians and percentages or interquartile ranges (in brackets).

HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease; ACLF, acute-on-chronic liver failure; AKI, acute kidney inury; u-NGAL, urinary Neutrophil gelatinase-associated lipocalin; uL-FABP, urinary Liver fatty acid-binding protein.

 # Transplanted patients were censored at the time of intervention

HR per 10 units increase

Table 3.- Independent predictive factors associated with 3-month mortality (up) and ACLF development (bottom).

3 month-mortality

Variable	Units	HR (LL – UL)	p value
MELD Na	1	1.135 (1.106 - 1.165)	0.0001
uL-FABP	10	1.026 (1.011 – 1.041)	0.0006

C-statistic: 0.810 (0.767 – 0.852).

AUC-ROC by time: 0.902 at 7d, 0.846 at 14d, 0.859 at 28d, 0.854 at 45d, 0.853 at 60d and 0.825 at 90d

MELD Na, model for end-stage liver disease - sodium; uL-FABP, urinary Liver fatty acid-binding protein; HR, Hazard-Ratio; LL, Lower Limit; UL, Upper Limit.

Variables included in multivariate analysis were: AKI, ascites, hepatic encephalopathy, ACLF, circulatory failure, renal failure, liver failure, coagulation failure, brain failure, ACLF grade, number of organ failures, serum creatinine, bilirubin, INR, leucocyte count, serum sodium, mean arterial pressure, uL-FABP, u-NGAL, MELD, MELD Na, Child Pugh score

ACLF development

Variable	Units	HR (LL – UL)	p value
MELD Na	1	1.321 (1.194 - 1.462)	<0.0001
uL-FABP	10	1.044 (1.017 – 1.072)	0.0014

C-statistic: 0.878 (0.808- 0.948)

AUC-ROC by time: 0.868 at 7d, 0.885 at 14d, 0.896 at 28d, and 0.902 after 45d

MELD Na, model for end-stage liver disease - sodium; uL-FABP, urinary Liver fatty acid-binding protein; HR, Hazard-Ratio; LL, Lower Limit; UL, Upper Limit.

Variables included in multivariate analysis were: AKI, ascites, hepatic encephalopathy, serum creatinine, bilirubin, INR, leucocyte count, serum sodium, mean arterial pressure, uL-FABP, u-NGAL, MELD, MELD Na, Child Pugh score

Table 4.- uL-FABP levels according to the presence of Organ Failures in patients with ACLF

	Yes	No	p value
Liver Failure	79 (36 – 136)	25 (13 – 60)	**<.0001**
Coagulation Failure	65 (25 – 136)	28 (15 – 65)	**0.0034**
Circulatory Failure	81 (39 – 148)	25 (14 – 60)	**<.0001**
Brain Failure	41 (19 – 97)	29 (15 – 67)	0.1198
Renal Failure	36 (15 – 84)	29 (15 – 65)	0.2661
Respiratory Failure	55 (22 – 110)	29 (15 – 68)	0.1371

Values are median and interquartile range (in brackets). Units are µg/g creatinine

Figure 1.- 90-day survival according to median MELD Na modulated by median uL-FABP

