

# Aspartate aminotransferase-to-platelet ratio index can predict the outcome in patients with stable decompensated cirrhosis

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## Abstract

**Background** Platelet (PLT)-based biomarkers have been studied for the evaluation of liver fibrosis and cirrhosis. There are no data regarding their prognostic significance in decompensated cirrhosis.

**Methods** We studied 525 stable decompensated patients from the 2 Greek transplant centers. We measured PLT values, mean PLT volume (MPV), red cell distribution width,  $\gamma$ -globulins, and calculated PLT-based scores: aspartate aminotransferase-to-PLT ratio index (APRI),  $\gamma$ -globulin-to-PLT model, and  $\gamma$ -glutamyl transpeptidase-to-PLT ratio (GPR).

**Results** We followed our cohort for 12 (range: 1-84) months. Baseline mean model for end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores were  $15\pm 6$  and  $8\pm 2$ , respectively. On univariate analysis, MPV/PLT (hazard ratio [HR] 3.75, 95% confidence interval [CI] 1-14.5;  $P=0.05$ ), APRI (HR 1.03, 95%CI 1.006-1.06;  $P=0.016$ ), GPR (HR 1.096, 95%CI 1.016-1.182;  $P=0.017$ ) were significantly associated with our patients' outcome (survival vs. death or liver transplantation). In a multivariate model without MELD and CTP scores, APRI was the only significant factor associated with the outcome (HR 1.054, 95%CI 1.009-1.101;  $P=0.018$ ). APRI had good discriminative ability for the outcome (area under the curve 0.723 vs. 0.675 and 0.656 for MELD and CTP scores, respectively). The optimal cutoff point was 1.3 (sensitivity 71%, specificity 65%). There were 200 patients (38%) with APRI scores  $<1.3$  who had better survival than patients with APRI  $>1.3$  (log rank 22.4,  $P<0.001$ ).

**Conclusions** This study found a prognostic role for APRI in stable decompensated cirrhosis, regardless of the underlying etiology of chronic liver disease. This suggests new perspectives for PLT-based noninvasive scores to discriminate patients' outcomes.

**Keywords** Decompensated cirrhosis, prognosis, platelet-based scores, platelets, aspartate aminotransferase-to-platelet ratio index

*Ann Gastroenterol* 2023; 36 (4): 442-448

Conflict of Interest: None

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Received 24 January 2023; accepted 27 March 2023; published online 25 May 2023

DOI: <https://doi.org/10.20524/aog.2023.0800>

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## Introduction

Traditionally, the natural history of liver cirrhosis has been intriguing for researchers, who have attempted to establish parameters that have prognostic value [1]. Moreover, cirrhosis belongs to a group of severe conditions for which survival remains the principal endpoint. Thus, the main objective of prognostic scores in cirrhotic patients is to estimate the probability of death within a given time interval [2].

Decompensation of cirrhosis represents a prognostic watershed, as the median survival drops to about 2 years, compared to more than 12 years for compensated cirrhosis [3]. Noninvasive tests to detect the hemodynamic threshold, indicative of clinically significant portal

hypertension and decompensating events, have been the object of an increasing number of studies in the last 20 years [4]. This represents the need to determine factors that may simply and accurately predict the course of the disease.

The experience of these markers comes from studies that used different indexes to predict the presence of significant fibrosis and cirrhosis [5,6]. For cirrhosis, there are few and scarce studies using noninvasive tests for disease prognosis. A low platelet (PLT) count, the most common hematologic abnormality in cirrhosis, has a substantiated correlation with the presence of features of portal hypertension, and represents a prognostic parameter in patients with end-stage liver disease [4,7]. Even mean PLT volume (MPV) has been considered as an independent biomarker for predicting mortality in patients with hepatitis B virus (HBV)-decompensated cirrhosis [8].

