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Galectin-3 is associated with glomerular filtration rate and outcome in patients with stable decompensated cirrhosis

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ABSTRACT

Background: Newly introduced galectin-3 (gal-3) has been associated to impaired renal function. Gal-3 may become prognostic biomarker in hepatic diseases.
Aim: To investigate the association of gal-3 with prognosis and renal function in patients with stable decompensated cirrhosis.
Method: We studied prospectively 100 stable decompensated patients in our Department between 2010 and 2017. We measured gal-3 in serum samples. Patients' renal function was assessed using ^{51}Chromium-EDTA ("true GFR").
Results: Seventy patients (70%) survived and 30 died (n = 16) or underwent LT (n = 14). Twenty nine patients (29%) had normal gal-3, 71 (71%) had ≥11.7 ng/mL; they differed significantly regarding mean "true"-GFR: 90 ± 20 mL/min vs. 76 ± 26 mL/min, p = 0.03 and mean creatinine: 0.83 ± 0.14 mg/dL vs. 0.97 ± 0.4 mg/dL, p = 0.05. Median gal-3 levels were 17.5 ng/mL (range 4.9–76.5 ng/mL); 49 patients with gal-3 ≥17.5 ng/mL had significantly higher MELD score, (15 ± 5 vs. 13 ± 4, p = 0.02) and worse "true" GFR (74 vs. 85 mL/min, p = 0.04). Gal-3 had good performance in predicting "true"-GFR < 60 mL/min; AUC: 0.71, 95%CI [0.58–0.85], best cut off value 17.5 ng/mL. Kaplan–Meier analysis, using median gal-3 (17.5 ng/mL) revealed different survival time for our patients (log-rank p = 0.04).
Conclusion: Gal-3 proved trustworthy marker of established chronic kidney disease, with predictive ability in stable decompensated cirrhosis. Gal-3 came also a significant factor for our patients' outcome.

1. Introduction

Cirrhosis is a major cause of morbidity and mortality. Cirrhosis has been seen to be not a single disease entity, but one that can be subclassified into distinct clinical prognostic stages [1]. Till now, prognostic scores used rely on a limited number of variables, estimate the probability of death within a given time interval and are also expected to address important issues that help to determine patients' therapeutic options [2].

Studies have shown that variables expressing renal dysfunction (serum creatinine and blood urea nitrogen/azotemia) arise as powerful prognostic indicators in cirrhotics [3,4]. In general, renal function is a well-established prognostic marker in cirrhosis, as indicated by the incorporation of serum creatinine into the MELD (Model for End-stage Liver Disease) score, which has high discriminant ability in triaging patients referred for liver transplantation (LT). [5] Moreover, the most reliable measurement of "true" Glomerular Filtration Rate (GFR) proved an important prognostic factor in patients with decompensated cirrhosis [6]. Though, assessment of "true" GFR is difficult for routine use, because it is more expensive, time-consuming and/or a nuclear medicine laboratory may be necessary [6,7].

At the same time, galectin-3 (gal-3), a member of the lectins family, has been shown to play a critical role in the development of several chronic diseases [8]. In general, it regulates basic cellular functions such as cell–cell and cell–matrix interactions, growth, proliferation, differentiation, and inflammation and is involved in the pathogenesis of many relevant human diseases, including cancer, fibrosis, chronic inflammation and scarring affecting many different tissues [8]. Moreover, upregulation of gal-3 expression

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has even been seen in neoplastically transformed cells conferring preferential survival to tumors [9].Interestingly, gal-3 reflects cardiac fibrosis in heart failure, but has also been associated to renal fibrosis and impaired renal function [10].

As for the liver, gal-3 proved to be a good marker of fibrosis in cirrhosis and toxic hepatitis, reflecting the stage of liver damage [11]. A more specific approach showed that gal-3 is implicated in hepatitis-C related fibrosis and especially cirrhosis, as serum gal-3 levels showed significant increase in these populations (22.7 ± 10.1 vs. 3.2 ± 1.3 in healthy controls, $p < 0.001$) [12]. Gal-3 seems to mediate the pathogenesis of liver metabolic disorders related to obesity and liver fibrosis, too. Recent study showed that it is implicated as an important regulatory factor in profibrotic pathways seen in hepatic fibrosis [13].

