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Systematic review and meta-analysis of biomarkers predicting decompensation in patients with compensated cirrhosis

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ABSTRACT

Background and aims The transition from compensated to decompensated cirrhosis is crucial, drastically reducing prognosis from a median survival of over 10 years to 2 years. There is currently an unmet need to accurately predict decompensation. We systematically reviewed and meta-analysed data regarding biomarker use to predict decompensation in individuals with compensated cirrhosis.

Methods PubMed and EMBASE database searches were conducted for all studies from inception until February 2024. The study was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The Quality of Prognosis Studies framework was used to assess the risk of bias. The meta-analysis was conducted with a random effects model using STATA software.

Results Of the 652 studies initially identified, 63 studies (n=31 438 patients) were included in the final review, examining 49 biomarkers. 25 studies (40%) were prospective with the majority of studies looking at all-cause decompensation (90%). The most well-studied biomarkers were platelets (n=17), Model for End-Stage Liver Disease (n=17) and albumin (n=16). A meta-analysis revealed elevated international normalised ratio was the strongest predictor of decompensation, followed by decreased albumin. However, high statistical heterogeneity was noted (I^2 result of 96.3%). Furthermore, 21 studies were assessed as having a low risk of bias (34%), 26 (41%) moderate risk and 16 (25%) high risk.

Conclusions This review highlights key biomarkers that should potentially be incorporated into future scoring systems to predict decompensation. However, future biomarker studies should be conducted with rigorous and standardised methodology to ensure robust and comparable data.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Decompensation heralds a significant change in the trajectory of cirrhosis. While scoring systems have been developed to predict mortality, there is an urgent unmet need to develop and validate prognostic biomarkers that can predict decompensation.

WHAT THIS STUDY ADDS

⇒ This study highlights current prognostic biomarkers with the most evidence for predicting decompensation. Based on this meta-analysis, international normalised ratio is the strongest predictor of decompensation followed by albumin. However, 25% of publications demonstrated a high risk of bias and there was significant heterogeneity between studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights which key biomarkers should be considered for incorporation into novel prognostic models. However, future biomarker studies should be conducted according to standardised guidelines to ensure the development of optimal scoring systems.

INTRODUCTION

Cirrhosis is a leading cause of liver-related death, accounting for 2%–3% of deaths globally, and in Europe is the second leading cause of years of working life lost.[1 2] Concerningly the epidemic of chronic liver disease is worsening, largely driven by the increasing prevalence of obesity and harmful alcohol consumption, with an associated unprecedented socioeconomic cost.[2 3]

The initial, asymptomatic phase of cirrhosis is termed compensated cirrhosis and carries a good prognosis with mortality tending to be due to non-liver-related causes such as cardiovascular disease, renal disease and malignancy.[4] However, once a patient develops liver-related complications, this signals the onset of decompensated cirrhosis with a drastic reduction in median survival from over 10 years to just 2 years.[5] The most recent BAVENO guidelines have defined decompensation by the development of overt ascites, overt hepatic encephalopathy (West Haven grade ≥II) or variceal bleeding.[6] Patients with acute decompensation (AD) of cirrhosis are at high risk of hospitalisation, and even despite optimal management, have short-term re-admission rates between 30% and

50%, with 3-month mortality rates in the sickest cohort reported over 50%.[7–9] Moreover, there is a substantial impact on quality of life with a significant reduction in independent living at 1 year, placing an extensive burden on patients and carers .[10 11]

Given that decompensation heralds a pivotal change in the disease trajectory of cirrhosis, there is an urgent unmet need to discover biomarkers that can predict its occurrence, in order to help prevent its onset. The ideal biomarker should demonstrate biological plausibility, high sensitivity and specificity, generalisability, undergo validation, be minimally invasive as well as easy to measure, demonstrate stability, and crucially, for healthcare services be affordable.[12] When performing biomarker research, it is imperative to use appropriate terminology, and while addressing prediction of decompensation, one is actually referring to prognostic biomarkers which identify the likelihood of a clinical event or disease progression.[12]

While liver disease scoring systems have been developed over time, such as the Child-Turcotte-Pugh (CP) Score and Model for End-Stage Liver Disease (MELD), they have generally focused on predicting mortality as opposed to decompensation, and often underperform in contexts other than those in which they were initially developed.[13 14] While a range of other prognostic biomarkers have emerged over recent years, few have been incorporated into clinical practice. This is likely due to a lack of clarity over which biomarkers are truly superior, whether they actually outperform existing scores and the high heterogenicity in published studies.

The aim of this systematic review and meta-analysis is to identify which biomarkers have the strongest evidence for determining future decompensation in compensated cirrhosis, to help guide future research and highlight potential therapeutic targets.