A variety of PLT-based scores have been assessed in studies focused on cirrhotic patients, and have demonstrated different roles. The MPV/PLT ratio has been studied as an indicator of the presence of hepatocellular carcinoma (HCC) [9]. The ratio of red cell distribution width (RDW) to PLT can predict significant fibrosis and cirrhosis in chronic hepatitis patients [10,11]. The aspartate aminotransferase (AST)-to-PLT ratio index, the APRI score, is thought to have acceptable potential for prognosis in cirrhosis [12,13]. Moreover, a recent study showed that it may serve as a predictor of mortality in hospitalized patients with HBV-related decompensated cirrhosis [14]. Although another PLT-based score,  $\gamma$ -globulin/PLT model (GP), was found to predict minimal fibrosis and cirrhosis in chronic HBV-infected patients [5], no implication for its prognostic role was investigated. Finally,  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT)-to-PLT ratio (GPR) has been used as a noninvasive index for the assessment of liver fibrosis in patients with chronic hepatitis B and nonalcoholic fatty liver disease (NAFLD) [15,16].

Our research goal was to investigate the role of PLT-based markers in clinically advanced liver disease, i.e., decompensated cirrhosis. Considering the existing knowledge, we decided to explore whether these scores have a prognostic role. Thus, we conducted a prospective study in stable decompensated patients with various kinds of cirrhosis etiology and decompensating events. We applied all the above mentioned PLT-based scores to our patients and looked for prognostic implications.

## Patients and methods

We prospectively evaluated a cohort of consecutive adult patients with decompensated cirrhosis admitted for pre-liver transplantation (LT) assessment in the 2 transplant centers of

Greece (“Hippokraton” General Hospital of Thessaloniki and “Laiko” General Hospital of Athens) between 2010 and 2022. Our patients were studied during a follow-up period until a significant clinical outcome was recorded (survival vs. death or LT), or until the end of the study.

Decompensated cirrhosis was defined as a history of ascites, variceal bleeding or encephalopathy in patients with cirrhosis. We excluded patients who underwent LT before their admission. Patients were considered to be stable regarding their chronic liver disease if they had no active variceal bleeding, or episode of encephalopathy or infection, such as spontaneous bacterial peritonitis (SBP), during the last month before their 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.

On admission, several demographic and clinical characteristics were prospectively recorded for each patient, including age, sex, cause of cirrhosis, previous complications of cirrhosis (i.e., variceal bleeding, encephalopathy or SBP), medication administered for the liver disease (duration and dosage), vital signs (blood pressure, pulse rate), and concomitant extra-hepatic diseases (e.g., diabetes mellitus, coronary artery disease). In addition, the following laboratory variables were evaluated: hematocrit, white blood count, PLT, MPV, RDW, creatinine, urea, electrolytes (sodium, potassium, magnesium, calcium, phosphate), AST, and alanine aminotransferase, alkaline phosphatase,  $\gamma$ -GT, bilirubin (total and direct), protein, albumin,  $\gamma$ -globulins, lactate dehydrogenase, as well as clotting profile (prothrombin time, international normalized ratio, activated partial thromboplastin time). Patients underwent further assessment of their renal function before being placed on the LT list. Specifically, we calculated the estimated glomerular filtration rate using the creatinine-based 4-variable modification of the diet in renal disease formula [17], to assess the presence of chronic kidney disease [18]. We evaluated the severity of liver disease and the prognosis of our patients by calculating the Child-Turcotte-Pugh (CTP) [19] and model for end-stage liver disease (MELD) [20] scores. The presence of HCC was also assessed.

Finally, we calculated PLT-based markers: ratios MPV/PLT, RDW/PLT, APRI, GP score, and GPR. These scores were studied in our decompensated patients' cohort to define their prognostic ability.

Only patients with full demographic and laboratory data were included in the study. The study protocol was approved by our Institutional Review Board and conformed to the ethical guidelines of the 2013 Declaration of Helsinki.