Thus, it seems that gal-3 may become emerging as a new diagnostic, prognostic biomarker and as a new promising therapeutic target in hepatic diseases [8]. However, no study has evaluated the impact of gal-3 in decompensated cirrhosis or search for implications with patients' features. We specifically considered to investigate its association with prognosis and renal function in patients with stable decompensated cirrhosis.

2. Materials and methods

We studied prospectively consecutive patients with stable decompensated cirrhosis presented for pre-LT evaluation in our Department between 2010 and 2017. Decompensated cirrhosis was defined as a history of ascites, variceal bleeding, encephalopathy in patients with known cirrhosis. Patients were stable regarding their chronic liver disease: i.e. they had no active variceal bleeding, encephalopathy or infection, such as spontaneous bacterial peritonitis (SBP), during the last month before admission. Detailed clinical evaluation, laboratory measurements (white blood cells, C-reactive protein, procalcitonin, blood cultures and ascitic fluid paracentesis) and radiological exams (chest x-ray, upper abdominal ultrasound), whenever necessary, were performed in order to exclude patients with clinical or subclinical infection.

We examined carefully our patients and recorded their demographic, clinical and laboratory characteristics; age; sex; cause and duration of liver disease; previous complications of cirrhosis [i.e. variceal bleeding, encephalopathy or SBP]; medication administered for the liver disease (duration and dosage); and vital signs (blood pressure, pulse rate). We estimated basic serum laboratory variables; albumin, protein, bilirubin (total and direct), clotting profile, creatinine, electrolytes [e.g. sodium (Na) and potassium (K)], aminotransferases (aspartate and alanine), alkaline phosphatase, γ-glutamyl transpeptidase and lactate dehydrogenase. We evaluated our patients prognosis by calculating their MELD [14] and Child-Pugh (CTP) [15] scores. Finally, we measured levels of gal-3 in serum samples using the Abbott Architect i1000SR Analyzer, which applies a method of Chemiluminescent Microparticle Immunoassay to determine gal-3 values; upper Limit of Normal (ULN) based on the biochemical laboratory: 11.7 ng/mL.

According to our protocol, patients underwent further evaluation before becoming subscribed in the LT list. Especially, their renal function ("true" GFR) was assessed using ^{51}Chromium-EDTA (^{51}Chr-EDTA) [16] along with estimated GFR (eGFR) using the creatinine-based 4 variables Modification of the Diet in Renal Disease (MDRD) formula [17].

Only patients with full demographic and laboratory data were included in the study. All patients were followed up prospectively, and their outcome was recorded, whether they were under supervision or got a liver transplant or died. Their features were analyzed.

The study protocol was approved by our Institutional Review Board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Table 1
Baseline clinical and laboratory characteristics of 100 patients with stable decompensated cirrhosis.

Variable	Patients, n = 100
Age (mean ± SD, years)	52 ± 11
Sex, male n, (%)	69 (69)
Aetiology of cirrhosis, n, (%)	
Viral hepatitis	36 (36)
Alcohol	25 (25)
NASH	16 (16)
Other	23 (23)
Hepatocellular carcinoma (HCC), n (%)	17 (17)
History of complications, n, (%)	
GI bleeding	28 (28)
Encephalopathy	35 (35)
SBP	12 (12)
Total bilirubin (median, range, mg/dL)	1.87 (0.24–34.7)
Albumin (median, range, g/dL)	3.5 (2–7)
Creatinine (median, range, mg/dL)	0.88 (0.49–2.95)
"true" GFR by ^{51}Chromium-EDTA (mean ± SD, mL/min)	80 ± 25
MDRD-estimated GFR (mean ± SD, mL/min)	88 ± 27
Galectin-3 (median, range, ng/mL)	17.5 (4.9–76.5)
Heart rate (/min, mean ± SD)	72 ± 13
CTP score (median, range)	8 (5–13)
MELD score, (mean ± SD)	14 ± 5

(NASH; Non-alcoholic steatohepatitis, GI; gastro-intestinal, SBP; spontaneous bacterial peritonitis, GFR; glomerular filtration rate, CTP; Child-Pugh score, MELD; Model for End stage Liver Disease, MDRD; Modification of the Diet in Renal Disease formula).