MATERIALS AND METHODS

Study design

To identify relevant studies, PubMed and EMBASE database searches were conducted from inception until February 2024. The bibliographies of relevant studies were also reviewed to ensure that no eligible publications were missed. Only full manuscripts with English versions were included. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines and registered on PROSPERO.[15] The inclusion and exclusion criteria for the study are detailed below and the full search terms used are detailed in online supplemental Materials and methods; figure S1.

Inclusion criteria

1. Adult patients (>18 years old).
2. Patients with compensated liver cirrhosis according to the Baveno VII guidelines.[6]
3. Studies in which the primary or secondary outcome is the prognostic or predictive role for cirrhosis decompensation events (variceal bleeding, ascites, or overt hepatic encephalopathy).
4. Cohort (prospective or retrospective), case–control and control arm of randomised control trials (RCTs).

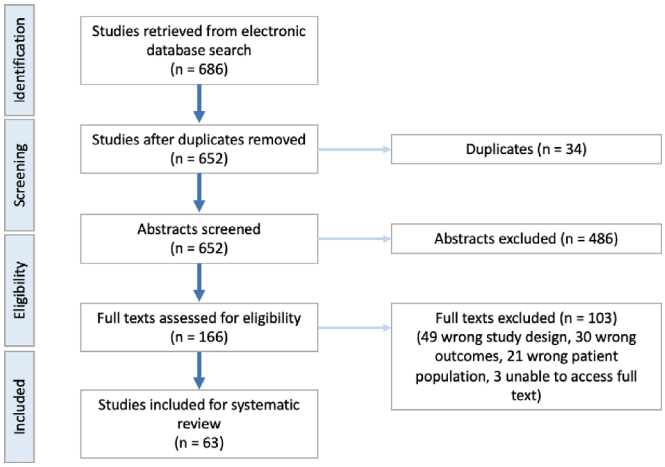

Figure 1 Flowchart showing the study selection process for the review.

Exclusion criteria

1. Experimental studies (ie, animal studies, in vitro studies).
2. Cross-sectional studies, case series, case reports, letters, editorials, reviews, systematic reviews and meta-analyses.
3. Studies performed only in patients with decompensated cirrhosis.
4. Studies performed only in patients with hepatocellular carcinoma.

Data extraction

The Covidence system was used for managing references.[16] The initial searches and obtaining of references were conducted independently by two investigators (KG and RS) with duplicates automatically removed. Initial screening of titles and abstracts was performed independently by the same two investigators, with studies only passing through to the next full-text phase if both investigators agreed. Any disagreements were resolved by a third reviewer (GM). The same process was repeated at the full-text phase to generate the final studies for inclusion, as demonstrated in figure 1.

Data extraction was performed using REDCap.[17] The parameters recorded included number of patients, age, gender, aetiologies of disease, study design, duration of follow-up and liver disease severity scores. Biomarker data, as well as outcome data in terms of decompensation events, were recorded along with statistical tests used.

Studies were classified a priori into six biomarker categories: blood-based, hepatic venous pressure gradient (HVPG), liver stiffness, physiological, imaging and miscellaneous. If a study reported on two or more cohorts, for example, a derivation and validation group, then the study would be considered two times (once for each cohort). Furthermore, if multiple biomarkers were

investigated in one study, then that study was considered multiple times resulting in the variable *biomarker study* and *biomarker patients*.

Assessment of quality

To evaluate the quality and risk of bias of eligible studies, the Quality in Prognosis Studies (QUIPS) tool was used.[18] This assessed study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting. Each paper was graded as a low, moderate or high risk of bias in each of the six domains, as well as overall.

Statistical methods

A descriptive analysis was performed reporting on the following measures of association where reported; mean±SD, median (P25–P75), OR, HR, area under the receiver operating characteristic curve (AUROC) with respective 95% CI, as well as biomarker thresholds. The meta-analysis was performed using a random effects model with a log transformation undertaken due to skewed data. Studies with HRs were included as this was the most commonly reported outcome measure. Statistical heterogeneity was assessed by the I^2 test. Finally, a funnel plot and Egger's regression test were performed to assess for bias. Statistical analyses were performed using STATA (StataCorp., 2019, Stata Statistical Software: Release 17, College Station, TX: StataCorp).

RESULTS

Summary

Of the 652 studies initially identified, 63 studies (n=31 438 patients) were included in the final review. The weaning of studies with reasons for final selection is demonstrated in figure 1.

Out of the 63 studies, 25 (40%) were prospective and 3 were RCTs. Heterogeneity was evident with sample size varying between 35 and 5123 patients, and mean/median age and follow-up ranging from 40 to 67 years and 12–455 months, respectively. The majority of studies looked at all-cause decompensation (57 (90%)), with only four looking at variceal bleeding alone and two addressing ascites. In total 49 biomarkers were assessed, and a summary of all studies and characteristics can be seen in online supplemental materials; table S1, subclassified by biomarker category.