## Statistical analysis

Continuous variables with normal distribution were presented as mean  $\pm$  standard deviation or median with interquartile range in non-normally distributed and

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comparisons of means/medians were performed using Student's *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables were expressed as frequencies or percentages and the chi-square test was used for comparisons. Cox regression analysis was carried out to identify factors associated with our patients' survival. Variables found significant ( $P < 0.05$ ) in the univariate analysis were included in the multivariate analysis, which was based on a Cox proportional hazards model. The discriminative ability of the prognostic scores to predict the outcome (survival vs. death or LT) of patients with decompensated cirrhosis was evaluated using the area under the receiver operating characteristic curve (ROC). This curve has the true-positive and false-positive rates on the vertical and horizontal axes, respectively. As the area under the curve (AUC) approaches 1.0, the model approaches 100% sensitivity and specificity [21]. A  $P$ -value  $< 0.05$  was considered statistically significant in all analyses. For our patients' survival rates, according to their PLT-based scores, we used Kaplan-Meier analysis and comparisons were made using the log rank sum test. The statistical analysis was carried out using SPSS (IBM SPSS software version 28.0 for Windows, Armonk, NY, USA) and MedCalc for Windows (MedCalc Software, Mariakerke, Belgium). Patients included had full demographic and laboratory data available. Only a few missing values were handled by the SPSS statistics, which estimated summary statistics and imputed missing values using statistical algorithms.

## Results

We studied 525 patients (377 males [72%], age  $54 \pm 11$  years) with stable decompensated cirrhosis. There were 339 patients from the Thessaloniki transplant center and 186 patients from Athens. We stratified patients consecutively during 2010-2022. Their median follow-up time was 12 (range: 1-84) months. Viral hepatitis was the cause of cirrhosis in 126 patients (24%), while 165 patients (31%) had alcoholic liver disease and 234 patients (45%) developed cirrhosis due to NAFLD or other chronic liver diseases (i.e., autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, primary sclerosing cholangitis). On first evaluation, our patients had mean MELD and CTP scores of  $15 \pm 6$  and  $8 \pm 2$ , respectively. Our patients' other characteristics and mean values of PLT-based ratios are presented in Table 1. In our cohort, the median (range) values were as follows: MPV/PLT: 0.11 (0.04-3.8), RDW/PLT: 0.18 (0.05-7), APRI: 2 (0.7-29), GP score: 4 (0.4-31), and GPR: 0.7 (0.04-14).

At the end of follow up there were 211 patients (40%) still alive, while the other 314 patients (60% of the cohort) died ( $n=188$ , 36%) or underwent LT ( $n=126$ , 24%). On univariate Cox regression analysis we found that, among the PLT-based scores, MPV/PLT (hazard ratio [HR] 3.75, 95% confidence interval [CI] 1-14.5;  $P=0.05$ ), APRI (HR 1.03, 95%CI 1.006-1.06;  $P=0.016$ ), and GPR ratio (HR 1.096, 95%CI 1.016-1.182;  $P=0.017$ ) significantly associated with our patients' outcome (Table 2A). In multivariate analysis, including all the variables which were significant in multivariate analysis, but excluding

**Table 1** Baseline clinical and laboratory characteristics of 525 patients with stable decompensated cirrhosis

| Variable   | Patients, n=525      |
|--|----------------------|
| Age (mean $\pm$ SD, years)                             | 54 $\pm$ 11          |
| Sex, male n, (%)                                       | 377 (72)             |
| Etiology of cirrhosis, n, (%)                          |                      |
| Viral hepatitis  | 126 (24)             |
| Alcohol  | 165 (31)             |
| NASH & other causes                                    | 234 (45%)            |
| Hepatocellular carcinoma, n (%)                        | 73 (14)              |
| History of complications, n, (%)                       |                      |
| GI bleeding  | 147 (28)             |
| Encephalopathy   | 173 (33)             |
| SBP  | 84 (16)              |
| Total bilirubin (median, range, IQR, mg/dL)            | 2.1 (0.24-40.5, 2.4) |
| Albumin (median, range, g/dL)                          | 3.2 (1.6-4.8)        |
| Creatinine (median, range, IQR, mg/dL)                 | 0.9 (0.49-3.3, 0.35) |
| MDRD (median, range, IQR, mL/min/1.73 m <sup>2</sup> ) | 85 (21-156, 39.6)    |
| PLT (median, range, / $\mu$ L)                         | 75000 (15000-260000) |
| RDW (median, range)                                    | 16 (11-20)           |
| MPV (median, range)                                    | 9.9 (6-14)           |
| AST (mean $\pm$ SD, IU/L)                              | 68 $\pm$ 10          |
| $\gamma$ -GT (median, range, IU/L)                     | 58 (10-2055)         |
| $\gamma$ -globulins (mean $\pm$ SD, g/dL)              | 3.6 $\pm$ 0.8        |
| MPV/PLT (median, range)                                | 0.11 (0.04-3.8)      |
| RDW/PLT (median, range)                                | 0.18 (0.05-7)        |
| APRI (median, range)                                   | 2 (0.7-29)           |
| GP (median, range)                                     | 4 (0.4-31)           |
| GPR (median, range)                                    | 0.7 (0.04-14)        |
| CTP score (mean $\pm$ SD)                              | 8 $\pm$ 2            |
| MELD score, (mean $\pm$ SD)                            | 15 $\pm$ 6           |

