



Red cell distribution width/platelet ratio predicts decompensation of metabolic dysfunction-associated steatotic liver disease-related compensated advanced chronic liver disease

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Abstract

Prognostication of compensated advanced chronic liver disease (cACLD) is of paramount importance for the physician-and-patient communication and for rational clinical decisions. The paper published by Dallio *et al* reports on red cell distribution width (RDW)/platelet ratio (RPR) as a non-invasive biomarker in predicting decompensation of metabolic dysfunction-associated steatotic liver disease (MASLD)-related cACLD. Differently from other biomarkers and algorithms, RPR is inexpensive and widely available, based on parameters which are included in a complete blood count. RPR is computed on the grounds of two different items, one of which, RDW, mirrors the host's response to a variety of disease stimuli and is non-specific. The second parameter involved in RPR, platelet count, is more specific and has been used in the hepatological clinic to discriminate cirrhotic from non-cirrhotic chronic liver disease for decades. Cardiovascular disease is the primary cause of mortality among MASLD subjects, followed by extra-hepatic cancers and liver-related mortality. Therefore, MASLD biomarkers should be validated not only in terms of liver-related events but also in the prediction of major adverse cardiovascular events and cardiovascular mortality and extra-hepatic cancers. Adequately sized multi-ethnic confirmatory investigation is required to define the role and significance of RPR in the stratification of MASLD-cACLD.

Key Words: Cirrhosis; Liver fibrosis; Natural course; Prognostication; Stratification

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Core Tip: A recent paper published in *World Journal of Gastroenterology* reports on the utility of red cell distribution width (RDW)/platelet ratio, a non-expensive and universally available biomarker based on RDW and platelet count, in predicting decompensation of metabolic dysfunction-associated steatotic liver disease (MASLD)-related compensated advanced chronic liver disease (cACLD) (MASLD-cACLD). We discuss these novel findings in the context of MASLD natural history and of a foreseeable research agenda pertaining to the stratification of MASLD-cACLD.

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INTRODUCTION

Prognostication of chronic diseases is of paramount clinical importance, as it provides strong grounds for the communication between physician and patients and is the basis for any decision-making process[1]. However, any single subject differs from the average patient population on which prognostic estimations are established; as a result, the available prognostic information is often difficult to apply to the individual patient, which is strong grounds for precision medicine approaches in hepatology[1,2].

In 2015, the definition of “compensated advanced chronic liver disease (cACLD)” was proposed to identify those asymptomatic patients who are at risk of developing clinically significant portal hypertension (CSPH)[3]. These subjects, who need hepatological referral and are often detected by transient elastography, belong, in a continuum, to the spectrum of severe fibrosis and cirrhosis, and distinguishing between the two is not invariably possible clinically[3]. In 2023, nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) were renamed metabolic dysfunction-associated steatotic liver disease (MASLD)[4]. Although this novel nomenclature poses some challenges[5] and has been received with some controversy[6], NAFLD and MASLD identify the same patient population and have the identical natural course[7].

With this backset, Dallio *et al*[8] have recently reported the utility of red cell distribution width (RDW)/platelet ratio (RPR) as a non-invasive biomarker in predicting decompensation of MASLD-related cACLD (MASLD-cACLD). At variance with other biomarkers and algorithms, RPR is cheap and universally available, being computed based on RDW and platelet count, which are part of a complete blood count. RDW is less specific; conversely, decreased platelet count is more specific and has been used in the hepatological clinic for decades.

The present invited editorial examines and comments on the novel findings by Dallio *et al*[8]. To this end, the natural history and non-invasive approach to the diagnosis of MASLD-cACLD are first reviewed. Next the physiological bases and clinical investigations regarding RPR are addressed, and the strengths and limitations of the study by Dallio *et al*[8] are discussed. Finally, we examine a research agenda aimed at confirming and expanding these novel findings.

NATURAL HISTORY, MODIFIERS, AND PHENOTYPES OF MASLD

Based on the NAFLD paradigm, it is reasonable to assume that the primary cause of mortality among MASLD subjects is cardiovascular, followed by extra-hepatic cancers while liver-related mortality ranks only third[9,10]. This implies that all biomarkers that aim at stratifying MASLD patients should also be validated in the context of major adverse cardiovascular events (MACE) and risk of extra-hepatic cancers[11,12] (Figure 1).

