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Early prediction of decompensation (EPOD) score: Non-invasive determination of cirrhosis decompensation risk

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Abstract

Background & Aims: Decompensation is a hallmark of disease progression in cirrhotic patients. Early detection of a phase transition from compensated cirrhosis to decompensation would enable targeted therapeutic interventions potentially extending life expectancy. This study aims to (a) identify the predictors of decompensation in a large, multicentric cohort of patients with compensated cirrhosis, (b) to build a reliable prognostic score for decompensation and (c) to evaluate the score in independent cohorts. **Methods:** Decompensation was identified in electronic health records data from 6049 cirrhosis patients in the IBM Explorys database training cohort by diagnostic codes for variceal bleeding, encephalopathy, ascites, hepato-renal syndrome and/

Abbreviations: AIC, Akaike information criterion; ALBI, Score consisting of Albumin & Bilirubin; AUROC, Area under the receiver operating characteristic; EHR, electronic health record; EPOD, Early prediction of decompensation; HCC, Hepatocellular carcinoma; HIPAA, Health Insurance Portability and Accountability Act; HITECH, Health Information Technology for Economic and Clinical Health Act; HR, Hazard ratio; HRS, hepato-renal syndrome; HVPG, hepatic venous pressure gradient; INR, International normalized ratio; IQR, Interquartile range; MELD, Model for end-stage liver disease; PALBI, Score consisting of Platelets, Albumin & Bilirubin; PMBB, Penn Medicine BioBank; ROC, Receiver operating characteristic; UKB, UK biobank.

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or jaundice. We identified predictors of clinical decompensation and developed a prognostic score using Cox regression analysis. The score was evaluated using the IBM Explorys database validation cohort (N = 17662), the Penn Medicine BioBank (N = 1326) and the UK Biobank (N = 317).

Results: The new *Early Prediction of Decompensation* (EPOD) score uses platelet count, albumin, and bilirubin concentration. It predicts decompensation during a 3-year follow-up in three validation cohorts with AUROCs of 0.69, 0.69 and 0.77, respectively, and outperforms the well-known MELD and Child-Pugh score in predicting decompensation. Furthermore, the EPOD score predicted the 3-year probability of decompensation.

Conclusions: The EPOD score provides a prediction tool for the risk of decompensation in patients with cirrhosis that outperforms well-known cirrhosis scores. Since EPOD is based on three blood parameters, only, it provides maximal clinical feasibility at minimal costs.

KEYWORDS
electronic health records, cirrhosis, proportional hazards models, regression analysis, risk scores

1 | INTRODUCTION

Cirrhosis is a growing global health burden and a major cause of death worldwide.[1,2] It is defined as the end-stage of chronic fibrotic remodelling, which may be caused by continuous liver injury due to chronic alcohol abuse, viral hepatitis or non-alcoholic fatty liver disease.[3,4] In the clinical routine differentiating between patients with compensated or decompensated cirrhosis is highly relevant as this status critically predicts prognosis.[5,6] Decompensation of cirrhosis is defined by the presence of variceal bleeding, encephalopathy, ascites, hepato-renal syndrome (HRS) and/or jaundice.[7]

Phase transition of patients with cirrhosis from a compensated to a decompensated state is estimated to occur at rates of 5–7% per year.[5] The risk of mortality strongly increases when a patient shifts to the state of decompensated cirrhosis.[5,6] Therefore, predicting the risk of decompensation in a patient with cirrhosis has major clinical implications. Moreover, there is an ongoing debate whether well-known prognostic indicators of survival such as the MELD-Score[8,9] or Child-Pugh Score[10] may predict survival less accurate in compensated cirrhosis.[5,11]

At present, clinical scores were mainly established to calculate the risk of death in patients with cirrhosis. In contrast, parameters that define the risk of decompensation were not studied in detail. To improve the surveillance strategy of patients with cirrhosis such a score that defines the risk of phase transition—compensated versus decompensated state—would have major advantages. A promising predictor of decompensation is the hepatic venous pressure gradient (HVPG) as it is a well-studied marker of portal hypertension.[11] However, in patients with compensated cirrhosis, it is difficult to justify invasive HVPG measurement.[12] Other studies identified anaemia, markers of systemic inflammation like IL-6[13] or vitamin D[14] levels as predictors of decompensation.

To date, there is no simple, routinely performed serum marker-based score to predict decompensation in cirrhotic patients. The aim of this study was therefore to (a) identify the predictors of clinical decompensation in a large, multi-centric cohort of patients with compensated cirrhosis, (b) to build a reliable prognostic model predicting clinical decompensation and (c) to evaluate the resulting score in three validation cohorts.

Lay summary

The EPOD score is a new score for the prediction of cirrhosis progression from a symptom-free to a symptomatic disease state (decompensation) and is calculated from three routinely measured blood parameters. In our study, the EPOD score correctly identified low- and high-risk patients and estimated the probability of decompensation within the next 3 years. The EPOD score and the predicted 3-year risk of decompensation can be calculated for scientific discussion using the EPOD score calculator (epod-score.com).

In summary, this large, multi-cohort study in patients with compensated cirrhosis identified platelets, albumin and bilirubin as predictors of clinical decompensation. The resulting *Early Prediction of Decompensation* (EPOD) score surpasses known cirrhosis scores (e.g. MELD and Child-Pugh Score) when predicting decompensation in three non-related validation cohorts. For scientific discussion, the EPOD score can be calculated using the EPOD score calculator (epod-score.com).