PLT, platelet; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; MPV, mean PLT volume; RDW, red cell distribution width; APRI, aspartate aminotransferase (AST)-to-PLT ratio index; GP score,  $\gamma$ -globulin-to-PLT model; GPR,  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT)-to-PLT ratio; NASH, nonalcoholic steatohepatitis; SD, standard deviation; SBP, spontaneous bacterial peritonitis; GI, gastrointestinal; IQR, interquartile range; MDRD, modification of the diet in renal disease

the components of prognostic scores, it was found that MELD score was the only factor independently associated with mortality (HR 1.104, 95%CI 1.063-1.146;  $P < 0.001$ ), as well as when CTP score was not included in the analysis (HR 1.16, 95%CI 1.11-1.22;  $P < 0.001$ ). When MELD score was excluded from the multivariate analysis, CTP score was the only factor significantly associated with mortality (HR 1.55, 95%CI 1.35-1.81;  $P < 0.001$ ).

Subsequently, we incorporated into a multivariate model the PLT-based scores that showed significant results in the univariate analysis (i.e., APRI, MPV/PLT, and GPR), though

**Table 2 (A)** Univariate analysis of variables associated with our patients' outcome

| Variables                   | Hazard ratio | 95% confidence interval |       | P-value |
|-----------------------------|--------------|-------------------------|-------|---------|
|                             |              | Lower-                  | upper |         |
| Age (years)                 | 1.007        | 0.99-                   | 1.02  | 0.2     |
| Sex, male (n)               | 0.74         | 0.55-                   | 1.006 | 0.05    |
| Total bilirubin (mg/dL)     | 1.04         | 1.01-                   | 1.06  | <0.001  |
| Albumin (g/dL)              | 0.7          | 0.57-                   | 0.87  | 0.001   |
| Creatinine (mg/dL)          | 1.51         | 1.1-                    | 2.07  | 0.009   |
| MDRD-estimated GFR (mL/min) | 0.99         | 0.98-                   | 0.99  | 0.01    |
| PLT (/ $\mu$ L)             | 1.00         | 1.00-                   | 1.00  | 0.4     |
| RDW                         | 1.004        | 0.99-                   | 1.01  | 0.2     |
| MPV                         | 0.99         | 0.98-                   | 1.009 | 0.73    |
| AST (IU/L)                  | 1.004        | 1.003-                  | 1.006 | <0.001  |
| $\gamma$ -GT (IU/L)         | 1.00         | 0.99-                   | 1.002 | 0.35    |
| $\gamma$ -globulins (g/dL)  | 0.95         | 0.8-                    | 1.12  | 0.5     |
| MPV/PLT                     | 3.75         | 1.00-                   | 14.5  | 0.05    |
| RDW/PLT                     | 1.27         | 0.94-                   | 1.7   | 0.11    |
| APRI                        | 1.03         | 1.006-                  | 1.06  | 0.016   |
| GP                          | 1.02         | 0.99-                   | 1.06  | 0.12    |
| GPR                         | 1.096        | 1.016-                  | 1.182 | 0.017   |
| CTP score                   | 1.18         | 1.1-                    | 1.23  | <0.001  |
| MELD score                  | 1.05         | 1.03-                   | 1.07  | <0.001  |

MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; MPV, mean platelet volume; PLT, platelet; RDW, red distribution width; APRI, aspartate aminotransferase-to-PLT ratio index; GP score,  $\gamma$ -globulin-to-PLT model; GPR,  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT)-to-PLT ratio; MDRD, modification of the diet in renal disease; GFR, glomerular filtration rate