Decompensation represents a dramatic turning point in the natural history of cirrhosis given that life expectancy of patients with compensated cirrhosis is > 12 years as compared to approximately 2 years for those with decompensated disease[1]. To make things more complex, in the MASLD context, analysis of competing risks (*i.e.*, extrahepatic outcomes) should also be conducted and assessment of liver fibrosis offers the best definition of the various hepatic and non-hepatic outcomes[12]. Although precisely defined by histological stages, liver fibrosis can also be assessed non-invasively with a variety of “dry” (imaging-based) and “wet” (blood-based) biomarkers, algorithms, and their sequential application[13-16].

Further to these, at least in the research arena, it is important to stratify patients accurately based on MASLD phenotypes comprising detailed genetic, clinical, biochemical, and histological profiles. For example, characterization of age, sex, ethnicity, lifestyle habits, genetics, obesity, glycemic control, and usage of drugs which may affect disease progression[17-21], and presence/or absence and quantification of steatosis, inflammation, and fibrosis are all key to defining the risk of future decompensation[22-25].

Various experts, reporting that MASLD exhibits different pathophysiological and clinical diversity, pinpoint the importance of precision medicine approaches in this arena[26-29]. Among the most significant contributions, Yi *et al*[30] leveraged cluster analysis to identify three distinct clinical and prognostic clusters with different metabolic profiles in a population-based cohort from the United States. Ye *et al*[31] using a different statistical approach in Chinese and United Kingdom population-based cohorts, identified five different clusters with variable odds of developing type 2 diabetes, coronary artery disease, stroke, survival, and all-causes mortality. Martínez-Arranz *et al*[32] with a combined approach