3. Statistical analysis

Continuous variables on our cohort were presented as mean ± standard deviation (normally distributed) or median with interquartile range (non-normally distributed). Categorical variables were expressed as frequencies or percentages. Comparisons of parameters between patients were performed using Student's t or Mann–Whitney U-tests, as appropriate for continuous variables, and chi-square test for categorical variables. Logistic regression analysis was carried out to identify factors associated with gal-3 levels. Our analysis was conducted using as a cut-off point the upper limit of gal-3 normal value and its median value. Variables that came significant in the univariate analysis were included in the multivariate model. Accordingly, we searched for those factors associated with the presence of chronic kidney disease (GFR <60 mL/min/1.73 m^2) [18], in a univariate and multivariate analysis.

The discriminative ability of gal-3 to predict the outcome (alive vs. death or LT) of patients with decompensated cirrhosis and to recognize the presence of chronic kidney disease (GFR <60 mL/min/1.73 m^2) was evaluated by using the area under the receiver operating characteristic curve (ROC). This has the true-positive and false-positive rates on the vertical and horizontal axes, respectively. As the AUC approaches 1.0, the model approaches 100% sensitivity and specificity [19]. P value <0.05 was considered statistically significant. Cox proportional hazard model was performed to estimate the association of gal-3 with patients' outcome. Patients' survival according to gal-3 levels was calculated using Kaplan–Meier analysis and compared with the log rank sum test. Statistical analysis was conducted by SPSS (version 25.0 IBM).

4. Results

Our study was a prospective evaluation of 100 stable decompensated patients (69 males, age 52 ± 11 years). Table 1 depicts their baseline features. All patients were extensively evaluated during their pre-LT assessment and no evidence of extra-hepatic malignancy, intrinsic chronic kidney disease or heart failure was found. Chronic viral hepatitis was the cause of cirrhosis in 36% of the patients. The mean value of MELD score was 14 ± 5 and

Table 2
Clinical and laboratory characteristics of patients with gal-3 levels ≤17.5 ng/mL and >17.5 ng/mL.

Variables	Patients with gal-3 levels ≤17.5 (n = 51, 51%)	Patients with gal-3 levels >17.5 (n = 49, 49%)	p value
Age (mean ± SD, years)	51.8 ± 11	52 ± 10	0.8
Sex, male n, (%)	36 (71)	33 (67)	0.7
Diabetes mellitus, n (%)	13 (25.5)	10 (20.5)	0.58
Hepatocellular carcinoma, n (%)	9 (17.6)	8 (16.3)	0.90
History of ascites, n (%)	43 (84.3)	42 (85.7)	0.92
Under no diuretic therapy, n (%)	21 (41)	16 (32.6)	0.31
Total bilirubin (median, range, mg/dL)	1.64 (0.24–10)	2.9 (0.39–34.7)	0.018
Albumin (mean ± SD, g/dL)	3.5 ± 0.5	3.4 ± 0.9 (2.2–7)	0.16
INR (mean ± SD)	1.3 ± 0.3	1.4 ± 0.3	0.44
History of complications, n, (%)			
GI bleeding	16 (31)	12(25)	0.44
Encephalopathy	16 (31)	19 (38)	0.47
SBP	7 (14)	5 (10)	0.48
Creatinine (mean ± SDmg/dL)	0.89 ± 0.2	0.97 ± 0.4	0.29
"true"-GFR by ^{51}Cr-EDTA (mean ± SD, mL/min)	85 ± 22	74 ± 27	0.04
MDRD-estimated GFR (mean ± SD, mL/min)	89 ± 18	85 ± 34	0.42
CTP score (mean ± SD)	7 ± 2	8 ± 2	0.017
MELD score (mean ± SD)	13 ± 4	15 ± 5	0.02