2 | METHODS

2.1 | IBM Explorys

IBM Explorys is a commercial real-world database containing electronic health record (EHR) data on patients from diverse points of care and institution types in the United States.[15] The data are fully compliant with

the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH). Therefore, no approval by the institutions' human research committee was required, and informed consent by the patients was not obtained. Patient data range from 1996 until now and are continuously updated. Patient data used for this publication were snapshotted on 8th November 2021. At this time, the database contained data on ~65 million patients. End of follow-up was defined as the last date of observation or death. SNOMED CT codes and LOINC codes were used to identify diagnoses and extract observations, respectively.

2.2 | PMBB

Participants in the Penn Medicine BioBank (PMBB) were recruited from clinical practice sites throughout the University of Pennsylvania Health System beginning in 2008. Participants consented for access to EHR data. For the PMBB cohort, ICD-9 and ICD-10 diagnosis codes were extracted from ongoing inpatient and outpatient records to identify diagnoses. The PMBB receives death notifications (age at death and primary ICD diagnosis that led to death) through linkage to the EHR. End of follow-up was defined as death or end of hospital inpatient data collection at the end of July 2020.

2.3 | UK biobank

The UK biobank (UKB) is a population-based cohort study conducted in the United Kingdom from 2006 to 2010, which recruited 502 505 volunteers aged 37–73 years at baseline. Details of the rationale, design and survey methods for UK Biobank can be obtained on the study website (http://www.ukbiobank.ac.uk). All participants were registered with the UK National Health Service and were encouraged by post to attend an assessment centre for an initial examination, which is followed by a long-term follow-up. Our study population comprises the baseline assessment (2006–2010), in which the participants provided demographic information, clinical data and blood sample extraction. All participants gave informed consent for data linkage to medical reports. Ongoing inpatient hospital records beginning in 1996 were used to identify diagnoses according to ICD-10 codes. All reported ICD-10 codes were related to the date of their first diagnosis. For the follow-up, hospital inpatient data, national cancer registries or death registration were used. Hospital inpatient data collection ended in March 2018. The UK Biobank receives death notifications (age at death and primary ICD diagnosis that led to death) through linkage to national death registries. End of follow-up was defined as death or end of death registration data collection in June 2020.

2.4 | Patient selection and data extraction

Cirrhosis patients were identified using SNOMED CT codes (Explorys), ICD-9/10 codes (PMBB) or ICD-10 codes (UKB). In case of the UKB, only patients were selected that had a cirrhosis diagnosis reported before attending the first assessment. The respective diagnosis codes are listed in Table S1. Patients below the age of 18 were excluded. Cirrhosis aetiology was defined as 'alcoholic cirrhosis', 'other' or 'unspecified cirrhosis' of the liver according to the diagnoses code. Viral aetiology of cirrhosis patients was assumed, when unspecified cirrhosis was preceded by the diagnosis of chronic hepatitis B. In Explorys, chronic hepatitis B diagnoses were not available.

Decompensation was defined as one of the following diagnoses: hepatic encephalopathy, jaundice, bleeding oesophageal varices, ascites or HRS. The type of the first decompensation event was determined using the respective diagnoses codes (Table S1).

Baseline serum parameters were extracted and used for all analyses. Within the Explorys and the PMBB cohort, baseline refers to the median value of all measurements of a parameter in a patient taken within 1 month before and after the diagnosis of cirrhosis. In the UKB, baseline refers to the initial assessment. To ensure that all analyses had chronic prognostic value and were not biased by acute events, patients that had a decompensation event within the first month after the cirrhosis diagnosis were excluded (Figure S1).

To make use of the large population size of the Explorys cohort not only for training but also for validation, a subpopulation of approximately 10% of the total population that matched the selection criteria comprising 6049 patients was randomly selected as a training cohort. The Explorys validation cohort was extracted from the total Explorys cirrhosis cohort using the selection criteria described above as well as the availability of baseline values that were needed to calculate the newly designed EPOD score, the Child-Pugh score and the MELD-score. This resulted in a total validation cohort of 17662 patients (for details, see Figure S1).

2.5 | Disease severity scores

The Child-Pugh score, MELD score, ALBI score and PALBI score were calculated at baseline. Baseline scores were only calculated when all parameters were available. The Child-Pugh score was calculated from albumin, the international normalized ratio (INR) and bilirubin. Encephalopathy and ascites were assumed to be absent since decompensation events before or within the first month after diagnosis were exclusion criteria for patient selection. Child-Pugh classes A, B and C were assigned to a score of 5–6, 7–9 or 10–15, respectively.[10,16]

The MELD score was calculated as

$$\mathrm{MELD} = 9.57 \times \ln\left(\mathrm{creatinine}\left[\frac{\mathrm{mg}}{\mathrm{dL}}\right]\right) + 3.78 \times \ln\left(\mathrm{bilirubin}\left[\frac{\mathrm{mg}}{\mathrm{dL}}\right]\right) + 11.2 \times \ln(\mathrm{INR}) + 6.43 \quad (1)$$

Values smaller than 1 were set to 1 and creatinine values above 4 were set to 4. If patients were dialyzed twice within the last 7 days, creatinine was set to 4 mg/dL. MELD score values were rounded to the nearest integer.[8,9] The UKB cohort did not contain data on INR.

Therefore, neither the MELD nor the Child-Pugh score could be calculated for the UKB cohort.