Most studies investigated multiple biomarkers. As explained in the methods, the number of biomarker studies and biomarker patients were also recorded with each study recorded multiple times depending on the number of biomarkers assessed and different cohorts studied. These collated results can be seen in table 1. Based on biomarker studies, the most well-studied biomarkers were platelets (n=17), MELD (n=17) and albumin (n=16).

Table 1 Summary of biomarker studies and biomarker patients subclassified by biomarker category

Type of marker	Number of biomarker studies	Number of biomarker patients
Blood markers	**Total n=113**	**Total n=87 220**
Bacterial infection/ translocation	2	354
Albumin	16	14 509
ALBI score (albumin, bilirubin)	2	502
ALBI-FIB4 score (albumin, bilirubin, age, AST, ALT)	3	5008
CHESS-ALARM score (age, platelets, gender, LSM)	1	633
ABIDE model (AST/ALT, bilirubin, INR, T2DM, EV)	1	543
EPOD score (albumin, platelets, bilirubin)	1	6049
Fibrosis markers (ELF score (TIMP-1, PIIINP and hyaluronic acid), serum hyaluronan, collagen IV, laminin)	4	1629
Haematological markers (Von Willebrand factor, haematological indices, prekallikrein)	3	448
Renin, proBNP and copeptin	1	307
Serum ferritin	1	101
Serum miR-181b-5p	1	105
Platelets	17	15 003
AST/ALT	7	1663
INR	9	7344
Creatinine	2	5291
ALP	1	91
Gamma GT	1	688
Bilirubin	8	12 801
Golgi protein-73	1	632
Insulin-like growth factor 1	1	148
Prognostic liver secretome signature (PLSec: (VCAM-1, IGFBP-7, gp130, matrilysin, IL-6, CCL-21, angiogenin and protein S))	1	122
CP score	11	6683
MELD score	17	6819
APRI score	1	101
HVPG	**Total n=7**	**Total n=1440**
HVPG	7	1440
Liver stiffness	**Total n=14**	**Total n=4319**
Liver stiffness	14	4319

Continued

Table 1 Continued

Type of marker	Number of biomarker studies	Number of biomarker patients
Physiological	**Total n=5**	**Total n=984**
BMI	1	161
Mean arterial pressure	1	402
6-minute walk test	1	55
Liver frailty index	2	366
Imaging	**Total n=11**	**Total n=3129**
Vascular		
Thallium shunt index	1	209
Portal haemodynamics on Doppler ultrasonography	1	110
Hepquant-shunt test	1	35
Spleen volume-based non-invasive tool	2	816
Non-vascular		
Liver surface nodularity measurement via CT	2	517
Liver-to-spleen volume ratio via CT	1	1027
201Tl heart-liver radioactivity uptake ratio	1	107
Subcutaneous fat density (via Analytic Morphomics CT)	1	111
T2-mapping in gadoxetic acid-enhanced MRI	1	197
Miscellaneous	**Total n=5**	**Total n=998**
Collagen proportionate area	2	219
Diabetes	1	457
Thick fibrous septa on liver biopsy specimens	1	168
Indocyanine green retention test	1	154
Total	**155 biomarker studies**	**98 090 biomarker patients**

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CP, Child-Turcotte-Pugh; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; MELD, Model for End-Stage Liver Disease.

Biomarker categories

As agreed a priori the studies were split into six different biomarker categories depending on which was the primary biomarker focus of the study if multiple biomarkers were studied. The number of studies per category in decreasing order was as follows; blood-based biomarkers (n=23), liver stiffness (n=12), imaging (n=11), HVPG (n=7), physiological markers (n=5) and miscellaneous (n=5). While not all studies will be explored in this section, the biomarkers with the most evidence will be highlighted.

With regard to blood-based biomarkers, all 16 studies that assessed albumin determined that lower serum levels were significant predictors of decompensation. Indeed, two studies both reported a cut-off of <3.6 g/dL.[19 20] While platelets had the joint greatest number of studies (n=17), one study demonstrated that platelets do not predict decompensation, while four of the remaining studies demonstrated significance at the univariable level of analysis, but this was lost at the multivariable level.[21–25] Seven out of nine studies demonstrated that increased international normalised ratio (INR)/PT were significant predictors of decompensation, while all eight bilirubin studies exhibited positive results with one study proposing a cut-off of >18 µmol/L.[19] Finally, the aspartate aminotransferase/alanine transaminase (ALT) ratio showed significant results in six out of seven studies, with contradictory results demonstrated for ALT.[20 26]

Seven different scoring systems were studied: MELD, CTP, ALBI, ALBI-FIB4, CHESS-ALARM, ABIDE and EPOD. An explanation of what each score is composed of can be seen in online supplemental materials; table S2. The most well-studied score was the MELD, with 13 out of 17 studies concluding that it is a significant predictor of decompensation with a threshold of ≥10 proposed in one study.[27] While the other scoring systems have fewer studies supporting them, the majority of them are suggested to be superior to MELD in their respective analyses.

