Development, validation, and prognostic evaluation of a risk score for long-term liver-related outcomes in the general population: a multicohort study

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Summary

Background Liver cirrhosis is a major cause of death worldwide. Cirrhosis develops after a long asymptomatic period of fibrosis progression, with the diagnosis frequently occurring late, when major complications or cancer develop. Few reliable tools exist for timely identification of individuals at risk of cirrhosis to allow for early intervention. We aimed to develop a novel score to identify individuals at risk for future liver-related outcomes.

Methods We derived the LiverRisk score from an international prospective cohort of individuals from six countries without known liver disease from the general population, who underwent liver fibrosis assessment by transient elastography. The score included age, sex, and six standard laboratory variables. We created four groups: minimal risk, low risk, medium risk, and high risk according to selected cutoff values of the LiverRisk score (6, 10, and 15). The model's discriminatory accuracy and calibration were externally validated in two prospective cohorts from the general population. Moreover, we ascertained the prognostic value of the score in the prediction of liver-related outcomes in participants without known liver disease with median follow-up of 12 years (UK Biobank cohort).

Findings We included 14 726 participants: 6357 (43·2%) in the derivation cohort, 4370 (29·7%) in the first external validation cohort, and 3999 (27·2%) in the second external validation cohort. The score accurately predicted liver stiffness in the development and external validation cohorts, and was superior to conventional serum biomarkers of fibrosis, as measured by area under the receiver-operating characteristics curve (AUC; 0·83 [95% CI [0·78–0·89]) versus the fibrosis-4 index (FIB-4; 0·68 [0·61–0·75] at 10 kPa). The score was effective in identifying individuals at risk of liver-related mortality, liver-related hospitalisation, and liver cancer, thereby allowing stratification to different risk groups for liver-related outcomes. The hazard ratio for liver-related mortality in the high-risk group was 471 (95% CI 347–641) compared with the minimal risk group, and the overall AUC of the score in predicting 10-year liver-related mortality was 0·90 (0·88–0·91) versus 0.84 (0·82–0·86) for FIB-4.

Interpretation The LiverRisk score, based on simple parameters, predicted liver fibrosis and future development of liver-related outcomes in the general population. The score might allow for stratification of individuals according to liver risk and thus guide preventive care.

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Introduction

Liver cirrhosis accounts for 2·4% of yearly deaths worldwide and is associated with a significant economic burden for health-care systems.[1] Notably, cirrhosis is the second leading cause of years of life lost in Europe.[2] Moreover, cirrhosis can lead to hepatocellular carcinoma, the incidence of which is increasing in many areas of the world.[3] Cirrhosis, characterised by diffuse hepatic fibrosis with nodular regeneration, is the final consequence of any chronic inflammatory process in the liver that might be caused by different factors, particularly hepatitis virus, excessive alcohol consumption, or metabolic syndrome, known as non-alcoholic fatty liver disease. Persistent liver inflammation is clinically silent but can result in liver fibrosis, eventually leading to cirrhosis. Although this process takes years or decades, the diagnosis is

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Research in context

Evidence before this study

Liver cirrhosis is a major cause of death worldwide. Cirrhosis usually occurs after a long period of asymptomatic chronic liver inflammation that results in a progressive hepatic fibrosis. The main causal factors for cirrhosis are hepatitis B and C virus, alcohol consumption, and metabolic syndrome, either acting alone or in combination. Despite the long period of disease evolution, diagnosis is usually made only in the stage of advanced cirrhosis when complications occur. Thus, a need exists for effective strategies to diagnose liver fibrosis early in asymptomatic people before cirrhosis develops. We searched PubMed for articles published from inception up to Oct 31, 2022, with the search terms "liver fibrosis markers", "non-invasive liver fibrosis tests", "serological markers of liver fibrosis", and "hepatic fibrosis" in various combinations for studies in English. We found 179 studies in hospital-based cohorts, but only 29 population-based studies done in individuals without known liver disease.