The ALBI score was calculated as

$$\begin{aligned}\text{ALBI} = 0.66 \times \log10\left(\text{bilirubin}\left[\frac{\mu\text{mol}}{\text{L}}\right]\right) \\ + -0.085 \times \log10\left(\text{albumin}\left[\frac{\text{g}}{\text{L}}\right]\right)\end{aligned} \quad (2)$$

ALBI grades 1–3 were assigned to score of ≤−2.6, >−2.6 to ≤−1.39 and >−1.39, respectively.[17]

The PALBI score was calculated as

$$\begin{aligned}\text{PALBI} = 2.02 \times \log10\left(\text{bilirubin}\left[\frac{\mu\text{mol}}{\text{L}}\right]\right) - 0.37 \times \log10\left(\text{bilirubin}\frac{\mu\text{mol}}{\text{L}}\right)^2 \\ - 0.04 \times \text{albumin}\left[\frac{\text{g}}{\text{L}}\right] - 3.48 \times \log10\left(\text{platelets}\left[\frac{1000}{\mu\text{L}}\right]\right) \\ + 1.01 \times \log10\left(\text{platelets}\left[\frac{1000}{\mu\text{L}}\right]\right)^2\end{aligned} \quad (3)$$

PALBI grades 1–3 were assigned to score of ≤2.53, > 2.53 to ≤2.09 and >2.09, respectively.[18]

2.6 | Statistical analysis

All statistical analyses were performed in the statistics software R and SPSS. Univariable Cox regression was performed on the Explorys training cohort to identify baseline predictors of decompensation in cirrhotic patients. To exploit the large amount of data, the analysis was performed in an explorative way without a prospective selection of covariates except for a cohort frequency threshold of a least 3%. The hazard ratio (HR) of each covariate was scaled to the interquartile range (IQR) of the respective parameter in the population to make the HRs comparable between covariates. *P*-values for all univariable analyses were corrected for multiple testing with Bonferroni correction. Multivariable Cox regression was performed with selected covariates in a forward selection approach on the Explorys training cohort. Selection criteria were a significant likelihood ratio test ($P < .01$) and a decrease in the Akaike information criterion (AIC). The risk score equation was constructed from the covariates of the final model and their regression coefficients. Additional modifications were applied to scale the score into an intuitive number regime. For validation and comparison to other scores, receiver operating characteristic (ROC) curves were constructed for the new EPOD score, the MELD score and the Child-Pugh. In a supplementary analysis, ROC curves for ALBI score and PALBI score were calculated. The area under the receiver operating characteristic (AUROC) was estimated for all ROC curves. Confidence intervals of AUROCs and *P*-values for comparison of AUROCs were calculated according to DeLong's test.

For categorization of patients into a high- and a low-risk group, a cut point was identified by determining the score value that exhibited 95% sensitivity in the Explorys training cohort for a 3-year interval. Kaplan-Meier analysis was performed for all three validation cohorts divided into the identified risk groups. Confidence intervals for Kaplan-Meier analysis were obtained using the log–log approach.

3 | RESULTS

To build a reliable prognostic model of decompensation in patients with compensated cirrhosis, we first identified predictors of clinical decompensation in the Explorys training cohort. These results were then validated in the Explorys validation cohort, the UK Biobank (UKB) and the Penn Medicine BioBank (PMBB).

In total, 6049 cirrhosis patients for training and 19305 cirrhosis patients from the three different databases for validation matched the inclusion criteria. In all, 1510 patients of the training cohort and 4857 patients of the validation cohorts developed decompensation during their follow-up time. The first decompensation event in the compensated cirrhosis patients mainly included ascites (57% in training cohort and 69% in validation cohorts), followed by bleeding of oesophageal varices (9.5% in training cohort and 12% in validation cohorts), jaundice (8.1% in training cohort and 14.3% in validation cohorts), encephalopathy (23.5% in training cohort and 2% in validation cohorts) and diagnosis of HRS (2% in training cohort and 3% in validation cohorts). Detailed baseline characteristics for all cohorts are listed in Table 1 and in Table S2.

3.1 | Identification of independent predictors of decompensation

Univariable Cox regression for 116 serum parameters was performed in the Explorys training cohort to identify baseline predictors defining the risk of decompensation in patients with compensated cirrhosis (Table S3). The strongest association was observed for the albumin–globulin ratio (HR: 0.46), the albumin concentration (HR: 0.47) and the platelet count (HR: 0.48) followed by the red blood cell parameters erythrocyte count (HR: 0.58), haematocrit (HR: 0.59) and haemoglobin concentration (HR: 0.60; Figure 1).

3.2 | Multivariable fitting of the EPOD score

Input variables for multivariable fitting were selected from the 10 top-scoring covariates of the univariable regression. The selection was performed considering the underlying pathophysiological processes and the clinical availability of routinely performed serum markers. Additionally, redundancies in the physiological translation of parameters such as for erythrocytes, haematocrit and haemoglobin concentration were avoided. The final input variables were (a) the albumin concentration, reflecting the synthesis capacity of the liver,[5] (b) the platelet count, reflecting portal hypertension,[19] (c) the erythrocyte count, reflecting potential bleeding due to reduced clotting factors produced by the liver,[20] (d) the calcium concentration, reflecting changes in the acid–base balance through reno-vascular vasoconstriction[21] and