the median value of CTP score was 8 (range: 5–13). Evaluation of renal function using ^{51}Chr-EDTA showed mean "true"-GFR at 80 ± 25 mL/min, while mean eGFR based on MDRD formula was 88 ± 27 mL/min. Seventeen patients (17%) had hepatocellular carcinoma (HCC). Most of the patients had a previous history of ascites (n = 85, 85%) and all of them had undergone to ascites paracentesis during the last 6 months from baseline. These patients, compared to those without a history of ascites (n = 15, 15%) had statistically similar levels of gal-3 (19.8 vs. 16.4 ng/mL, p = 0.43). Regarding ongoing diuretic therapy, 37 (37%) patients were not under furosemide and/or spironolactone at baseline. These patients, compared to those under diuretics (n = 63, 63%) had similar levels of gal-3 (18.7 vs. 19.6 ng/mL, p = 0.71). The patients with diabetes mellitus (n = 23, 23%), compared to those without diabetes mellitus (77%) had similar gal-3 levels (16.8 vs. 19 ng/mL, p = 0.28) and "true" GFR (79.5 vs. 80 mL/min, p = 0.95). Finally, the underlying cause of decompensated cirrhosis had no impact on gal-3 levels (data not shown). The median follow up period was 14.5 months (range: 1–48) for all 100 consecutive patients. At the end of the study, 70 patients (70%) survived and 30 (30%) died (n = 16, 16%) or underwent LT (n = 14, 14%). Median serum gal-3 levels were 17.5 (range 4.9–76.5 ng/mL) with no difference between men and women; 51 (51%) patients had gal-3 levels lower than median value and 49 (49%) had values ≥17.5 ng/mL; 29 patients (group 1, 29%) had gal-3 levels within normal range, while 71 (group 2, 71%) had values higher than 11.7 ng/mL.

4.1. Characteristics of patients associated with galectin-3 values (univariate logistic regression analysis)

The two gal-3 groups (group 1 and group 2) were evaluated regarding their baseline characteristics. Their renal function was significantly different as estimated by "true"-GFR and serum creatinine levels; group 1 vs. group 2 had mean "true"-GFR levels: 90 ± 20 mL/min vs. 76 ± 26 mL/min, p = 0.03 and mean serum creatinine levels: 0.83 ± 0.14 mg/dL vs. 0.97 ± 0.4 mg/dL, p = 0.05, respectively. However, group 1 and 2 patients had similar MDRD-estimated GFR (95 + 14 vs. 85 + 30 mL/min, p = 0.12). We also divided our patients into two groups based on median gal-3 values. The 49 patients with gal-3 levels higher than 17.5 ng/mL, compared to those with gal-3 levels ≤17.5 ng/mL, had significantly higher total bilirubin (2.9 vs. 1.64 mg/dL, p = 0.018), MELD score, (15 ± 5 vs. 13 ± 4, p = 0.02) and CTP score (8 ± 2 vs. 7 ± 2, p = 0.017). In addition, they had significantly worse "true" GFR (74 ± 27 vs. 85 ± 22 mL/min, p = 0.04), but similar MDRD-estimated GFR (85 + 34 vs. 89 + 18 mL/min, p = 0.42) (Table 2).

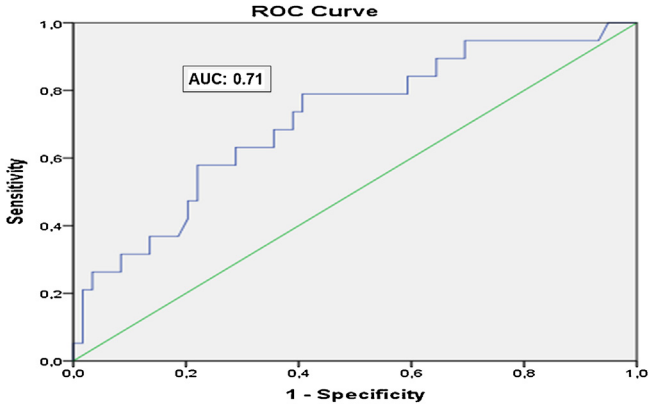

Fig. 1. ROC curve for the discriminative ability of galectin-3 to detect chronic kidney disease ("true"-GFR <60 mL/min/1.73^2) in our decompensated patients.