With regard to liver stiffness, all studies demonstrated that increasing measurements can predict decompensation over varying time periods until 4 years. Various thresholds have been suggested ranging from ≥13 kPA to ≥40 kPA but most studies suggest cut-offs in the 20s.[28–34] With respect to other markers of fibrosis, both increased splenic stiffness (>54 kPA) and increased ELF test results were demonstrated to be predictors of decompensation.[23 35]

All 11 imaging studies included demonstrated significant findings. With regards to imaging available in routine practice, a liver-spleen ratio <2.9, increased spleen size and increased liver surface nodularity all demonstrated positive findings.[27 36–39] With respect to routine vascular imaging available, portal haemodynamics on Doppler ultrasonography also demonstrated significant predictive potential.[20]

With regards to HVPG measurements, all seven studies demonstrated that increasing levels are associated with an increased risk of liver-related events. Thresholds of ≥12–16 mm Hg have been reported, as well as the protective effect of having HVPG <10 mm Hg which is associated with a 90% chance of being decompensation-free until 4 years.[25 40–42] Rincón *et al* also demonstrated a marginal improvement in a model combining HVPG and albumin versus HVPG alone (AUROC 0.727 vs 0.704).[24]

Finally, with regard to physiological parameters, obesity has been suggested to be associated with the highest risk of decompensation, followed by a moderate risk with

overweight patients and the lowest risk among those with a normal body mass index (BMI).[43] The liver frailty index (LFI) has been demonstrated to independently predict decompensation as too does the 6-minute walk test with a threshold of <401.8 m.[44–46]

Quality assessment

Using the QUIPS framework 21 studies (34%) were assessed as having a low risk of bias, 26 (41%) moderate risk and 16 (25%) high risk as demonstrated in table 2. With respect to biomarker categories, 5/23 (22%) blood-based biomarker studies, 5/12 (42%) liver stiffness studies, 4/11 (36%) imaging studies, 1/7 HVPG (14%) and 0/5 (0%) physiological studies were deemed high risk. When observing the studies at high risk of bias, key areas of potential bias included weak prognostic factor measurement, a lack of multivariable analyses, a lack of accounting for confounding variables and incomplete descriptions of subjects lost to follow-up, including if there were any important differences in those who completed studies compared with those who did not.

Meta-analysis

A meta-analysis was performed as demonstrated in figure 2, with log transformation performed due to skewed data. Elevated INR was the strongest predictor of decompensation with a pooled effect size of 0.76, followed by decreased albumin with an effect size of −0.35. However, the majority of weighting in the pooled estimate was allocated to the platelet studies (92.9%). Furthermore, a high I^2 result of 96.3% was obtained suggesting significant statistical heterogeneity. A funnel plot was also generated as demonstrated in figure 3 with an Egger's test ruling out significant publication bias (p=0.58). It was not possible to do a meta-analysis to predict decompensation at specific time points due to a lack of clear reporting of follow-up times in the included studies.

CONCLUSIONS

This systematic review and meta-analysis on biomarkers predicting future decompensation in patients with compensated cirrhosis has identified three important conclusions. First, blood-based biomarkers and in particular platelets, MELD and albumin seem to be the most extensively researched. Second, based on the meta-analysis the strongest biomarker to predict decompensation is INR followed by albumin. Third, high statistical heterogeneity in the meta-analysis and almost 25% of studies having a high risk of bias highlights the need for future studies to have robust and standardised methodology.

The fact that both an increasing INR and decreasing albumin are leading predictors of liver-related outcomes is not surprising given that they both reflect the synthetic function of the liver.[47] As liver disease severity increases there is impaired synthesis of clotting factors and albumin, hence the incorporation of both INR and albumin in the CP score in predicting cirrhosis mortality.[13] Indeed the utility of INR is further demonstrated by its incorporation into two further prognostic scoring systems for cirrhosis, the MELD and CLIF-C Acute Decompensation Score.[14 48] While bilirubin did not exhibit as strong an effect size in the meta-analysis, all studies investigating bilirubin as a biomarker demonstrated positive results. Given that with worsening liver disease severity, there is increased synthesis and impaired clearance of bilirubin, it is logical that it has been incorporated into CP and MELD scores as well.