TABLE 1 Baseline characteristics of all cohorts

Characteristics	Explorys training cohort	Explorys validation cohort	PMBB	UKB
n	6049	17662	1326	317
Age [years]	61 (54–68)	61 (54–68)	66.2 (60.1–72.0)	59 (53–63)
Missing information	0 (0.0)	1 (<0.1)	1 (0.1)	0 (0.0)
BMI [kg/m^2]	29.4 (24.9–34.7)	28.8 (24.4–34.1)	28.5 (25.0–33.0)	28.2 (25.0–32.7)
Missing information	1353 (22.4)	1238 (7.0)	200 (15.1)	0 (0.0)
Diabetes mellitus	2245 (37.1)	6262 (35.5)	560 (42.2)	85 (26.8)
Follow-up time [years]	5 (3.8–7.9)	4.8 (3.0–6.9)	3.5 (1.1–6.3)	10 (6–12)
Sex				
Male	3300 (54.6)	10246 (58.0)	919 (69.3)	220 (69)
Female	2748 (45.4)	7416 (42.0)	406 (30.6)	97 (31)
Missing information	1 (<0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Ethnicity				
Caucasian	4528 (74.9)	13391 (75.8)	815 (61.4)	288 (90.9)
African American	746 (12.3)	2193 (12.4)	405 (30.5)	5 (1.6)
Asian	40 (0.7)	203 (1.1)	18 (1.4)	13 (4.1)
Hispanic/Latino	38 (0.6)	74 (0.4)	47 (3.5)	0 (0)
Multi-racial	25 (0.4)	0 (0.0)	2 (0.2)	2 (0.6)
Other	126 (2.1)	547 (3.1)	23 (1.7)	7 (2.2)
Missing information	546 (9.0)	1254 (7.1)	16 (1.2)	3 (1.0)
Aetiology				
Alcoholic	576 (9.5)	2373 (13.4)	214 (16.1)	170 (54)
Hepatitis B	—	—	600 (45.2)	39 (12)
Hepatitis C	—	—	Untreated: 58 (4.4) Treated: 3 (0)	1 (1)
Other	4202 (69.5)	12539 (71.0)	451 (34.0)	117 (37)
Missing information	1271 (21.0)	2750 (15.6)	0 (0.0)	0 (0.0)
Scores				
Child-Pugh Score	6 (5–7)	6 (5–7)	6 (5–7)	
Missing information	4060 (67.1)	0 (0.0)	1027 (77.5)	317 (100)
MELD score	9 (7–13)	9 (7–13)	9.7 (6.1–15.0)	
Missing information	4258 (70.4)	0 (0.0)	1037 (78.2)	317 (100)
First decompensation	1510 (25.0)	4286 (24.3)	496 (37.4)	75 (23.7)
Ascites	860 (14.2)	3119 (17.7)	198 (14.9)	52 (16.4)
Encephalopathy	355 (5.9)	31 (0.2)	43 (3.2)	0 (0)
Bleeding oesophageal varices	143 (2.4)	400 (2.3)	167 (12.6)	15 (4.7)
Jaundice	122 (2.0)	644 (3.6)	50 (3.8)	2 (0.6)
Hepato-renal syndrome	30 (0.5)	92 (0.5)	38 (2.9)	6 (1.9)
HCC				
Patients with HCC diagnoses during follow-up before first decompensation	—	1865 (10.6)	187 (14.1)	27 (8.5)
Missing information	6049 (100)	—	—	—

Continuous characteristics are given as median (25th–75th percentiles). Discrete characteristics are given as count (percentage). Missing information rows indicate the number of patients for which the respective information was not available.

Abbreviations: HCC, hepatocellular carcinoma; PMBB, Penn Medicine BioBank; UKB, UK biobank.

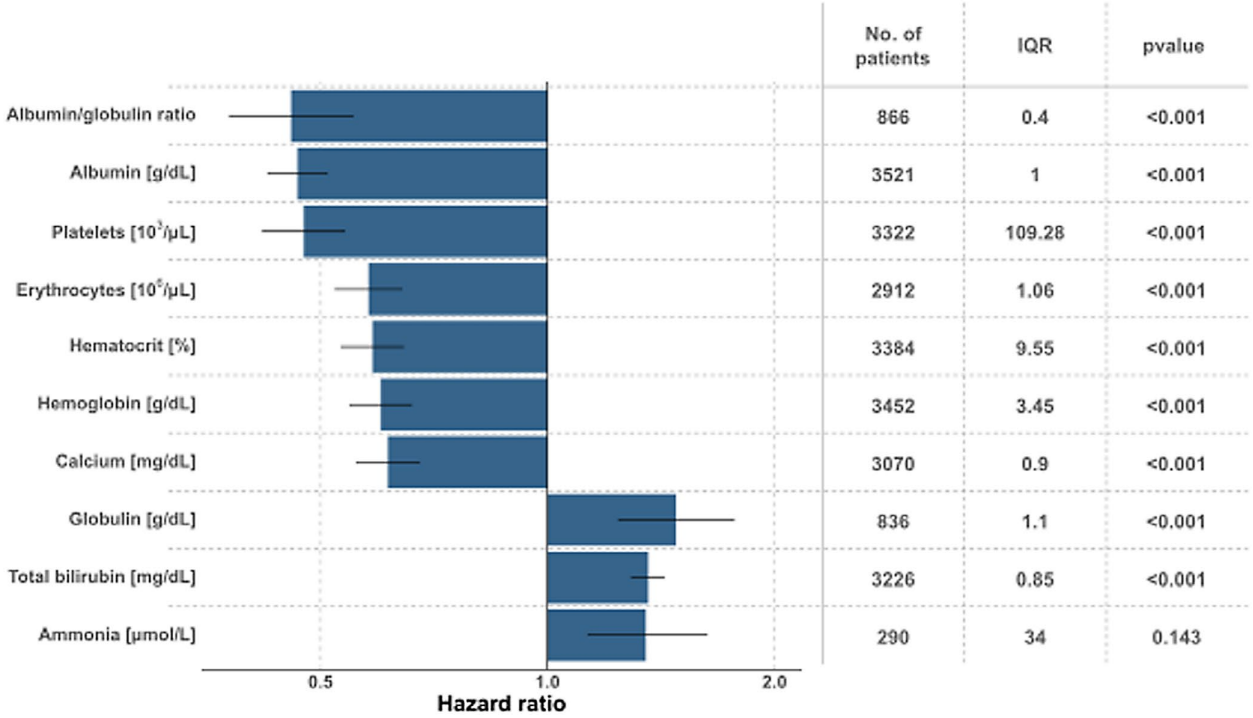


FIGURE 1 Univariable cox regression analysis. Explorative cox regression in the Explorys training cohort (n = 6049). The top 10 covariates according to the Hazard ratio are shown. Hazard ratios are scaled to interquartile ranges of the Explorys training cohort. More covariates are listed in Table S3. Platelet counts, erythrocyte count, haematocrit and haemoglobin were measured in full blood. All other parameters refer to measurements in serum or plasma

(e) the bilirubin concentration, reflecting the detoxification capacity of the liver.[22] In a stepwise forward selection approach, the best model was identified using the Explorys training cohort, consisting of the albumin and total bilirubin concentration and the platelet count (Table 2).