Added value of this study

We report on the LiverRisk score, which predicts accurately in an adult general population without known liver disease the degree of liver fibrosis, as estimated by liver stiffness measured by transient elastography. The LiverRisk score comprises six simple laboratory variables (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, glucose, cholesterol, and platelet count) together with age and sex. The LiverRisk score (https://www.liverriskscore.com) also accurately predicts long-term liver-related outcomes, including liver-related mortality, liver-related hospitalisation, and primary liver cancer, thus allowing stratification of individuals from the community according to risk of future liver disease outcomes.

Implications of all available evidence

Sparse data are available regarding the use of scores developed for identification of individuals in the general population without known liver disease who are at high risk of developing advanced fibrosis or cirrhosis. The LiverRisk score outperformed the most commonly used scores for non-invasive fibrosis estimation. The LiverRisk score could be used for early diagnosis of chronic liver disease with advanced fibrosis before the development of liver cirrhosis and its complications, or liver cancer. This early diagnosis can be made in primary care and linked to personalised therapeutic interventions aimed at stopping or reducing the effects of the causal factors responsible for chronic liver disease (metabolic syndrome, alcohol, or hepatitis virus). The effect of the interventions could be halting disease progression and reducing liver-related hospitalisations and mortality, thereby reducing the burden of liver diseases in the world.

generally made only at later stages when the disease becomes symptomatic and patients develop severe complications related to liver failure or portal hypertension that require hospital admission, or liver cancer.[2,4] Most of these symptomatic patients die of liver disease unless liver transplantation is performed. Although the prevalence of cirrhosis due to hepatitis C virus infection is decreasing worldwide because of effective oral antiviral drugs, that of non-alcoholic fatty liver disease is increasing markedly, owing to the epidemics of obesity and type 2 diabetes.[2,4]

Early identification of individuals at risk for progressive fibrosis would enable lifestyle modifications or therapeutic interventions to prevent the development of cirrhosis and would facilitate selection of patients for specialist referral. However, existing non-invasive tools for identification of patients in the population at risk for progressive hepatic fibrosis and, therefore, the long-term development of cirrhosis and liver-related death have substantial limitations.[5] Techniques such as transient electrography that measure liver stiffness, a surrogate for hepatic fibrosis, are accurate, but application of elastography to population screening is limited by expense and lack of availability outside of specialist settings.[2,4] Risk scores based on liver blood tests, such as fibrosis-4 index (FIB-4) or aspartate aminotransferase (AST) to platelet ratio index (APRI) scores show some utility in predicting the long-term development of cirrhosis or liver-related death in the general population.[5] However, because these indices were designed for fibrosis assessment in patients with hepatitis C virus infection and high prevalence of fibrosis, their predictive accuracy for the general population is modest.[5,6]

Hence, there is an unmet medical need to develop more accurate tools using easily available laboratory or clinical variables for the identification of individuals at risk for the long-term development of cirrhosis, liver-related complications, and death. Such predictive tools would enable case-finding and individualised follow-up for people with progressive liver disease in primary care and other non-liver health-care settings, before development of cirrhosis or its complications, and subsequently allow application of preventive measures such as weight loss in patients with overweight or obesity with non-alcoholic fatty liver disease and alcohol rehabilitation in patients with high alcohol consumption.[7,8] Therefore, we aimed to develop a liver risk score to identify patients at risk for future liver-related outcomes.

Methods

Study design

This study consists of two distinct parts. The aim of the first part was to develop and validate a diagnostic liver risk score (LiverRisk score) in individuals from the general population that predicted individual values of liver stiffness by using a combination of standard demographic, clinical, and laboratory variables. The aim

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of the second part was to assess whether the LiverRisk score is useful for the prediction of future liver-related outcomes in individuals without known liver disease in the general population.