4.2. Patients' features associated with their renal function (univariate and multivariate analysis)

Moreover, patients were divided into two groups based on their relatively preserved renal function; those with "true"-GFR ≥60 mL/min (n = 76, 76%) and the other 24 patients with "true"-GFR < 60 mL/min (group 2, 24%). The former group of patients had significantly lower gal-3 levels against the latter group of patients; 15.1 (4.2–62.4) vs. 24 (7.1–76.5) ng/mL, p = 0.01. The two groups had also significantly different CTP scores; (median values, range): 7 [5–12] vs. 9 [6–13], respectively, p = 0.03 (Table 3). In the multivariate analysis, including all significant factors found in the univariate analysis, the only factor independently expressing renal function was gal-3 (OR: 0.869, 95%CI [0.761–0.994], p = 0.04). Accordingly, we examined the ability of gal-3 in discriminating patients based on their preserved renal function. ROC analysis showed that it had good performance in predicting renal impairment, i.e. "true"-GFR <60 mL/min; AUC: 0.71, 95%CI [0.58–0.85], best cut off value 17.5 ng/mL, sensitivity 0.59, specificity 0.79, PPV: 0.41, NPV: 0.88 (Fig. 1). The results were similar when HCC patients (n = 17) were excluded from the analysis (AUC: 0.72, 95%CI [0.60–0.86] with the same best cut off value).

4.3. Galectin-3 levels and patients' survival

During the follow up period 16 patients died, all of them from liver related deaths [spontaneous bacterial peritonitis (n = 4), liver failure/encephalopathy (n = 8), variceal bleeding (n = 2), HCC pro-

Table 3
Clinical and laboratory characteristics of patients with "true"-GFR ≥60 mL/min and <60 mL/min). Abbreviations.

Variables	Patients with "true"-GFR ≥60 mL/min (n = 76, 76%)	Patients with "true"-GFR <60 mL/min (n = 24, 24%)	p value
Age (mean ± SD, years)	49 ± 11	57 ± 7	0.016
Sex, male n, (%)	20	49	0.02
Total bilirubin (median, range, mg/dL)	1.97 (0.24–34)	1.86 (0.39–33)	0.6
Albumin (median, range, g/dL)	3.5 (2.2–7)	3.3 (2–4.9)	0.13
Aetiology of cirrhosis, n, (%)			
Viral hepatitis	30 (39)	6 (25)	0.5
Alcohol	18 (24)	7 (29)	0.7
NASH	13 (17)	3 (12.5)	0.3
History of complications, n, (%)			
GI bleeding	29 (38)	7 (29)	0.4
Encephalopathy	27 (35)	8 (33)	0.6
SBP	8 (10)	4 (16)	0.3
Creatinine (median, range, mg/dL)	0.81 (0.49–1.18)	1.17 (0.62–2.95)	<0.001
MDRD-estimated GFR (mean ± SD, mL/min)	56 ± 16	100 ± 23	<0.001
Galectin-3 (median, range, ng/mL)	15.1 (4.2–62.4)	24 (7.1–76.5)	0.01
CTP score (median, range)	7 (5–12)	9 (6–13)	0.03
MELD score (mean ± SD)	14 ± 4	16 ± 6	0.09

Table 4
Clinical and laboratory characteristics of 100 patients with stable decompensated cirrhosis associated with the outcome (univariate analysis).