**Table 2 (B)** Multivariate analysis of new platelet-based scores for our patients' prognosis

| Variables | Hazard ratio | 95% confidence interval |       | P-value |
|-----------|--------------|-------------------------|-------|---------|
|           |              | Lower-                  | upper |         |
| GPR       | 1.039        | 0.93-                   | 1.15  | 0.46    |
| MPV/PLT   | 0.7          | 0.09-                   | 5.11  | 0.72    |
| APRI      | 1.05         | 1.009-                  | 1.101 | 0.018   |

PLT, platelet; GPR,  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT)-to-PLT ratio; MPV, mean PLT volume; APRI, aspartate aminotransferase-to-PLT ratio index

excluding MELD and CTP scores. This model showed that the APRI score was the only one significantly associated with our patients' outcome (HR 1.054, 95%CI 1.009-1.101;  $P=0.018$ ) (Table 2B). Multicollinearity was not present, since the variance inflation factors for APRI, MPV/PLT, and GPR were 1.5, 1.6 and 1.2, respectively.

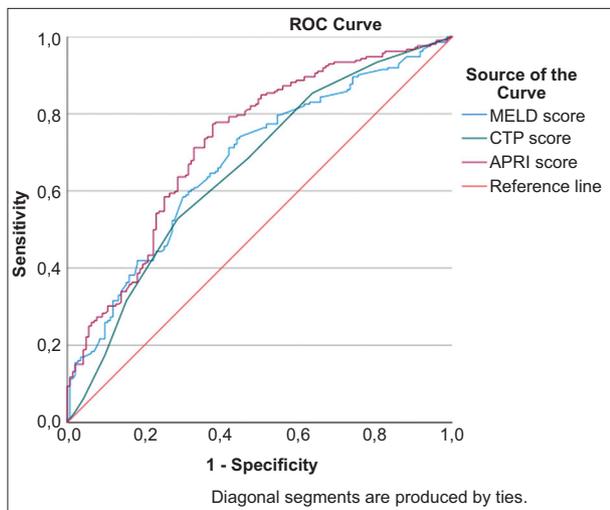
Expanding the analysis in our decompensated patients, we used the suggested discriminative value of 1 for APRI score in order to perform survival analysis. Based on this, patients with an APRI score <1 had better survival (Kaplan-Meier: log rank chi-square 26,  $P<0.001$ ) than those with an APRI score >1.

### Correlation of APRI with cirrhosis severity scores

We investigated whether there was a correlation between APRI and the basic cirrhosis severity scores, MELD and CTP. Spearman's test found a significant positive correlation with both scores:  $r=0.386$ ,  $P<0.001$  for MELD; and  $r=0.311$ ,  $P<0.001$  for CTP.

### Discriminative ability of APRI, MELD, CTP scores

The APRI score had good discriminative ability for our patients' outcome (AUC 0.726, 95%CI 0.672-0.78), based on ROC analysis. ROC analysis for MELD and CTP scores in our cohort gave the following results: AUC 0.675, 95%CI 0.618-0.731 for MELD and AUC 0.656, 95%CI 0.598-0.715 for CTP ( $P>0.05$  for both) (Fig. 1). The results were similar when the patient who underwent LT was excluded (AUC for APRI, MELD and CTP, 0.77, 0.75, 0.74, respectively,  $P>0.05$ ). The APRI score cutoff value with the best sensitivity and specificity and the optimal discriminative ability was calculated to be 1.3 (sensitivity 71%, specificity 65%). There were 200 patients (38%) with an APRI score below 1.3 and 325 patients (62%) with values higher than 1.3. Analyzing patients' characteristics,