While the results of the meta-analysis are insightful, caution must be taken due to the high level of statistical heterogeneity (I^2=96.3%) which is potentially due to inconsistent definitions of decompensation and varying patient populations. Whilst concerns have been raised over the validity of I^2 as a measure of statistical heterogeneity, these findings are supported by significant study bias as highlighted in the QUIPS assessment, as well as the funnel plot in figure 3 suggesting potential methodological and clinical heterogeneity between studies.[49] A further comment regarding the meta-analysis is that the majority of the weighting was allocated to the platelet studies due to larger sample sizes and smaller CIs. It is logical that worsening thrombocytopaenia would be a predictor of decompensation due to decreased hepatic thrombopoietin production and increased sequestration of platelets within the spleen, with platelets being a surrogate marker of portal hypertension.[50] Indeed, this explains their incorporation into recent novel scoring systems (ALBI-FIB4, CHESS-ALARM, VITRO and EPOD). However, the pooled effect size of the platelets was small in our meta-analysis, with one negative study and four studies not showing it to be an independent predictor at the multivariable level. Finally, while the funnel plot suggested possible publication bias due to asymmetry, this was not confirmed by the Egger's regression test. This suggests that alternative factors such as issues with study methodology which may have exaggerated effect size, or alternatively true heterogeneity between the study populations may exist.

INR, albumin, bilirubin and platelets all demonstrate desirable qualities of a biomarker in terms of being biologically plausible, sensitive, validated, easy to measure, stable and inexpensive.[12] However, they lack specificity and are influenced by other comorbidities, malnutrition, malabsorption, malignancy and medications.[47] Furthermore, it is unlikely that a single biomarker will suffice, but more likely a combination of biomarkers that target different pathophysiological mechanisms driving decompensation. It is this premise that has led to the evolution of different scoring systems. While the MELD score has been the most well-studied and validated, there are limitations. There have been several modifications over time, including the addition of sodium as well as the latest version (MELD 3.0) incorporating gender and albumin.[51 52] However, despite these modifications, concerns still remain as patients with low scores are still at

Table 2 Summary of quality assessment of studies using Quality of Prognosis Studies framework

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Allen *et al*[21] 2022	Low	Moderate	Moderate	Low	Low	Moderate	Moderate
Are *et al* 2021[61]	Moderate	Low	Low	Low	Low	Low	Low
Asesio *et al*[22] 2022	Low	Low	Low	Low	Low	Low	Low
Bajaj *et al* 2023[62]	Moderate	Moderate	Low	Low	Low	Low	Moderate
Berzigotti *et al*[43] 2011	Low	Low	Low	Low	Low	Low	Low
Berzigotti *et al*[36] 2008	Low	Low	Low	Low	Low	Low	Low
Boonpiraks *et al*[63] 2024	Low	High	Low	Low	Moderate	Low	Moderate
Calvaruso *et al*[64] 2015	Low	Low	Low	Low	Low	Low	Low
Calzadilla-Bertot *et al*[65] 2021	Low	Moderate	Low	Low	Low	Low	Low
Chen *et al*[66] 2023	Low	Moderate	Low	Low	Low	Low	Low
Colecchia *et al*[23] 2014	Low	Moderate	Low	Low	Low	Low	Low
Cordova *et al*[67] 1986	High	Moderate	High	Low	High	High	High
Dillon *et al*[68] 2018	Low	Moderate	Moderate	Low	High	Low	High
Elkassem *et al*[37] 2022	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate
Fallahzadeh *et al*[69] 2021	Low	Moderate	Low	Low	Low	Low	Low
Fujiwara *et al*[70] 2022	Moderate	High	Low	Low	Low	Moderate	High
Garcia Garcia de Paredes *et al*[71] 2021	Low	Low	Low	Low	Low	Moderate	Low
Gatselis *et al*[72] 2020	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate
Gidener *et al*[73] 2021	Low	Moderate	Low	Low	Low	Low	Low
Gidener *et al*[74] 2022	Moderate	Moderate	Low	Low	Low	Low	Moderate
Vilar Gomez *et al*[75] 2014	Low	Moderate	Low	Low	Low	Low	Low
Guéchot *et al*[19] 2000	Moderate	Moderate	Low	Low	Low	Low	Moderate
Guha *et al*[76] 2019	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Hartl *et al*[77] 2021	Low	Moderate	Moderate	Low	Low	Low	Moderate
Henrique *et al*[46] 2021	Low	Moderate	Low	Low	High	Low	Moderate
Hsu *et al*[78] 2021	Low	Moderate	Low	Low	High	Low	Moderate
Innes *et al*[79] 2022	Low	Moderate	Low	Low	Low	Low	Low
Jain *et al*[80] 2021	Low	Moderate	Low	Low	Low	Low	Low
Jindal *et al*[40] 2020	Low	High	Low	Low	Low	Low	Moderate
Jindal *et al*[30] 2022	Low	High	Low	Low	Low	Low	Moderate
Joly *et al*[41] 1971	High	High	High	Moderate	High	Moderate	High
Kim *et al*[28] 2012	Low	Moderate	Low	Low	Low	Low	Low