Variables	Hazard ratio	p value	95% Confidence Interval Lower	95% Confidence Interval Upper
Age (mean ± SD, years)	1.01	0.54	0.97	1.05
Sex, male n, (%)	0.7	0.37	0.33	1.5
Total bilirubin (median, range, mg/dL)	1.05	0.01	1.01	1.08
Albumin (median, range, g/dL)	0.6	0.1	0.33	1.1
Aetiology of cirrhosis, n, (%)				
Viral hepatitis	1.18	0.46	0.75	1.85
Alcohol	1.43	0.36	0.65	3.12
NASH	0.9	0.9	0.7	1.4
History of complications, n, (%)				
GI bleeding	0.44	0.1	0.17	1.17
Encephalopathy	1.2	0.62	0.57	2.52
SBP	0.26	0.2	0.03	1.97
Creatinine (median, range, mg/dL)	2.03	0.11	0.84	4.9
"true"-GFR by ^{51}Cr-EDTA (mean ± SD, mL/min)	0.99	0.6	0.98	1.01
MDRD-estimated GFR (mean ± SD, mL/min)	0.99	0.7	0.98	1.03
Galectin-3 (median, range, ng/mL)	1.032	0.008	1.008	1.057
CTP score (median, range)	1.19	0.07	0.98	1.43
MELD score, (mean ± SD)	1.1	0.006	1.03	1.18

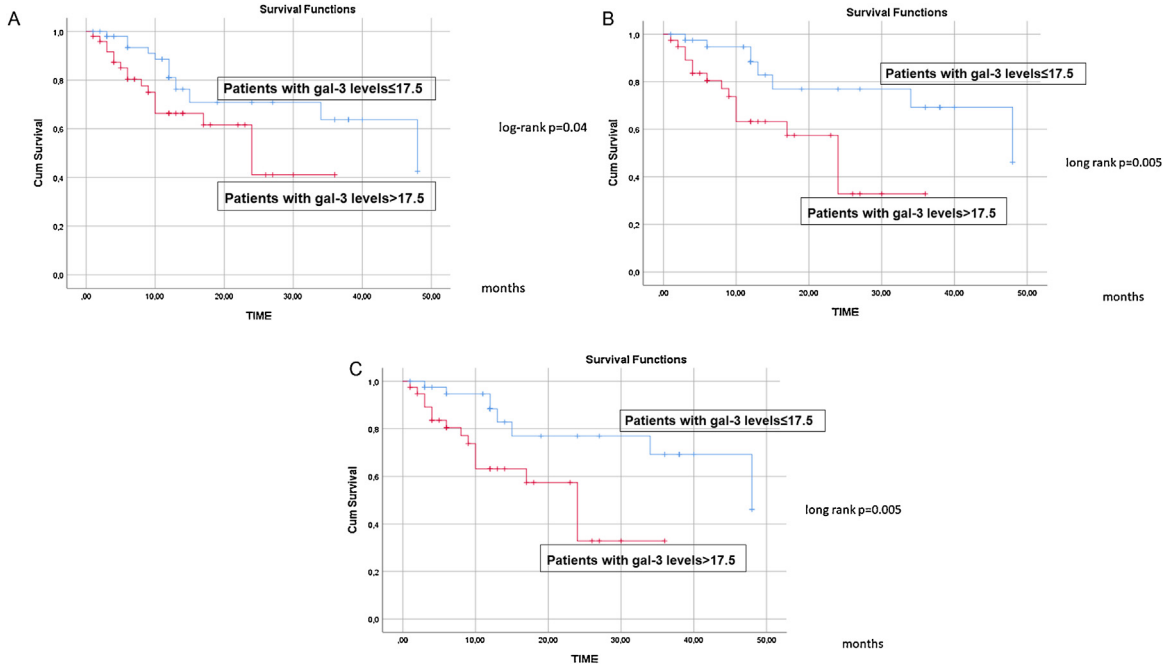

Fig. 2. Kaplan–Meier curves showing difference of survival among decompensated patients based on median gal-3 levels; (A) whole cohort; (B) excluding HCC patients. Kaplan–Meier curves showed no difference of survival among decompensated patients based on ULN gal-3 levels (C).