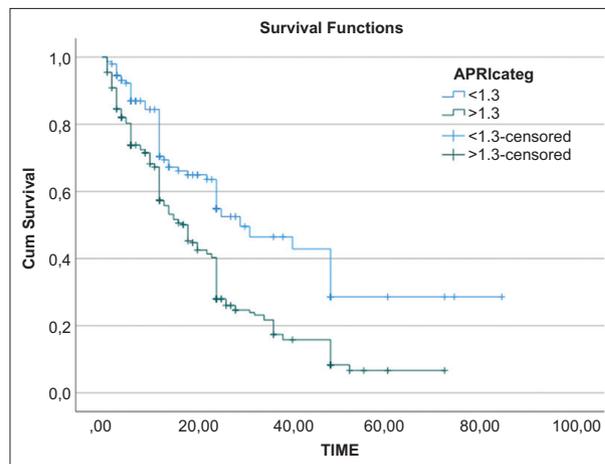


**Figure 1** ROC analysis for all predictive scores, MELD (AUC: 0.675), CTP score (AUC: 0.656) and APRI (AUC: 0.723,  $P < 0.001$ ), showing their discriminative ability for our decompensated patients. In our cohort APRI had the best performance in relation to the outcome MELD, model for end-stage liver disease; ROC, receiver operating characteristic curve; CTP, Child-Turcotte-Pugh; APRI, aspartate aminotransferase-to-platelet ratio index; AUC, area under the curve

we found that those with lower APRI score values (i.e.,  $< 1.3$ ) had significantly better values of creatinine (mg/dL) [0.9 (0.5-3) vs. 0.9 (0.8-3.3),  $P = 0.04$ ], albumin (g/dL) [3.5 (1.4-4.8) vs. 3.1 (1.6-4),  $P < 0.001$ ], and PLTs (/L) [120000 (59000-260000) vs. 70000 (15000-200000),  $P < 0.001$ ]. Moreover, they had distinct mean values of AST (IU/L) [ $37 \pm 15$  vs.  $87 \pm 58$ ,  $P < 0.001$ ], GP [ $2.7 \pm 1.2$  vs.  $6.4 \pm 5$ ,  $P < 0.001$ ], GPR [ $0.9 \pm 0.6$  vs.  $2.6 \pm 1.7$ ,  $P < 0.001$ ], ratios MPV/PLT: PV/PLT ( $0.06 \pm 0.03$  vs.  $0.17 \pm 0.14$ ), RDW/PLT ( $0.12 \pm 0.07$  vs.  $0.32 \pm 0.28$ ),  $P < 0.001$ , and better CTP ( $7 \pm 2$  vs.  $8 \pm 2$ ) and MELD ( $12 \pm 4$  vs.  $17 \pm 6$ ) scores,  $P < 0.001$  (Table 3). We performed survival analysis using this cutoff and we found significant difference between the 2 groups of patients; patients with APRI score  $< 1.3$  had better overall survival than patients with APRI  $> 1.3$  (log rank 22.4,  $P < 0.001$ ) (Fig. 2). The first group of patients had a median survival time of 29 (range: 18-39) months, while the other group had 18 (range: 14-21) months.

## Discussion

Here we present our results after analyzing PLT-based scores in a large cohort of patients with stable decompensated cirrhosis. To our knowledge, this is the first study in which the prognostic significance of these markers has been investigated. In our study, we found that the PLT-based indexes MPV/PLT ratio ( $P = 0.05$ ), APRI ( $P = 0.016$ ), and GPR ( $P = 0.017$ ) were significantly associated with our patients' survival over a median follow up of 12 months, while in the multivariate analysis we found a significant association between APRI and our patients' survival. APRI has been validated for predicting significant fibrosis and cirrhosis [6], and a value of 1 has been considered the threshold



**Figure 2** Kaplan-Meier curves showing difference of survival among decompensated patients based on suggested APRI optimal discriminative value: patients with APRI  $< 1.3$  had better survival than patients with APRI  $> 1.3$  (log rank 22.4,  $P < 0.001$ ) MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; APRI, aspartate aminotransferase-to-platelet ratio index

for severe fibrosis (61% sensitive and 64% specific) and cirrhosis (76% sensitive and 72% specific) [22].

It is generally accepted that we need prognostic scores to simply and accurately define outcomes in patients with decompensated cirrhosis. The previously defined MELD and CTP scores are the cornerstone of comparison when analyzing new markers. We already know that alterations in PLT numbers and function are common in liver diseases, and they have a role as markers in the evaluation of chronic and acute liver disease progression, including cirrhosis, acute liver failure and HCC [23]. Thus, it comes as no surprise that PLT count and combined indexes have been proposed as noninvasive markers to identify clinically significant events [4]. For this reason, we decided to study whether they have prognostic impact.