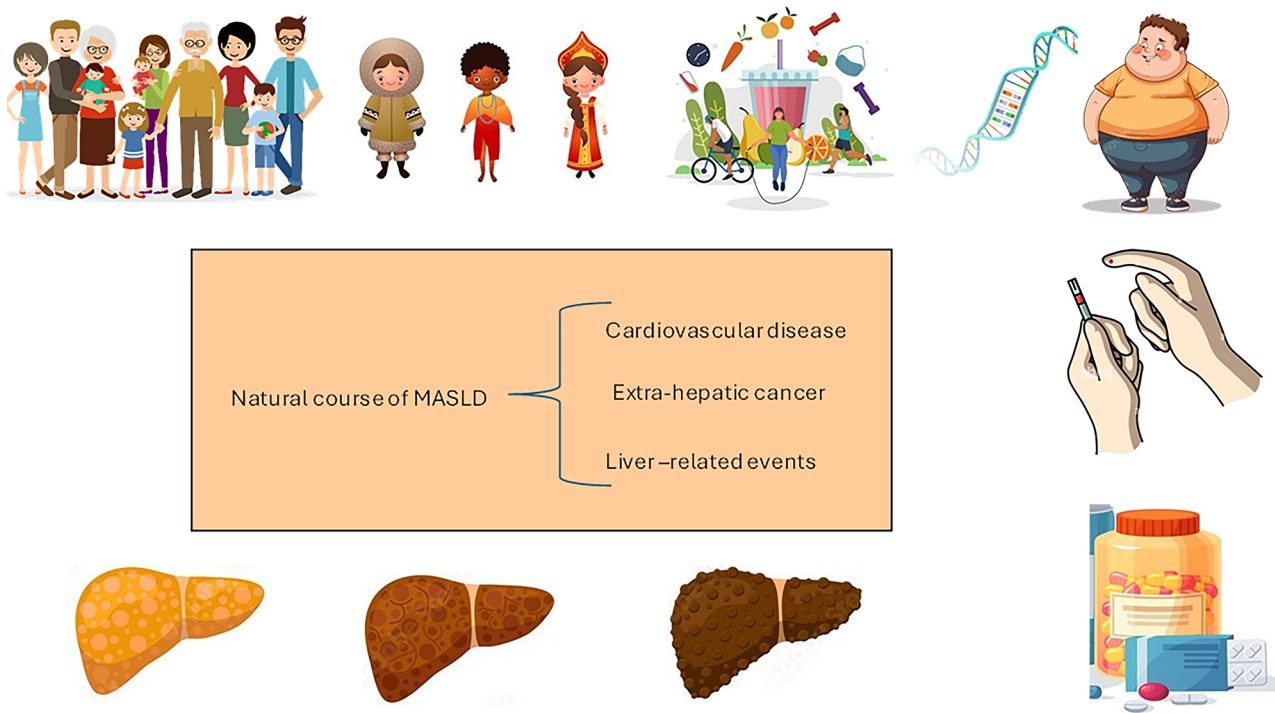


Figure 1 Modifiers of the natural course of metabolic dysfunction-associated steatotic liver disease. Schematic illustration of multiple factors [schematically depicted in the upper line clockwise: (1) Age; (2) Ethnicity; (3) Lifestyle; (4) Genetics; (5) Obesity; (6) Diabetes; and (7) Medications] which, further to the fundamental components of metabolic dysfunction-associated steatotic liver disease (MASLD) histology [shown in the bottom-line, from left to right: (1) Steatosis; (2) Steatohepatitis; and (3) Cirrhosis], can potentially modulate the natural course of MASLD and the odds of decompensation of MASLD-related compensated advanced chronic liver disease. MASLD: Metabolic dysfunction-associated steatotic liver disease.

comparing experimental mouse model and serum metabolome from a large cohort of subjects with biopsy-proven MASLD, identified three MASLD phenotypes which, irrespective of liver histology, may explain variable (hepatic versus cardiovascular) outcomes, thereby providing clinically relevant risk stratification. Finally, Ampuero *et al*[33] in a large multi-center patient cohort, identified three distinct patterns of altered liver enzymes, which portend useful information on liver histology and mortality.

RPR: PHYSIOLOGICAL GROUNDS AND CLINICAL INVESTIGATIONS

General considerations

Changes in RDW values have been associated with extremely diverse clinical conditions spanning from elevated glycosylated hemoglobin in the elderly[34], to autoimmune disorders[35], cancers[36], sepsis[37], aortic diseases[38], acute appendicitis[39], and carbon monoxide poisoning[40]. Therefore, RDW seemingly mirrors the entity of the host's pathophysiological (inflammatory and/or immuno-metabolic) response to a variety of disease stimuli. Conversely, decreased platelet count is a more specific finding, which has been used in the hepatological clinic to discriminate cirrhotic from non-cirrhotic chronic liver disease (CLD) since the early 1980s[41].

RPR in non-hepatic conditions

These general considerations may help to understand the impressive heterogeneity of the non-hepatic conditions in which RPR has been qualified as a useful biomarker (Table 1)[42-56].

Indeed, it would be quite difficult to understand what such clinically and physiopathologically diverse conditions as those shown in Table 1 (spanning from acute pancreatitis, to MACE in myocardial infarction, hemodynamically significant patent ductus arteriosus, colorectal cancer, dementia, early onset neonatal sepsis, intracranial hemorrhage, mortality in neonatal intensive care units, multiple system atrophy, and necrotizing enterocolitis) have in common other than the strength of the host's physiologic response to such different disease states[42-56].

Probably the same physiopathological explanation accounts for the finding that RPR predicts mortality among those with myocardial infarction[42,57] and heart failure[58].

RPR in liver disease

However, as shown in Table 2, RPR has also been used in the assessment of the severity of liver fibrosis across a variety of different etiologies of CLD[59-73]. Findings tend to consistently indicate that RPR is an accurate descriptor of fibrosis severity and may be therefore of value in distinguishing cirrhotic from non-cirrhotic CLD owing to different viral and