gression (n = 2)]. We conducted Cox regression analysis to detect factors associated with our patients' outcome. Gal-3 proved significant risk factor associated with our patients' negative outcome (HR: 1.032, 95%CI [1.008–1.057], p = 0.008). Total bilirubin (HR: 1.05, 95%CI [1.01–1.08], p = 0.01) and MELD score (HR: 1.1, 95%CI [1.03–1.18], p = 0.006) were important risk factors, too. (Table 4) However, in the multivariate analysis, the only factor independently associated with our patients' outcome was MELD score (HR: 1.08, 95%CI [1.004–1.163], p = 0.04). When excluding the MELD score, in the multivariate analysis gal-3 was the only factor associated with the outcome (HR: 1.028, 95%CI [1.002–1.054], p = 0.033). Kaplan–Meier analysis, using the median values revealed different time of survival for our patients (log-rank p = 0.04) (Fig. 2A). In addition, when excluding HCC patients (n = 17), Kaplan–Meier analysis showed that patients with gal-3 higher than 17.5 ng/mL compared to those with less than 17.5 ng/mL had significantly worse outcome (log-rank p = 0.005) (Fig. 2B). Finally, using the ULN as cut-off for gal-3, showed no difference regarding our patients' survival (log-rank p = 0.733) (Fig. 2C).

4.4. Discriminative ability of galectin-3 based on ROC curve

We also evaluated the discriminative ability of newly introduced gal-3 to define patients' outcome. Based on ROC analysis and AUC, gal-3 had poor discriminative ability to predict the outcome in our cohort (AUC: 0.596, 95%CI [0.475, 0.717]), which was inferior but not significantly lower, compared to discriminative ability of MELD score (AUC: 0.69, 95%CI [0.56, 0.81], p = 0.12).

5. Discussion

In this study we tried to clarify the role of gal-3 in patients with stable decompensated cirrhosis. More specifically, we tried to discover its association with the preserved renal function of these patients. We proved that gal-3 is an important risk factor regarding patients' prognosis. At the same time, we showed that gal-3 manages to discriminate patients with true-GFR <60 mL/min.

It is already known that gal-3 is a good marker of fibrosis in cirrhosis and reflects the stage of liver damage [11]. Published data support its utility in detecting hepatitis C-related liver fibrosis [12]. Moreover, galectin's role has been studied in models of non-alcoholic steatohepatitis, suggesting implications in the pathogenesis of liver fibrosis and proposing that galectin-targeting drugs may have potential in patients with non-alcoholic steatohepatitis associated fibrosis [20]. This interesting theory introduces new, non-invasive markers for fibrosis assessment. Moreover, the expression of gal-3 from neoplastic transformed hepatocytes [9], implies an association with tumorigenesis of hepatocellular carcinoma. Collectively, gal-3 is a marker that could be studied in different stages of liver diseases.

From another point of view, published studies mainly support the role of gal-3 in renal function of patients with heart failure. At first, increased gal-3 levels in these patients, could be attributed to reduced renal clearance [21] and deteriorating renal function [10]. One recent study showed that among patients with heart failure, those patients with gal-3 plasma concentrations above the median values (16.90 ng/mL) had significantly lower eGFR (55 vs. 80 mL/min, p < 0.001) (estimated by the Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) and this association remained significant in multivariate regression analysis (p < 0.001) [10]. Moreover, the relationship between plasma concentrations of gal-3 and eGFR is well established [8], so it carries the potential to be a renal biomarker.