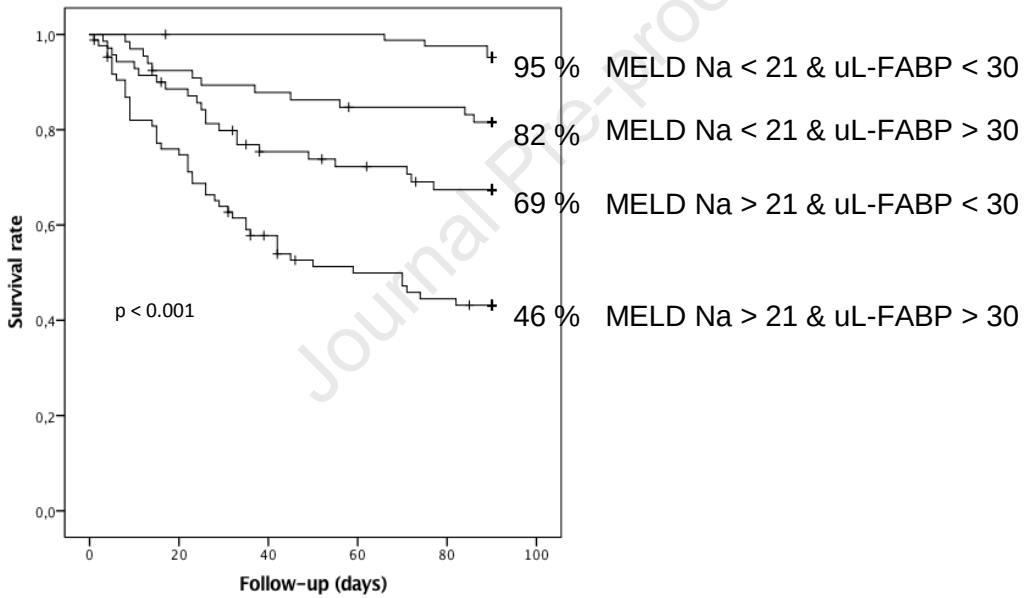


Figure 2.- Survival plot with the observed (step lines) and predicted (marks) probabilities of death from the Kaplan-Meier and Cox model for the study (STU) and validation (VLD) cohorts.