Table 1 Red cell distribution width/platelet ratio in non-hepatic conditions

Ref.	Method	Findings	Conclusion
Acute conditions			
Cetinkaya <i>et al</i> [43], 2014	Totally 102 patients with AP were recruited	RPR with a cutoff value of 0.000067 presented an area under the receiver operating characteristic curve of 0.783 (95% CI: 0.688–0.878) and predicted the mortality of approximately 80% of the patients	RPR is a valuable biomarker of mortality in AP
Pusuroglu <i>et al</i> [44], 2015	Totally 470 consecutive patients with STEMI submitted for primary PCI were prospectively enrolled	At LRA, high RPR was an independent predictor of one-year cardiovascular mortality ($P = 0.003$, OR = 3.106, 95% CI: 1.456–6.623)	RPR is an inexpensive and readily available biomarker which offers additional risk stratification in predicting long-term MACE and cardiovascular mortality in STEMI
Celik <i>et al</i> [42], 2015	Totally 580 STEMI patients were divided into two groups according to thrombolysis in myocardial infarction flow grades after primary PCI	At LRA, RPR was among the independent predictors of no-reflow after primary PCI. In its turn, being in the no-reflow group compared to the reflow patients was associated with higher odds of in-hospital MACE, and cardiovascular mortality	RPR is among the independent predictors of no-reflow and in-hospital MACE among patients with STEMI undergoing primary PCI
Karabulut and Arcagok [45], 2020	RPR was compared to C-reactive protein and procalcitonin to investigate the potential to predict EOS in newborns	RPR and other biomarkers had higher values in proven EOS than in the controls	RPR may be used in the diagnosis of EOS among newborns as a good alternative to other tools
Lehmann <i>et al</i> [46], 2021	Totally 102 subjects with deep-seated ICH were included	At LRA elevated RPR ≥ 0.06 was among the independent predictors of 90-day mortality	RPR, as a biomarker of inflammation, might serve for prognostic assessment in deep-seated ICH
Jiang <i>et al</i> [47], 2022	Totally 47 individuals with MSA, 125 subjects with Parkinson's disease, and 124 healthy controls were enrolled	At LRA, RPR was associated with the risk of MSA	Patients with MSA probably have peripheral inflammatory reaction
Liu <i>et al</i> [48], 2022	Totally 3367 patients with sepsis were enrolled	After adjustment for confounders, high RPR was significantly associated with increased mortality both for categorical and continuous variables (adjusted HR = 1.210, 95% CI: 1.045–1.400; and adjusted HR = 2.826, 95% CI: 2.025–3.944, respectively)	Elevated RPR values predict 28-day mortality in patients with sepsis
Wang <i>et al</i> [49], 2022	Totally 45 newborns were included in each of three groups of different severity; mild, moderate, and severe conditions based on SNAPE-II	A positive correlation was found between the SNAPE-II scores and RPR among newborns in NICU	Further to the SNAPE-II, also RPR can be used as a supplementary predictor biomarker for the assessment of neonatal morbidity and mortality in NICU
Liang <i>et al</i> [50], 2023	Retrospective cohort study of 2823 adults with ICH	After adjustment for confounding factors, the 3 rd tertile of RPR values, compared to the 1 st tertile, was associated with increased odds of 30-day death in patients with ICH (HR = 1.37, 95% CI: 1.15–1.64)	Among subjects with ICH, elevated RPR levels predict 30-day mortality
Kasirer <i>et al</i> [51], 2024	Totally 69 infants with NEC and 78 controls were enrolled	RPR was significantly associated with both NEC diagnosis ($P < 0.0001$) and mortality ($P = 0.01$). However, at LRA only variations of platelet count from birth to diagnosis remained significant	The often-elusive attempts to definitively diagnose NEC among preterm newborns may benefit from largely available, cheap, and easily calculated platelet indices
Chronic and acute-on chronic conditions			
Özer Bekmez <i>et al</i> [52], 2018	A cohort of 112 infants with medically treated hspDA and 96 controls were recruited	At LRA analysis, high RPR (OR = 3.3, 95% CI: 1.438–5.872, $P < 0.05$) was one of the independent risk factors for hspDA	RPR is a promising biomarker for the diagnosis of hspDA
Bilgin <i>et al</i> [53], 2019	Totally 312 CRC patients were enrolled	Among subjects with right-sided advanced cancer, OS was statistically significantly better for those with RPR ≥ 0.05 compared to those with RPR < 0.05 (median OS; RPR ≥ 0.05 : 24.8 months <i>vs</i> < 0.05 : 13.9 months; $P = 0.035$)	After validation, RPR can be used as a prognostic marker in CRC
Dagistan and Cosgun [54], 2019	Retrospective survey of 1342 subjects submitted to cranial MRI	A statistically significant difference was found in RPR values among the various study groups (Fazekas 0 to Fazekas 3) ($P < 0.001$)	Increased RPR values may suggest higher Fazekas's score and dementia in cranial MRI studies
Guler Kazanci <i>et al</i> [55], 2019	Totally 481 infants were recruited (169 with hspDA and 312 controls)	RPR was significantly higher in the hspDA group ($P < 0.05$). At LRA RPR > 0.070 (risk ratio = 5.33; 95% CI: 3.28–8.65; $P < 0.001$) was among the independent predictors of hspDA	High RPR values in the first hours of life are a risk factor for hspDA (and hspDA refractive to ibuprofen treatment) in preterm infants