Combining these data, we conducted an innovative study of this new serum marker in patients with stable decompensated cirrhosis. Accurate evaluation of renal function in patients with decompensated cirrhosis is crucial, but serum biomarkers, such as serum creatinine, have several limitations. In addition, different equations have been derived to provide an estimation of GFR (such as MDRD), but these formulae have been reported to overestimate or underestimate "true" GFR in patients with decompensated cirrhosis [4,7]. Our results showed that gal-3 levels could predict the presence of chronic kidney disease in this group of patients. Indeed, patients with normal gal-3 values (≥11.7 ng/mL) had significantly better "true"-GFR (90 ± 20 vs. 76 ± 26, p = 0.03), and mean serum creatinine levels (0.83 ± 0.14 vs. 0.97 ± 0.4, p = 0.05), but similar MDRD-estimated GFR (95 ± 14 vs. 85 ± 30 mL/min, p = 0.12). Moreover, patients with gal-3 levels above the median values (17.5 ng/mL) had significantly worse "true" GFR (74 vs. 85 mL/min, p = 0.04), but no difference was observed regarding MDRD-estimated GFR (Table 2). On the other hand, patients with well-preserved renal function ("true" GFR >60 mL/min) had significantly lower gal-3 levels, (17.2 ± 10 vs. 26.8 ± 16 ng/mL, p = 0.01). Finally, applying a multivariate model, the only factor independently expressing renal function was gal-3 (OR: 0.869, 95%CI [0.761–0.994] p = 0.04), but not serum creatinine or MDRD-estimated GFR. Interestingly, the results justified the use of gal-3 in evaluating the renal impairment seen in those patients and may be used as an accurate and plausible biomarker of renal dysfunction irrespectively of several baseline characteristics, such as underlying liver disease, hepatocellular carcinoma, diabetes mellitus, ascites or administration of diuretics. Besides, ROC analysis showed that it had good performance in predicting the presence of "true"-GFR <60 mL/min; AUC: 0.71, 95%CI [0.58–0.85]. Interestingly, the best cut off value of gal-3 proved 17.5 ng/mL, showing sensitivity 0.59, specificity 0.79, PPV: 0.41, and NPV: 0.88. The results were similar when HCC patients (n = 17) were excluded from the analysis.

Until today, studies tried to find an association of gal-3 with liver diseases, though have never evaluated its prognostic role. In our study, gal-3 proved to be also a significant risk factor associated with our patients' negative outcome (HR: 1.03, 95%CI [1.008–1.057], p = 0.008). In the multivariate analysis the only factor independently associated with our patients' outcome was MELD score (HR: 1.08, 95%CI [1.004–1.163], p = 0.04). Though, when excluding MELD score, gal-3 remained the only significant factor (HR: 1.028, 95%CI [1.002–1.054], p = 0.033). The results were similar when HCC patients (n = 17) were excluded from the analysis. Interestingly, nor serum creatinine neither "true" GFR were significantly associated with the outcome in multivariate analysis. Furthermore, when dividing our patients into two groups based on median gal-3 values (17.5 ng/mL) they significantly differed regarding their MELD score, (15 ± 5 vs. 13 ± 4, p = 0.02) and CTP score (8 ± 2 vs. 7 ± 2, p = 0.017), and consequently their disease burden. Finally, we did manage to detect different survival times for our patients based on their gal-3 levels. Kaplan–Meier analysis, using the median values revealed different survival times (log-rank p = 0.04) (Fig. 2A). We did not find such a difference when using the ULN as cut-off for gal-3 (log-rank p = 0.733). Collectively, we could propose the specific value of 17.5 ng/mL gal-3 levels as a discriminating factor for the presence of kidney disease in patients with decompensated cirrhosis. Finally, although gal-3 was an independent prognostic factor (excluding MELD score), it had poor predictive ability for patients' outcome (AUC: 0.596).

We acknowledge that further studies are needed to establish the prognostic utility of gal-3 regarding cirrhotic patients. Ideally, a larger cohort of patients could investigate our findings. Certainly, there are restrictions as it is a single center study, too. Though, we managed to present significant results for this new marker. In conclusion, our study showed, for the first time, strong evidence that gal-3 is a new, trustworthy serum marker with good

predictive ability for the presence of established chronic kidney disease in stable decompensated cirrhosis patients. In addition, gal-3 >17.5 ng/mL showed a significant association with worse outcome, even when excluding patients with HCC, but its predictive ability was poor.

Conflict of interest

None declared.

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