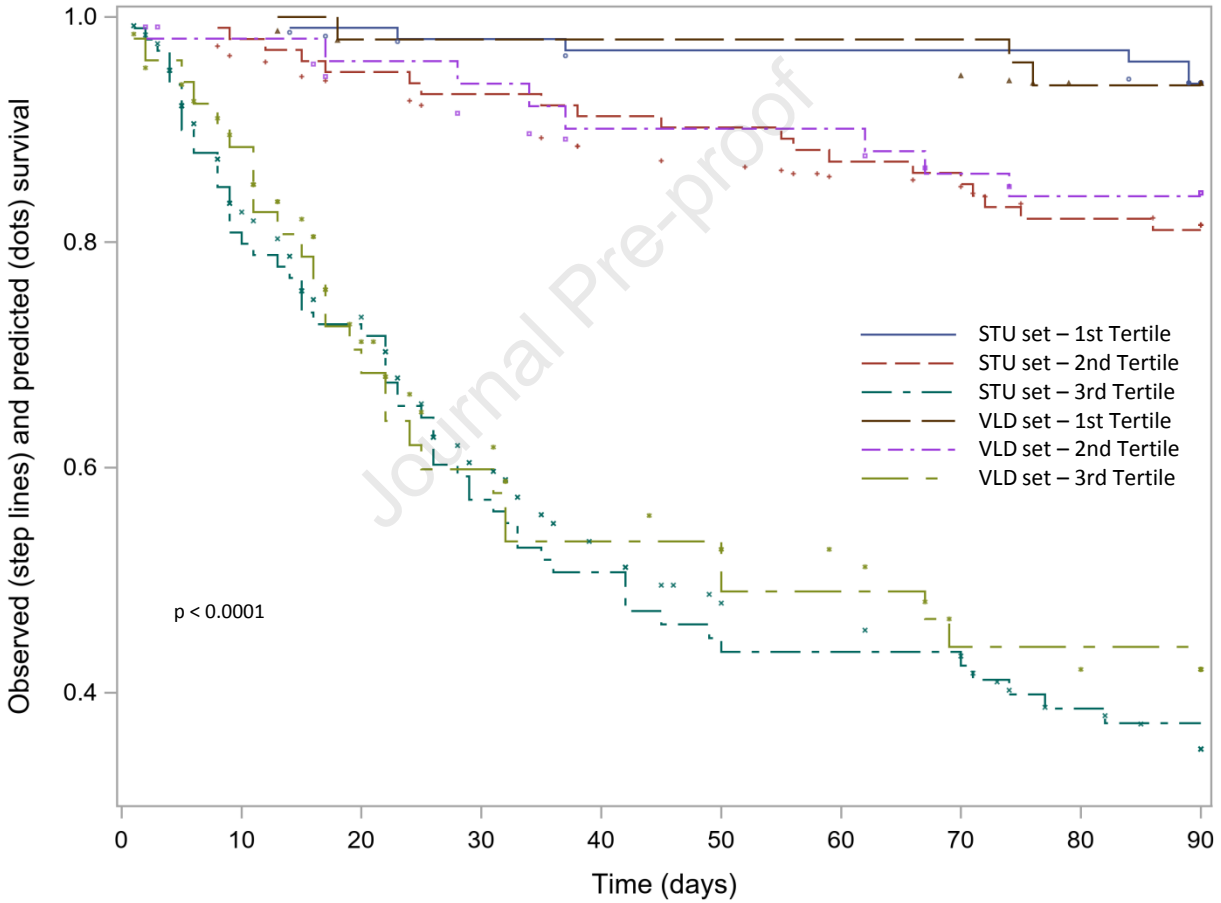


Figure 3. Calibration plot comparing the observed and predicted probabilities of death from the Kaplan-Meier and Cox model for the training and validation cohorts

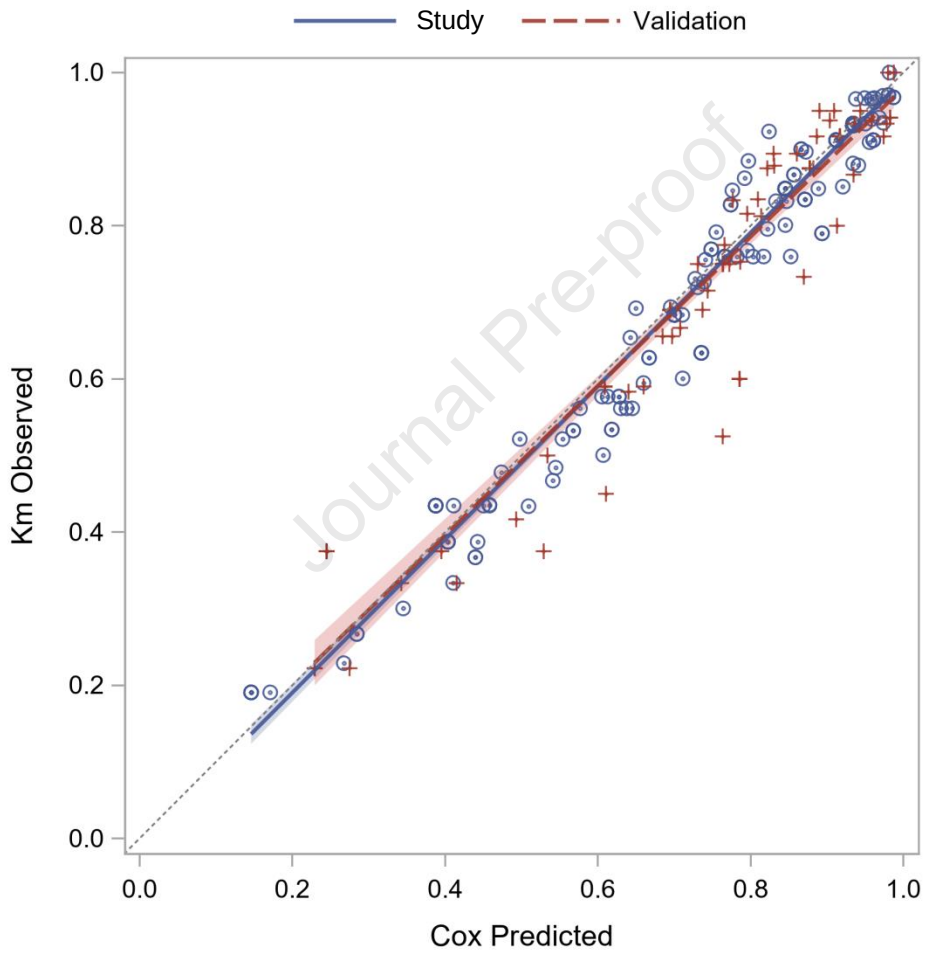
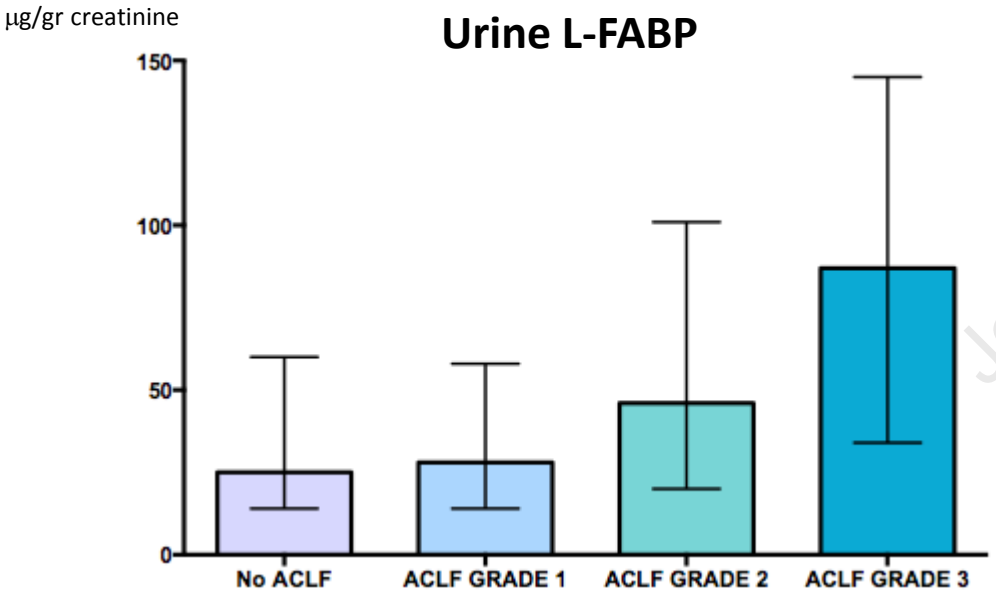
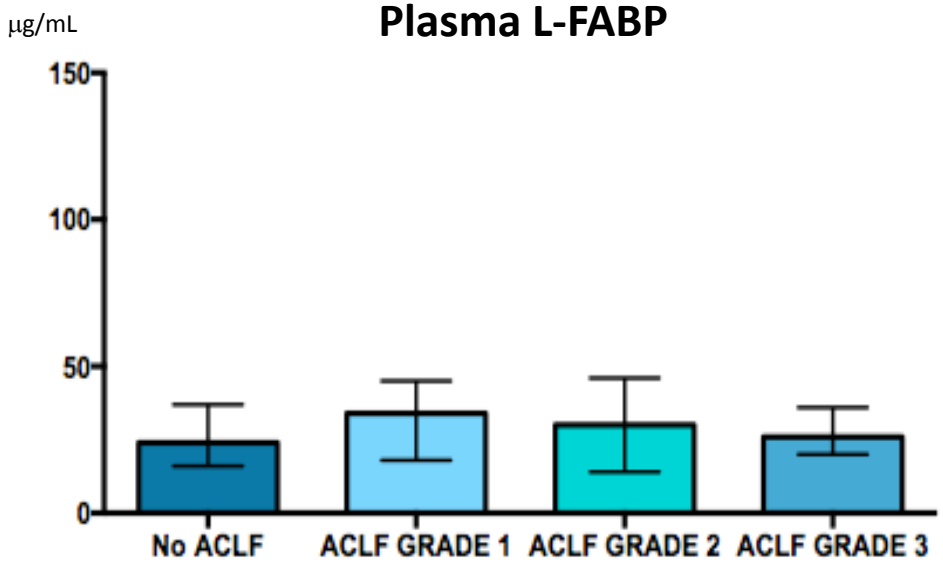


Figure 4 – Urinary and plasma L-FABP levels according to the presence and severity of ACLF.



uL-FABP (µg/gr creatinine)	25 (15 – 60)	28 (14 – 58)	46 (20 – 101)	87 (34 – 145)	p = 0.005



Plasma L-FABP (µg/mL)	24 (16 – 37)	34 (18 – 45)	30 (14 – 46)	26 (20 – 36)	p = 0.099

Highlights

- L-FABP is a mediator for lipid metabolism and has been associated with liver injury
- Urinary L-FABP was analyzed in two independent cohorts with over 400 patients
- uL-FABP and MELD Sodium were associated with 90-day mortality
- uL-FABP correlates with ACLF grade and liver, coagulation and circulatory failures
- Moreover, uL-FABP was related with development of ACLF