Chen <i>et al</i> [56], 2023	Totally 1922 AECOPD adults participating in the MIMIC-III and MIMIC-IV; and 1738 AECOPD patients from Emergency Intensive Care Unit Collaborative Research Database were recruited	After adjusting for confounders, Log (RPR×1000) was associated with elevated risk of in-hospital mortality of AECOPD patients (OR = 1.36, 95%CI: 1.01–1.84)	Among AECOPD patients RPR was associated with in-hospital mortality
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AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; AP: Acute pancreatitis; CRC: Colorectal cancer; EOS: Early onset sepsis; HR: Hazard ratio; ICH: Intracerebral hemorrhage; HsPDA: Hemodynamically significant patent ductus arteriosus; LRA: Logistic regression analysis; MACE: Major adverse cardiovascular events; MIMIC: Medical Information Mart for Intensive Care; MSA: Multiple system atrophy; MRI: Magnetic resonance imaging; NEC: Necrotizing enterocolitis; NICU: Neonatal intensive care units; OR: Odds ratio; OS: Overall survival; PCI: Percutaneous coronary intervention; RPR: Red cell distribution width/platelet ratio; SNAPE-II: Score for neonatal acute physiology and perinatal extension II; STEMI: ST-segment elevation myocardial infarction.

Table 2 Red cell distribution width/platelet ratio in liver disease

Ref.	Method	Findings	Conclusion
Taefi <i>et al</i> [60], 2015	Totally 152 subjects with native livers and 70 with transplanted livers were recruited	In the native liver group RPR showed the strongest correlation with the degree of fibrosis ($P < 0.001$), AUC for cirrhosis = 0.684. However, in the transplanted liver group, none of the variables was significantly correlated with the stages of fibrosis nor did it predict cirrhosis	While it can be a strong predictor of the stage of fibrosis and cirrhosis in patients with CHB hepatitis and native liver, the use of RPR is limited among those with transplanted livers
Cengiz and Ozenirler[61], 2015	Totally 123 consecutive individuals with biopsy-proven NAFLD were analyzed	AUROC of the RPR was 0.69 in predicting significant fibrosis ($\geq F2$), 0.81 in advanced fibrosis ($\geq F3$), and 0.85 in F4, and all were statistically significant ($P < 0.001$). RPR was correlated with fibrosis ($r = 0.37$, 95%CI: 0.21–0.52, $P < 0.001$). At LRA, RPR independently predicted both significant and advanced fibrosis ($P < 0.05$)	The finding that RPR predicted liver fibrosis may be useful to reduce liver biopsy burden in NAFLD
Koksal <i>et al</i> [62], 2016	Totally 228 individuals with biopsy-proven CHB were enrolled	Statistically significant increases in all scores, including RPR, and decrease in platelet count were observed as the fibrosis level increased. However, RPR (and platelet count) were best in demonstrating advanced fibrosis	While they cannot replace liver biopsy for diagnosis, noninvasive scores such as APRI score can be used for monitoring the response to treatment with entecavir and tenofovir
Karagöz <i>et al</i> [63], 2016	Totally 98 biopsy-proven treatment-naïve CHC patients were recruited	The AUC of RPR (cut-off = 0.07 FI) for predicting significant fibrosis was 0.705, which was superior to other non-invasive indices of fibrosis	RPR values, being significantly higher in patients with CHC, and associated with the severity of fibrosis, can be used to predict advanced liver histology, thereby decreasing the need of liver biopsy
Huang <i>et al</i> [64], 2017	Totally 256 CHB subjects were recruited	The diagnostic performance of GPR was not significantly different from APRI, FIB-4, and RPR in identifying significant fibrosis, advanced fibrosis, and cirrhosis, but it was significantly superior to area at risk and neutrophil-to-lymphocyte ratio in both HBeAg positive CHB and HBeAg negative CHB	GPR does not show any advantages over APRI, FIB-4, and RPR in identifying significant liver fibrosis, advanced liver fibrosis, and liver cirrhosis among Chinese subjects with HBeAg positive CHB or HBeAg negative CHB
Ferdous <i>et al</i> [65], 2018	Totally 40 subjects with CHB were enrolled	RPR was positively correlated with stages of hepatic fibrosis (Spearman's correlation coefficient = 0.749, $P < 0.001$)	Among CHB patients RPR values are strongly associated with stages of increasing severity of hepatic fibrosis