Initially, we found that, according to Cox regression analysis, 3 PLT-based ratios were important markers associated with survival: MPV/PLT, GPR ratio, and APRI. As regards the MPV/PLT ratio, the prognostic role of MPV in cirrhosis is controversial [7,8]. It has been stated that high MPV can be considered as an independent biomarker for predicting 3-month mortality in patients with HBV-decompensated cirrhosis [8], and the ratio *per se* has been studied in patients with HCC as an indicator of the presence of a tumor (74.5% sensitivity and 96.5% specificity, AUC=0.884) [9]. No specific data for a prognostic usefulness in decompensated cirrhosis are available, and our study is the first to prove such an association.

The GPR ratio has been used to assess liver fibrosis in patients with chronic hepatitis B and NAFLD, with remarkable discriminative ability (AUC around 0.8) [15,16], but it has never been studied in decompensated cirrhosis. In our analysis, GPR showed an association with patients' outcomes in univariate Cox regression analysis (HR 1.096, 95%CI 1.016-1.182;  $P = 0.017$ ).

Interestingly, in the same analysis the APRI score performed well in the univariate model as a significant risk factor associated

**Table 3** Comparing the 2 groups of patients, according to the optimal discriminative APRI value

| Variable   | Group 1 (APRI <1.3)   | Group 2 (APRI >1.3)  | P-value |
|--|-----------------------|----------------------|---------|
| Age (mean±SD, years)                                   | 56±9                  | 53±11                | 0.009   |
| Sex, male n, (%)                                       | 145 (27.6)            | 232 (44.2)           | 0.9     |
| Total bilirubin (median, range, IQR, mg/dL)            | 1.29 (0.2-15)         | 2.8 (0.29-40)        | <0.001  |
| Albumin (median, range, g/dL)                          | 3.5 (1.4-4.8)         | 3.1 (1.6-4)          | <0.001  |
| Creatinine (median, range, IQR, mg/dL)                 | 0.9 (0.5-3)           | 0.9 (0.8-3.3)        | 0.18    |
| MDRD (median, range, IQR, mL/min/1.73 m <sup>2</sup> ) | 85 (23-150)           | 89 (21-150)          | 0.06    |
| PLT (median, range, /μL)                               | 120000 (59000-260000) | 70000 (15000-200000) | <0.001  |
| RDW (median, range)                                    | 15 (11-15)            | 16 (12-14)           | 0.2     |
| MPV (median, range)                                    | 10 (7-11)             | 10 (6-14)            | 0.3     |
| AST (mean±SD, IU/L)                                    | 37±15                 | 87±58                | <0.001  |
| γ-GT (median, range, IU/L)                             | 55 (10-840)           | 62 (10-2000)         | 0.08    |
| γ-globulins (mean±SD, g/dL)                            | 3.6±0.7               | 3.6±0.8              | 0.6     |
| MPV/PLT (median, range)                                | 0.07 (0.04-0.21)      | 0.13 (0.05-0.3.8)    | <0.001  |
| RDW/PLT (median, range)                                | 0.11 (0.05-1.5)       | 0.23 (0.05-7)        | <0.001  |
| GP (median, range)                                     | 2.5 (0.4-6.5)         | 4.8 (1.3-31)         | <0.001  |
| GPR (median, range)                                    | 0.4 (0.04-4.8)        | 0.86 (0.21-14)       | <0.001  |
| CTP score (mean±SD)                                    | 7±2                   | 8±2                  | <0.001  |
| MELD score, (mean±SD)                                  | 12±4                  | 17±6                 | 0.001   |