Continued

Table 2 Continued

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk of bias
Kondo *et al*[20] 2016	Low	High	Low	Low	Low	Low	Moderate
Kwon *et al*[27] 2021	Low	Low	Low	Low	Low	Low	Low
Lee *et al*[81] 2013	Low	High	Low	Low	Low	Low	Moderate
Lisotti *et al*[82] 2016	Low	Moderate	Moderate	Low	High	Moderate	High
Merchante *et al*[83] 2018	Low	High	Moderate	Moderate	High	Low	High
Merchante *et al*[29] 2012	Low	High	Moderate	Moderate	Low	Low	High
Merchante *et al*[31] 2017	Low	Moderate	Moderate	Moderate	High	Low	High
Merchante *et al*[32] 2015	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Navadurong *et al*[84] 2023	Low	Moderate	Low	Moderate	Moderate	Low	Moderate
Pérez-Latorre *et al*[33] 2014	Low	High	Low	Low	Low	Low	Moderate
Qamar *et al*[85] 2009	High	High	Moderate	Low	Low	Moderate	High
Rincón *et al*[24] 2013	Low	Moderate	Moderate	Low	Low	Low	Moderate
Ripoll *et al*[25] 2007	Low	Moderate	Low	Low	Low	Low	Low
Saeki *et al*[86] 2023	Low	High	Low	Moderate	Moderate	Low	Moderate
Schneider *et al*[55] 2022	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Schwarzer *et al*[87] 2020	Low	High	Moderate	Moderate	Low	Low	High
Semmler *et al*[34] 2022	Moderate	High	High	Moderate	High	Low	High
Siramolpiwat *et al*[44] 2021	Low	Moderate	Low	Low	Low	Low	Low
Smith *et al*[38] 2017	Moderate	Moderate	Low	Low	High	Low	High
Tae *et al*[88] 2014	Moderate	High	Low	Low	Low	Moderate	High
Tapper *et al*[89] 2020	Moderate	Moderate	Low	Low	Low	High	High
Tornai *et al*[90] 2021	Low	High	Moderate	Low	Low	Low	Moderate
Turco *et al*[42] 2018	Low	Moderate	Low	Low	Low	Low	Low
Wang *et al*[91] 2014	Low	Moderate	Low	Low	Low	Low	Low
Wang *et al*[45] 2022	Low	Moderate	Low	Moderate	Low	Low	Moderate
Wong *et al* 2022[92]	Low	Moderate	Low	Moderate	Low	Low	Moderate
Yang *et al*[93] 2021	Low	Moderate	Low	Low	Low	Low	Low
Yoo *et al* 2024[94]	Low	Moderate	Low	Moderate	Low	Low	Moderate
Yuan *et al*[26] 2019	Low	High	Low	Low	Low	Low	Moderate
Yu *et al*[39] 2022	Low	High	Moderate	Moderate	High	Low	High
Zarski *et al*[35] 2020	Low	Moderate	High	Moderate	Low	Low	High