Liu <i>et al</i> [66], 2019	Totally 123 individuals with CHB were enrolled	The AUC values for RPR for the diagnoses of substantial fibrosis, severe fibrosis, and cirrhosis were 0.692, 0.732, and 0.808, respectively	Among CHB patients two-dimensional shear wave elastography is significantly more accurate than other non-invasive indices, including RPR, in the diagnosis of substantial fibrosis, severe fibrosis, and cirrhosis ($P < 0.05$)
Milas <i>et al</i> [67], 2019	Meta-analysis of 18 published studies totaling approximately 1800 patients for each outcome	Sensitivity, specificity, and AUC were as follows: (1) Significant fibrosis: 0.635, 0.769, and 0.747; (2) Advanced fibrosis: 0.607, 0.783, and 0.773; and (3) Cirrhosis: 0.739, 0.768, and 0.818. Similar findings, in all outcomes, were registered for CHB. Subgroup analysis indicated a high specificity for advanced fibrosis detection in PBC. For patients with advanced fibrosis, studies outside of China showed a higher sensitivity than investigations performed in China	With AUC > 0.7 for all outcomes and AUC > 0.8 for cirrhosis, RPR is a good biomarker of fibrosis, particularly among the most advanced forms of CLD
Jiang <i>et al</i> [68], 2020	Totally 118 biopsy-proven PBC subjects were recruited	The AUROC of RPR for predicting advanced fibrosis was 0.517	The AUROC of the total bile acid to platelet ratio in diagnosing fibrosis among PBC subjects was higher than that of other non-invasive serological models, including RPR

Gozdas and Ince [69], 2020	Totally 81 subjects with HCV chronic infection were enrolled	RPR values of those with severe fibrosis were significantly higher than those of the mild fibrosis group ($P < 0.05$). However, MPV/P had the biggest AUROC in the prediction of advanced fibrosis	MPV/P is an easy and practical biomarker to gain a preliminary insight into advanced fibrosis among subjects with chronic HCV infection
O'Hara <i>et al</i> [70], 2020	Cross-sectional survey of 8099 individuals in South-Western Uganda	In this study, RPR scores were excluded from further statistical analysis given that only few individuals had an elevated score	This population-based cohort study did not have statistical power sufficient to detect any factors associated with abnormal RPR scores given that only few subjects had an elevated RPR score
Chen <i>et al</i> [71], 2020	Retrospective analysis of 1005 CHB patients submitted to liver biopsies and laboratory profiling	Stepwise applying RPR, GPR, and easy liver fibrosis test would accurately discriminate 60% of patients as having either cirrhosis or no cirrhosis	Stepwise applying routine tests could be a strategy for cirrhosis detection in resource-limited settings
Ramzy <i>et al</i> [72], 2021	Cross-sectional analysis of 197 Egyptians with CHC	RPR values were significantly different among subjects with various fibrosis stages ($P < 0.01$) and RPR cut-off values of 0.007 and 0.008 were reliable predictors of significant and advanced fibrosis, respectively. However, at LRA, RPR was not an independent predictor of fibrosis	While having fair sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for predicting significant fibrosis in patients with CHC, RPR was not an independent predictor of fibrosis at LRA
Zhang <i>et al</i> [59], 2023	Totally 168 HBVDC patients were enrolled	At LRA, RPR (together with MELD score) was an independent predictor of mortality at 30 days. RPR and MELD score had similar predictive value and the combination of the two indexes further improved their predictive value for mortality	RPR is a reliable biomarker for the prediction of mortality at 30 days among HBVDC subjects
Nawalerspanya <i>et al</i> [73], 2024	Retrospective cross-sectional study of 139 individuals with biopsy-proven AIH or AIH-PBC overlap syndrome	With an AUROC of 0.742, RPR distinguishes cirrhosis from non-cirrhosis stages of CLD better than FIB-4 and APRI	In distinguishing cirrhotic from non-cirrhotic CLD among individuals with either AIH or AIH-PBC, RPR is more accurate than other non-invasive biomarkers of fibrosis