Using the resulting regression coefficients, the EPOD score was constructed as

$$\mathrm{EPOD}_{\mathrm{native}} = (-0.55)\times\mathrm{albumin}\left[\frac{\mathrm{g}}{\mathrm{dL}}\right] + (-0.004)\times\mathrm{platelets}\left[\frac{10^3}{\mu\mathrm{L}}\right] + 0.16\times\mathrm{bilirubin}\left[\frac{\mathrm{mg}}{\mathrm{dL}}\right] \quad (4)$$

Further modification was applied to shift the score into an intuitive number regime:

$$\mathrm{EPOD} = (\mathrm{EPOD}_{\mathrm{native}} + 5.38)\times 4 \quad (5)$$

Leading to the final formula for the EPOD score:

$$\mathrm{EPOD} = \left((-0.55)\times\mathrm{albumin}\left[\frac{\mathrm{g}}{\mathrm{dL}}\right] + (-0.004)\times\mathrm{platelets}\left[\frac{10^3}{\mu\mathrm{L}}\right] + 0.16\times\mathrm{bilirubin}\left[\frac{\mathrm{mg}}{\mathrm{dL}}\right] + 5.38\right)\times 4 \quad (6)$$

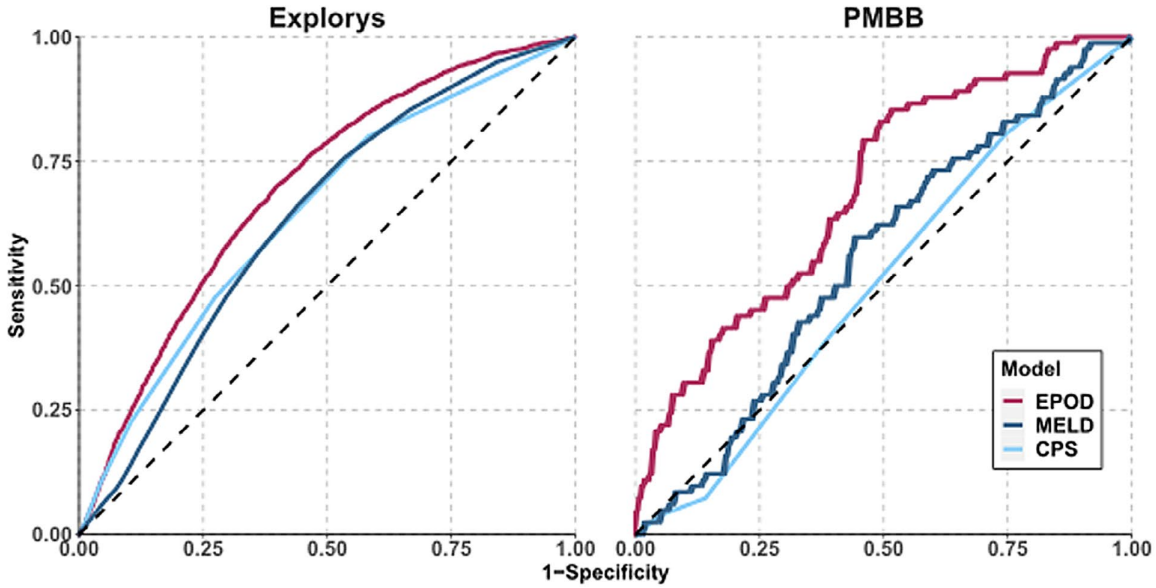
3.3 | Score validation and application

To evaluate the performance of the EPOD score, the baseline score was calculated for all patients in the three validation cohorts, for whom the required measurements were reported. ROC analyses after 3 years show that the EPOD score performs well in the Explorys validation cohort (AUROC: 0.694; Figure 2), the PMBB cohort (0.692; Figure 2) and the UKB cohort (AUROC: 0.770; Figure

TABLE 2 Results of multivariable cox regression in the Explorys training cohort

Input covariates	Patients number	Selected for final model	IQR	HR	95% confidence interval	Beta	*P* value
Albumin	2009	Albumin	1	0.58	0.54–0.69	−0.55	<.001
Bilirubin		Bilirubin	0.85	1.15	1.07–1.23	0.16	<.001
Platelets		Platelets	109.28	0.65	0.57–0.78	−0.004	<.001
Erythrocytes							
Calcium							

Hazard ratios are scaled to interquartile ranges. The final model was identified from the input covariates using a forward feature selection approach.
Abbreviations: HR, hazard ratio; IQR, interquartile range.