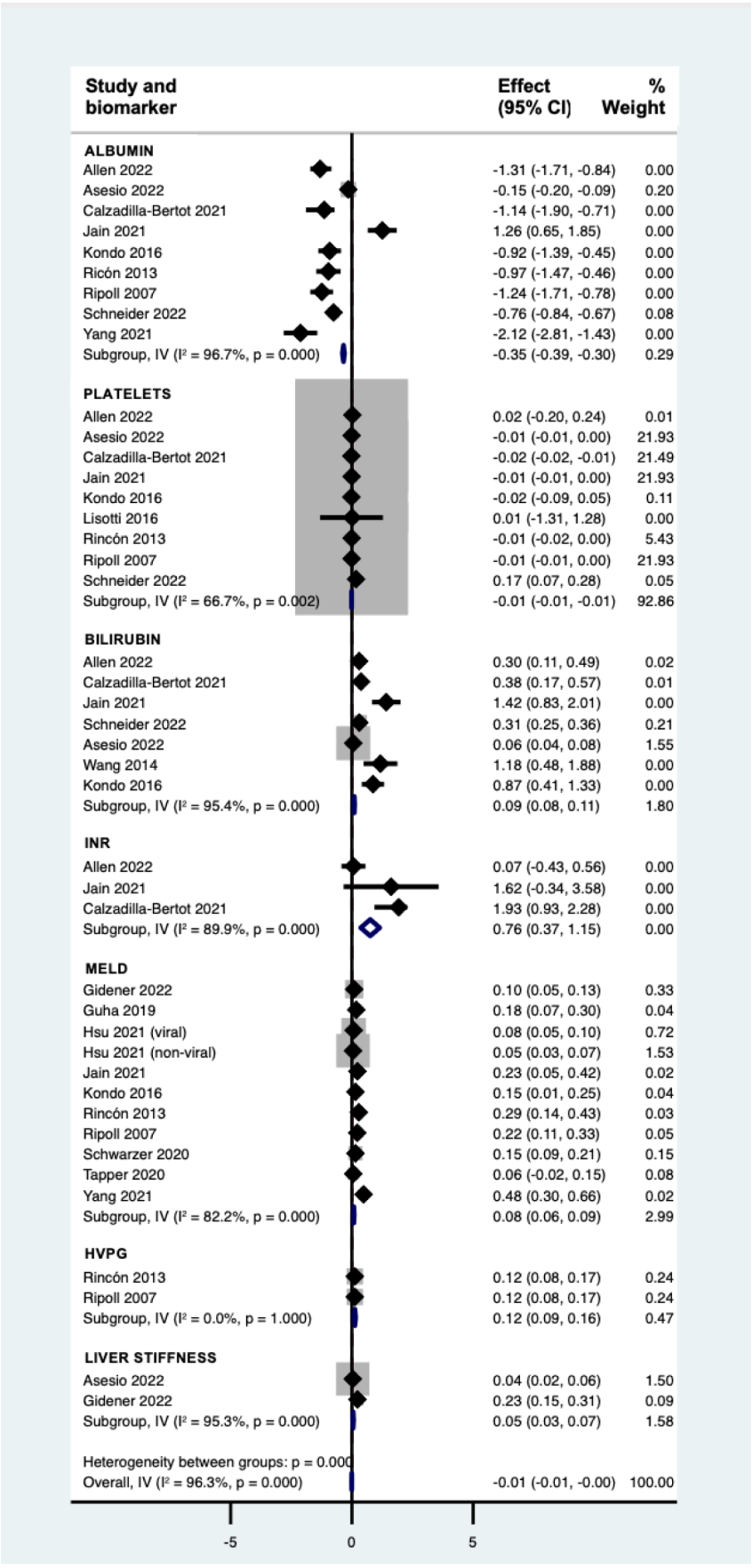

Figure 2 Forest plot for studies predicting decompensation categorised by biomarker (log-transformed). The shaded boxes are proportional to the weighting of each study.

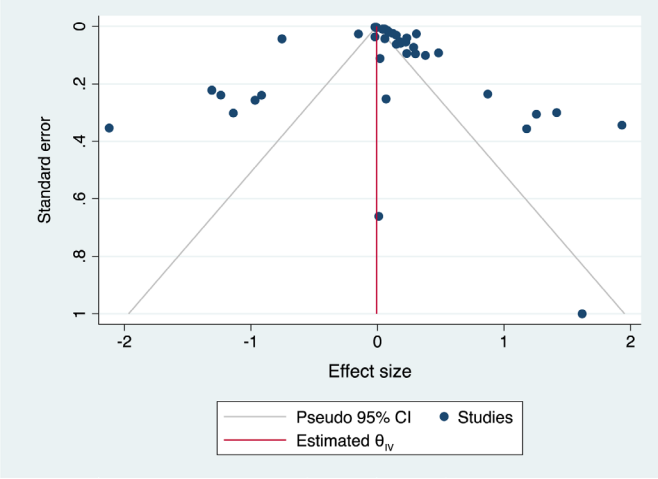

Figure 3 Funnel plot for studies predicting decompensation.

high risk of liver-related death, and it seems to underestimate mortality in the sickest cohort of patients with acute on chronic liver failure.[53 54]

New scoring systems have emerged over recent years all demonstrating superiority over existing scores including the MELD score, albeit older versions of the score. Many of the scores are composed of liver function tests and markers of synthetic function already detailed in this discussion section in varying combinations. Other variables that have been included are the presence of type 2 diabetes and oesophageal varices as a marker of portal hypertension in the ABIDE score, and Von Willebrand Factor antigen in the VITRO score as a marker of endothelial dysfunction. While these novel scores are promising, they have only been developed in recent years and require further validation to justify their use in predicting decompensation.