AIH: Autoimmune hepatitis; APRI: Aspartate aminotransferase/platelet ratio index; AUC: Area under the curve; AUROC: Area under the receiver operating characteristic curves; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; CLD: Chronic liver disease; GPR: Glutaryl transpeptidase to platelet ratio; FIB-4: Fibrosis 4; HbeAg: Hepatitis e antigen; HBVDC: Hepatitis B virus-associated decompensated cirrhosis; HCV: Hepatitis C virus; LRA: Logistic regression analysis; MELD: Model for end-stage liver disease; MPV/P: Mean platelet volume to platelet ratio; NAFLD: Nonalcoholic fatty liver disease; PBC: Primary biliary cholangitis; RPR: Red cell distribution width/platelet ratio.

non-viral causes. While the others evaluated fibrosis, only one prior study by Zhang *et al* [59], looked at mortality. These authors assessed 168 subjects with hepatitis B virus-decompensated cirrhosis, 21 of whom died within 30 days. At multivariate analysis, RPR and model for end-stage liver disease (MELD) score were independent predictors of outcome. Interestingly, RPR had a predictive value like that of the MELD score and combined RPR and MELD score further improved the predictive accuracy for mortality.

The study by Dallio *et al* [8]

Of 150 consecutive MASLD-cACLD patients [identified with liver stiffness measurement (LSM)], 28.6% progressed to decompensated advanced CLD after a median of 28.9 months. At the baseline, cACLD subjects had higher RPR [as well as MELD, Child-Pugh class, aspartate aminotransferase/platelet count ratio (APRI), fibrosis-4 (FIB-4), Albumin-Bilirubin, and LSM] than 40 consecutive healthy controls. RPR ($P = 0.02$) and the presence of baseline-CSPH [defined according to the Baveno VI criteria [3] were associated with the event of decompensation ($P = 0.02$ and $P = 0.04$, respectively)]. Patients who, at the baseline, had CSPH and RPR > 0.472 exhibited significantly more elevated odds of hepatic decompensation ($P = 0.0023$). Finally, changes of RPR and LSM occurring during follow-up were strongly correlated to each other, which suggests that RPR faithfully mirrors the dynamic course of CLD.

Although this is a well-designed and well-conducted investigation, future large-sized, multi-ethnic confirmative studies are necessary with direct assessment of portal hypertension and, ideally, liver histology assessment. In this regard, it must be emphasized that portal hypertension may be found also among non-cirrhotic MASLD patients owing to a variety of mechanobiological pathomechanisms that characterize this condition [74].

CONCLUSION

MASLD is a recent re-definition of NAFLD and MAFLD, and cACLD is a descriptor of asymptomatic subjects with elevated LSM and in need of hepatological evaluation. Stratification of the risk of decompensation among MASLD-cACLD, a fundamental piece of information to implement any decision making, may be based on a variety of non-invasive biomarkers and algorithms previously discussed in the present editorial and other promising ones that appear on the horizon [75,76].

To these, the recent study by Dallio *et al*[8] has added also RPR. Given the striking heterogeneity of MASLD pathogenesis, phenotypes, and trajectories, additional studies are awaited to validate RPR as a clinically meaningful option across a variety of patient populations and for different outcomes. These research arenas comprise non-MASLD etiologies of CLD, comparison of compensated *vs* decompensated CLD, acute-on-chronic liver failure; and comparison with consolidated scoring systems, such as MELD and others. Finally, the role of RPR in predicting extra-hepatic outcomes is also another research priority.

FOOTNOTES

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