PLT, platelet; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; MPV, mean PLT volume; RDW, red cell distribution width; APRI, aspartate (AST) aminotransferase-to-PLT ratio index; GP score, γ-globulin-to-PLT model; GPR, γ-glutamyl transpeptidase (γ-GT)-to-PLT ratio; MDRD, modification of the diet in renal disease; SD, standard deviation; IQR, interquartile range

with prognosis (HR 1.03, 95%CI 1.006-1.06; P=0.016). In fact, it was the only factor among the PLT indexes that showed statistical significance in the multivariate Cox regression analysis (HR 1.054, 95%CI 1.009-1.101; P=0.018). Once again, this score has been widely used to assess liver fibrosis [24]. It was also studied as a predictive model of post-hepatectomy liver failure in patients with HBV-related HCC (AUC: 0.717) [25]. In another study involving 12,055 patients undergoing hepatic resection, it was shown to be a surrogate marker of liver dysfunction, as it was significantly associated with postoperative liver dysfunction, 30-day mortality, and liver dysfunction-associated 30-day mortality, [26]. Regarding chronic liver diseases, in 10 studies of NAFLD patients APRI demonstrated an ability to stratify patients for liver-related morbidity and mortality (range of reported AUC 0.52-0.73) [27]. The only study to focus on prognosis in decompensated cirrhosis included 193 hospitalized chronic HBV-infected patients; the results showed that elevated APRI was associated with increased severity of liver disease and 3-month mortality (multivariate analysis, odds ratio 1.456, 95%CI 1.021-2.077; P<0.001) [14]. In our multivariate model, Cox regression analysis confirmed the importance of APRI in a much larger cohort of 525 decompensated patients, regardless of disease etiology.

Taking the abovementioned findings into consideration, we carried out a survival analysis using the proposed cutoff point of 1, the threshold for severe fibrosis [22]. We showed that patients with lower values had significantly better survival (Kaplan-

Meier log rank chi-square 26; P<0.001). In our cohort, however, we sought the optimal cutoff point to discriminate survival according to APRI. Performing ROC analysis, we confirmed APRI's discriminative ability with an AUC of 0.723. Interestingly, in our cohort APRI performed better than the traditionally measured predictive scores MELD (AUC: 0.675) and CTP (AUC: 0.656). We also proposed the threshold of 1.3 as the discriminating cutoff point for our patients' survival (sensitivity 71%, specificity 65%). This value detected significantly better survival times (29 months vs. 18 months, P<0.001), in patients with APRI<1.3, who also had better values of creatinine (P=0.04), albumin (P<0.001), obviously PLT (P<0.001), as well as better CTP (7±2 vs. 8±2) and MELD (12±4 vs. 17±6) scores (P<0.001).

We acknowledge that our study has limitations. Our findings are based on collected data analyzed retrospectively. Further evaluation of the PLT-based markers presented here is needed to confirm their prognostic role in decompensated cirrhosis, given that there are so far no other data supporting their application in such a cohort of patients. Ideally, a validation cohort could investigate our findings. Moreover, it is not clear whether there is a pathophysiological basis to support the association of these scores with patients' outcomes. We did not search for such an explanation. However, given that the APRI score was able to assess liver function sufficiency in post hepatectomy patients, it could reflect an underlying clinical mechanism. The main strength of our study is that its results were derived from a large cohort, covering 2 transplant centers in Greece.

To conclude, a model well known for its use in liver fibrosis and cirrhosis is now introduced as a predictive factor with prognostic ability in decompensated cirrhosis. Its easy and accurate measurement makes it a simple noninvasive marker. The validated threshold of 1.3 could be used to discriminate decompensated patients based on their expected prognosis. The results presented herein provide promising support for a prognostic role of APRI in patients with stable decompensated cirrhosis, regardless of the underlying etiology of the chronic liver disease.

### Summary Box

#### What is already known:

- Noninvasive platelet (PLT)-based biomarkers have been used to assess liver fibrosis and cirrhosis
- Aspartate aminotransferase-to-PLT ratio index (APRI) has been associated with postoperative liver dysfunction, 30-day mortality, and liver dysfunction-associated 30-day mortality, in patients undergoing hepatic resection
- APRI has been used to stratify patients with nonalcoholic fatty liver disease for liver-related morbidity and mortality

#### What the new findings are:

- The mean PLT volume/PLT ratio,  $\gamma$ -glutamyl transpeptidase/PLT ratio and APRI are significant risk factors associated with decompensated patients' prognosis
- APRI was established as significant factor associated with survival
- The APRI cutoff point of 1.3 had very good discriminative accuracy for the outcome (survival vs. death or liver transplantation) in stable decompensated cirrhosis

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