All HVPG studies in this review demonstrated statistically significant findings. This is not surprising given that portal hypertension is the most common haemodynamic abnormality caused by liver cirrhosis and is the main cause of decompensation. Currently, HVPG is the most accurate, reliable and reproducible measure of portal hypertension.[6] Furthermore, compared with the blood-based biomarker category which had a significantly higher risk of bias, only one of the HVPG studies was deemed high risk. This emphasises the robustness of these studies and the reliability of their results, particularly as they are reproducible. Only one paper evaluated HVPG in combination with another biomarker, albumin, and this demonstrated only mild improvement.[24] However, despite its efficacy, HVPG is invasive, costly and can be hard to justify in clinically well patients with compensated cirrhosis given the risk of procedural complications.[55]

With a shift towards the development of non-invasive biomarkers, liver stiffness has grown in increasing popularity. Indeed, the recent BAVENO guidelines have suggested a rule of 5 for liver stiffness by transient elastography (TE) (5-10-15-20-15kPA) should be used to denote progressively higher risks of decompensation regardless of the aetiology of liver disease.[6] Additionally, liver stiffness has also been incorporated in the novel CHESS-ALARM score. However, when focusing on the studies highlighted in this review, a large range of different cut-offs have been proposed. Furthermore, over 40% of studies exhibited a high risk of bias, so caution must be taken with their interpretation. Finally, questions remain over the best technique, whether that be ultrasound based such as TE or acoustic radiation force impulse, which are cheaper but operator dependent, versus other techniques such as magnetic resonance elastography which are more time intensive and expensive, but potentially more accurate.[56]

The remaining categories of imaging, physiological and miscellaneous markers all displayed significant potential. However, their use in clinical practice is currently limited by the scarce number of studies with small sample sizes. The physiological markers highlighted in this review (BMI, mean arterial pressure and LFI) are non-invasive and easy to measure and crucially none exhibited a high risk of bias. Similarly, most of the imaging studies used ultrasound, CT or MRI techniques, which are already readily available in clinical practice. However, as per all imaging techniques, costs and time taken must be considered, as well as radiation exposure with CT imaging. Furthermore, some imaging studies, such as those involving nuclear medicine or advanced imaging techniques, are unlikely to be incorporated into clinical practice in the foreseeable future. Finally, the majority of the miscellaneous category also required liver histology, which is not likely to be indicated in most patients with compensated cirrhosis who are clinically well.

The main limitations of this review are that there was significant heterogeneity between the different studies. First, the populations were heterogenous with some studies evaluating the risk of first decompensation, while others included patients who may have had previous decompensation; these cohorts are increasingly being recognised as two separate populations.[6] Second, this review was made more challenging by the evolving definition of decompensation over time. The most recent BAVENO guidelines were the criteria used in this review, and they define decompensation by the development of ascites, HE or variceal bleeding only. Crucially they have excluded jaundice which is in previous EASL guidelines, and infection which was used in previous large European multicentre cirrhosis trials (CANONIC and PREDICT) due to an increasing acceptance that infection is not a true decompensating event itself, but rather a precipitant.[8 57 58] Therefore, some studies which used different definitions historically may not have been included in this review. Despite this, we feel this is a high-quality study which has a stringent methodology and has yielded important findings. In addition, two conceptually different types of decompensation have recently been described; AD which occurs rapidly and tends to be associated with hospitalisation, and non-acute which occurs

insidiously over months/years.[59] It is likely that future biomarker studies will need to study these populations separately.

In summary, while the novel biomarkers highlighted in this review have not yet clearly outperformed current scoring systems, we highlight key biomarkers to help guide future research. A single biomarker in isolation will not be the answer to this crucial unmet need. These scores will need to be composed of several components that target different pathophysiological pathways that drive decompensation including portal hypertension, systemic haemodynamics, systemic inflammation, metabolic dysfunction and the microbiome. Indeed, while not the focus of this review, dynamic scores which can predict prognosis over time as well as response to therapies are not only desirable but should be actively pursued. It is also worth noting that the role of modifiable risk factors such as alcohol intake, smoking and diabetic control which have not been addressed here, would likely have significant impacts on the incidence of decompensation. Future research should explore mixed modality scores targeting non-modifiable as well as modifiable risk factors, although which exact combinations remain elusive currently. Furthermore, creating such a composite score will be a challenge to both develop and validate, and it is imperative that it is available to all to prevent inequity in healthcare, overcoming socioeconomic, rural and ethnic disparities. Crucially, given that different aetiologies exhibit substantial differences in the risk of decompensation, these tests must be tailored to individuals as opposed to using a 'one size fits all' model.[60]

While creating individualised models with multiple components may seem unattainable, there is an increase acceptance across healthcare settings that this is what we must strive for. In order to achieve this, greater national and international collaboration is imperative, generating large data sets that can employ techniques such as machine learning, deep learning and artificial intelligence. Finally future biomarker studies should be conducted with rigorous methodology. The creation of a biomarker study checklist or guidelines would ensure that robust and comparable data is generated. Only then will we be able to successfully predict and hopefully prevent decompensation.

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