	Explorys	PMBB
EPOD score	**0.694** (0.686, 0.704)	**0.692** (0.625, 0.759)
MELD score	**0.635** (0.626, 0.645) p-value: $< 2.2 \times 10^{-6}$	**0.555** (0.482, 0.628) p-value: 7.53×10^{-4}
Child Pugh score	**0.645** (0.635, 0.654) p-value: $< 2.2 \times 10^{-6}$	**0.508** (0.434, 0.581) p-value: 5.773×10^{-5}

FIGURE 2 ROC curves for decompensation for the EPOD score, the MELD score and the Child-Pugh score evaluated after 3 years of follow-up. The table below gives the respective AUROCs, their 95% confidence intervals and the *P*-value when compared to the EPOD score using DeLong's test. Cohort sizes comprised 17 662 patients in the Explorys validation cohort and 296 patients in the PMBB in which all needed baseline values were available. CPS, Child-Pugh score

S2). Notably, it significantly surpasses the common liver survival scores (MELD score and Child-Pugh score) in the Explorys validation cohort and the PMBB. The UKB lacked measurements of blood coagulation. Therefore, MELD score and Child-Pugh score could not be calculated for the UKB cohort. Moreover, two scores known to predict survival in hepatocellular carcinoma (HCC) patients, PALBI and ALBI, which also use albumin, bilirubin (and platelets) were as well significantly outperformed by the EPOD score in the Explorys validation cohort and the UKB cohort (Figure S2).

For the stratification of patients into a high- and low-risk group, a cut point was calculated at a score value that exhibited 95% sensitivity in the Explorys training cohort after 3 years of follow-up. By that, 95% of those patients that decompensated in the Explorys training cohort were classified as high risk and only 5% were falsely classified as low risk. The cut score value was 10. Figure 3B shows the score distribution within the three validation cohorts with colour-coded risk groups. The proportions of high- and low-risk patients are similar in the Explorys validation cohort and the PMBB cohort with the highest percentage of patients in the high-risk group (Explorys: 86.3%, PMBB: 86%). However, the UKB patients are mostly classified as low-risk patients (61%) with only a smaller proportion of high-risk patients (39%). Figure 3A shows the stratified Kaplan-Meier curves for all three validation cohorts (for longer follow-up time, see Figure S3). In the low-risk groups, less than 10% of the patients decompensate within the first 3 years of follow-up. This is consistent throughout all three cohorts. In the high-risk cohorts of the Explorys validation cohort and the PMBB cohort, approximately 33% and 41% of patients decompensate. In the UKB cohort only 23% decompensate within the same time frame. This is in agreement with the lower median score of the UKB high-risk groups compared to those of the Explorys validation and the PMBB high-risk groups.

In general, patients of the low-risk group reveal a rather homogeneous and small-risk distribution due to the 95% sensitivity cut

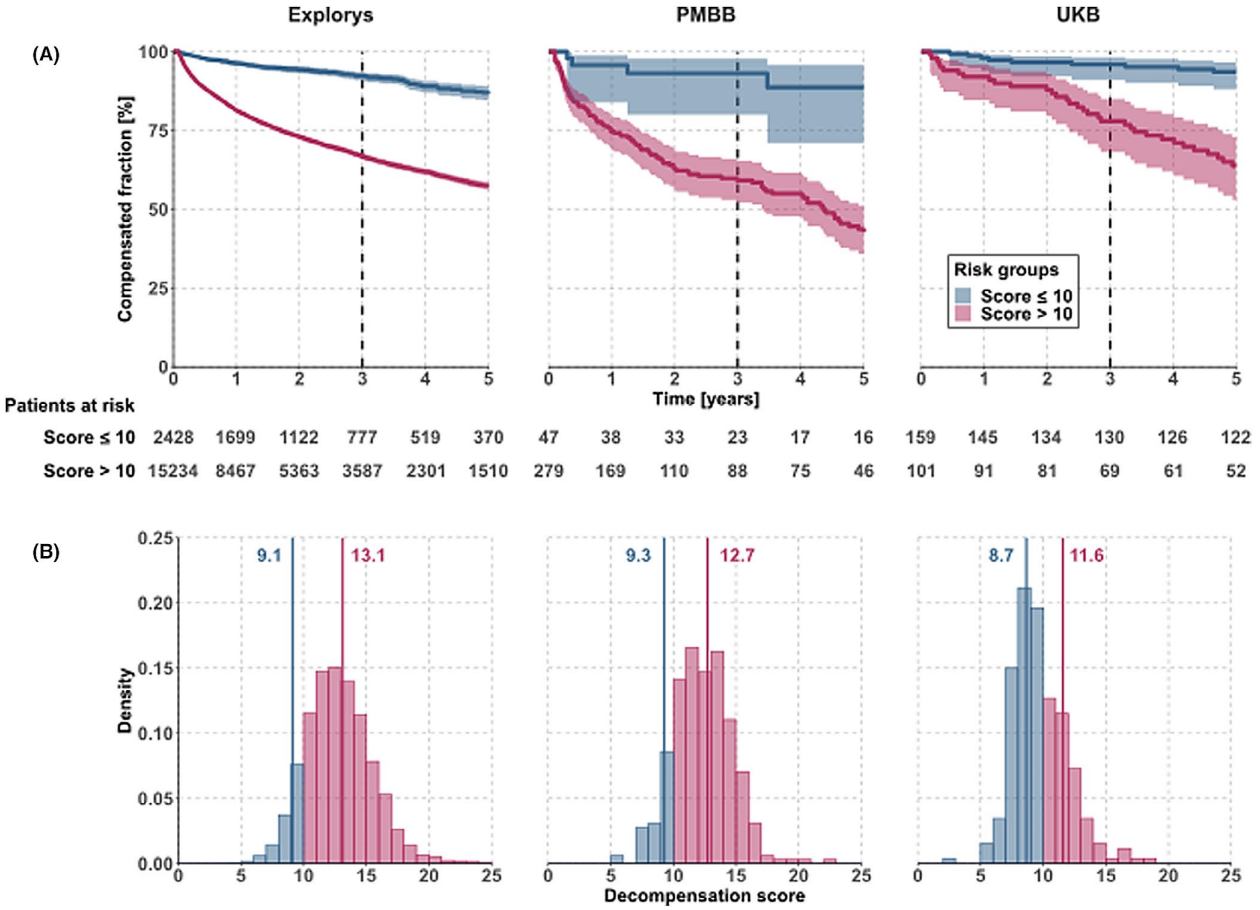


FIGURE 3 Stratification of patient cohorts into high-risk and low-risk groups according to the EPOD score for the Explorys validation cohort, the PMBB cohort and the UKB cohort. (A) Kaplan-Meier curves with log–log type 95% confidence intervals. The dashed line after 3 years indicates the time point of score validation (Figure 3—ROC curves and Table 3—Prognosis estimation). Longer follow-up time is shown in Figure S3. (B) EPOD score distribution within the different cohorts. Vertical lines and associated numbers represent the median EPOD score of the respective risk groups

point criterion. Vice versa, the high-risk group contains heterogeneous patients regarding their prognosis. For the clinical usage of the EPOD score, it is of interest to derive a prognostic risk of decompensation for cirrhosis patients. Using the underlying regression equation of Cox regression analysis, the relation between the probability of staying compensated ($C[t]$) until time point t can be described as

$$C(t) = C_0(t)^{e^{\frac{(Score - Score_0)}{4}}} \quad (7)$$

with $C_0(t)$ being the probability of staying compensated until time point t of an average patient, $Score_0$ being the EPOD score of an average patient and *Score* being the current EPOD score of the patient of interest. The division of the score difference by four results from the score shifting described before (Equation 5). For an average patient the median of the respective risk group of the Explorys training cohort was used with median scores of 8.9 and 12.7 and a compensated fraction of 92.1% and 61.6% in the low-risk and the high-risk groups, respectively, after 3 years of follow-up. The relation was tested for all three validation cohorts after 3 years of follow-up (Table 3). The predicted probabilities of staying compensated matched the observed compensated fractions with only the prediction of the Explorys validation high-risk group deviating from the confidence interval by 8% points. The EPOD score as well as the risk group and the decompensation prognosis can be calculated for scientific discussion on using the EPOD score calculator (epodscore.com).

4 | CONCLUSIONS

Phase transition in patients with cirrhosis from a compensated to a decompensated state is a critical step since it changes their prognosis as well as quality of life. Early identification of patients at high risk of decompensation could impact surveillance and treatment of the patients, likely improving their prognosis. To date, there is no simple, routinely performed serum marker-based score to predict phase transition in compensated patients with cirrhosis.

TABLE 3 Prognosis estimation compared to observed compensated fraction of all three validation cohorts after 3 years of follow-up

Database	Median EPOD score	Observed compensated fraction [%]	Prognosis using EPOD score [%]
Low risk			
Explorys Training cohort	8.9	92.1 (89.0, 94.4)	—
Explorys validation cohort	9.1	92.4 (90.9, 93.6)	91.8
PMBB	9.3	93.1 (80.0, 97.7)	91.4
UKB	8.7	95.9 (91.1, 98.1)	92.6
High risk			
Explorys training cohort	12.7	61.6 (58.9, 64.3)	—
Explorys validation cohort	13.1	66.8 (65.8, 67.8)	58.8
PMBB	12.7	59.1 (52.5, 65.4)	61.8
UKB	11.6	76.8 (66.9, 84.1)	69.7

The probability of staying compensated within 3 years of follow-up was estimated using the relation $C(t) = C0(t)^{exp}([EPOD - EPOD0]/4)$ with the compensated fraction of the Explorys training cohort in the respective risk sup-group after 3 years as $C0(t = 3\ years)$, the median score of the Explorys training cohort risk sup-group as EPOD0 and the score of the respective group EPOD. The baseline values C0 and EPOD0 are given in the table for the low-risk and the high-risk groups of the Explorys training cohort.

Abbreviations: EPOD, early prediction of decompensation; PMBB, Penn Medicine BioBank; UKB, UK biobank.

In this study, predictors of decompensation were identified and used to build a risk score (EPOD score) consisting of platelet count in blood, albumin and total bilirubin concentration in plasma. Analyses in three independent validation cohorts showed that the EPOD score predicts the risk of decompensation in cirrhosis patients with high accuracy.

The three parameters of the EPOD score quantify three different pathophysiological changes in early cirrhosis namely reduction in hepatic synthesis (albumin), impaired detoxification (bilirubin) and portal hypertension (platelets). They are well-known surrogate markers of liver function and predictors of survival. As such, they have also been identified as prognostic markers of survival in HCC patients resulting in the ALBI (albumin and bilirubin) and PALBI (platelets, albumin and bilirubin) score.[17,18] In our study, these two scores were also tested as decompensation predictors but were outperformed by the EPOD score (Figure S2). Albumin and bilirubin are also part of the Child-Pugh score while the latter one is used in the MELD score.[8-10] Again, these two scores are designed for predicting survival, especially in late-stage cirrhosis. Therefore, their performance for predicting phase transition towards decompensation was limited. Moreover, INR, which is used in the MELD as well as in the Child-Pugh score, is a suboptimal predictor in participants with liver diseases especially in a compensated stage. In addition to interlaboratory variability, INR values in participants with cirrhosis have been shown to be unreliable.[23-26]

Albumin is a well-known predictor of decompensation, as well as the HVPG.[11] HPVG is a marker of portal hypertension, but the invasive procedure is rarely justified in patients with compensated cirrhosis due to the risk of procedural complications. Other studies identified anaemia, markers of systemic inflammation like IL-6[13] or vitamin D[14] levels as predictors of decompensation. No data on IL-6 or vitamin D were available in the Explorys cohort but anaemia is indirectly represented by erythrocyte count, haematocrit and haemoglobin concentration. All three parameters were found to be strongly negatively associated with the risk of decompensation in the univariable regression analysis. Regardless of the cause, low erythrocyte count can lead to a reduced microvascular oxygen distribution, thereby contributing to secondary organ failure or decompensation. Nevertheless, the erythrocyte count did not add predictive accuracy to a model of albumin, platelets and bilirubin and was, consequently, not included in the EPOD score. The reason for this might be that anaemia can have various causes, for example, malabsorption, occult bleeding, chronic inflammation or malnutrition.

To advise patients with cirrhosis in predicting their risk of decompensation, we translated our findings, into risk categories that are useful for clinical routine. We defined the optimal cut-off that predicts decompensation with more than 95% sensitivity after 3 years of follow-up. Application of the risk categories to the three validation cohorts resulted in a big proportion of high-risk patients in the Explorys and the PMBB cohort but only a smaller proportion of high-risk patients in the UKB cohort. This reflects the overall UKB cohort well, as the UKB is known to consist of a quite healthy population compared to other cohorts.[27]

Using 95% sensitivity as a cut-off criterion, patients classified as low risk homogenously have a very high probability of staying compensated. Naturally, a high sensitivity implies lower specificity, leading to a potential misclassification of actual low-risk into high-risk patients. However, a safe classification strategy is preferable over misclassifying high-risk patients. Calculation of individual risks addresses the resulting heterogeneity within the high-risk group. We could show that the EPOD score was able to predict the decompensation risk in three independent study cohorts with a clinically relevant precision. We therefore assume that the score is suitable to predict individual decompensation risks in clinical routine.

A limitation of the study is that in all three cohorts, the selection of patients with cirrhosis and the identification of outcomes is based on codes (ICD-9/10 or SNOMED CT). Selection based on ICD or SNOMED codes is likely to suffer from some degree of misclassification or underdiagnosis. Moreover, the study is limited by the retrospective design. Another challenge is the highly variable follow-up times especially in the Explorys cohort. They lead in consequence to a lot of censoring in the survival analysis. Also, real-world data are not generated according to a study protocol following an overarching research goal at cohort level. It is only possible to investigate the relevance of clinical parameters that have been assessed in a sufficiently high proportion

of patients in clinical practice. Therefore, information on therapy received is scarce and the effects of alcohol abstinence or hepatitis therapy on the EPOD Score should be explored in the future. However, the large number of patients and parameters in this study compensates for these shortcomings. It also provides the possibility to work with an explorative approach, which is an established approach in analyses of biobanks, rather than preselecting few parameters. All results obtained in the training cohort were corroborated in three validation cohorts, confirming the performance and robustness of the score. Since the settings and data collection processes of the three validation cohorts are different from each other, we assume the score to be widely applicable and not limited to special patient populations. An advantage of the used cohorts is their community-based setting mimicking the general population. Together, all three validation cohorts contain over 120 000 person-years of data on cirrhosis patients and therefore have a reasonable overall power. The strengths of our study include the large sample size, and the availability of data on a wide range of potential predictors of decompensation in different cohorts.

In conclusion, in this large study, we describe the EPOD score calculated from the platelet count, albumin, and bilirubin concentration. The EPOD score robustly predicts phase transition towards decompensation in patients with cirrhosis providing maximal clinical feasibility at minimal costs. It can identify patients at high risk of decompensation to adapt their surveillance and treatment accordingly, ultimately improving their clinical outcome. The EPOD score can be calculated for scientific discussion using the EPOD score calculator (epod-score.com).

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CONFLICT OF INTEREST

A.R.P.S., S.S, C.D., K.C., H.M., R.B., J.L. and J.-F.S. are employees of Bayer AG, Germany. L.K. has been an employee of Bayer AG, Germany, at the time of the research project. V.B. is an employee of esqLABS GmbH. A.R.P.S., S.S., H.M., R.B., J.L. and L.K. have stock ownership with Bayer AG, Germany.

AUTHORS' CONTRIBUTIONS

Study concept and design: A.R.P.S, C.V.S, L.K., J.-F.S., C.T., R.B. and J.L. Acquisition of data: A.R.P.S, C.V.S, K.M.S, D.J.R and C.A.T. Analysis and interpretation of data: A.R.P.S and C.V.S. Drafting of the manuscript: A.R.P.S and C.V.S. Critical revision of the manuscript for important intellectual content: A.R.P.S, C.V.S, K.M.S, V.B., S.S., C.D., K.C., H.M., W.G., J.T., L.M.B., R.B., J.L., L.K., J.-F.S. and C.T. Figures and tables: A.R.P.S. Statistical analysis: A.R.P.S and C.V.S. Obtained funding: C.V.S. Administrative, technical or material support: S.S., C.D., K.C. and H.M. Study supervision: L.K., J.-F.S. and C.T.

ETHICS APPROVAL AND PATIENTS' CONSENT

The data of the IBM Explorys database are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH). Therefore, no approval by the institutions' human research committee was required, and informed consent by the patients was not obtained. The UK Biobank and the PMBB cohorts have ethical approval from their local institutions. All relevant ethical regulations were followed. For the UK Biobank and the PMBB cohort, appropriate consent was obtained from each participant.

DATA AVAILABILITY STATEMENT

The data underlying this article that were accessed from the UK Biobank and PMBB can be downloaded after submitting a reasonable application. Information regarding submitting proposals and accessing data from UK Biobank may be found on the study website (http://www.ukbiobank.ac.uk).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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