Participants

Derivation cohort for the LiverRisk score

We used patient-level data from seven independent prospective studies using transient elastography to assess liver stiffness in the development of the model aimed at predicting the presence of liver fibrosis. These studies included participants from Denmark,[9] Hong Kong,[10] Germany,[11] France,[12] the UK,[13] and Spain.[14,15]

Information on sex, age, alcohol consumption, BMI, waist circumference, arterial pressure, diabetes, arterial hypertension, fasting glucose, creatinine, total cholesterol, HDL cholesterol, triglycerides, AST, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), bilirubin, leukocyte, haemoglobin, and platelet count were available from these databases. The outcome of interest was a validated liver stiffness value (in kPa), as measured by transient elastography.[5] All quantitative measurements, including biomarkers and liver stiffness, were standardised across all cohorts. A model was developed from this cohort to generate the LiverRisk score, to predict of the measured liver stiffness value (in kPa), which estimates the presence of hepatic fibrosis.[5]

Validation cohorts for the LiverRisk score

The LiverRisk score obtained from the derivation cohort was validated in two external cohorts. The first external validation cohort included participants in the Rotterdam Study,[16] a population-based study of individuals older than 45 years who underwent liver stiffness measurement, and the second validation cohort included individuals participating in the LiverScreen Study, a European, multicentre, prospective, diagnostic study also assessing the presence of liver fibrosis in the population using liver stiffness by transient elastography.[17]

Prognostic evaluation cohort of the LiverRisk score

The prognostic cohort was obtained from the UK Biobank dataset.[18] The UK Biobank is a large population-based cohort that includes over 500 000 individuals with baseline demographic, serological, lifestyle, and genetic measurements initiated in 2007. UK Biobank collects information on all participants, including baseline demographic, environmental, and lifestyle characteristics of all individuals, as well as information on hospitalisation and death from all participants. Data on death, including primary and secondary causes of death, are recorded from the International Classification of Diseases, 10th edition (ICD-10), codes from the death registry and are updated two to three times every year. Data on hospitalisations are also based on ICD-10 codes and updated every year. Exclusion criteria for our assessment were diagnosis of liver disease before enrolment, diagnosis of viral hepatitis at baseline or at any point during follow-up, or incomplete laboratory variables. We did a complete case analysis only in the cohort without missing variables.

The investigated outcomes were liver-related mortality, first liver-related hospitalisation, and incident liver cancer.[2] We also selected non-liver-related mortality, first non-liver-related hospitalisation, and incident cancer as negative control outcomes.

Ethics approval was obtained to analyse all study cohorts. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate in the UK Biobank study.

Statistical analysis

Model development

Variable selection in the development sample was performed using a recursive feature elimination (RFE) algorithm.[19] RFE is a technique that ranks the most relevant predictors in a dataset, by training models with and without all potential predictor combinations. Next, to identify the optimal number of variables we assessed the incremental gain in predictive performance associated with each variable and stopped at the inflexion point. After variable selection with RFE, we trained four statistical models with centred and scaled selected predictors because of the different scales of the predictors and to ease the intercept of models to the mean liver stiffness, including a linear regression model[20] quantile regression model,[21] gradient boosting model,[22] and a random forest model.[23] No further functional transformations of the predictors were used, and no interaction terms were included in the linear model. To assess the degree of potential over-fitting of each algorithm, we trained them using a 5-fold 5-repeat cross-validation procedure. The sample size considerations for model development are shown in the appendix (p 3).

Model assessment

To assess the discriminatory accuracy of the developed model, in all three diagnostic cohorts, we used the area under the receiver-operating characteristics curve at three values of the LiverRisk score that estimate levels of fibrosis severity in population-based studies: 6 kPa or more, 10 kPa or more, and 15 kPa or more thresholds.[24–26] Using these cutoffs, we categorised participants into four risk groups according to the predicted risk of liver fibrosis: minimal-risk group, (LiverRisk score <6), low-risk group (LiverRisk score 6 to <10), medium-risk group (LiverRisk score 10 to <15), and high-risk group (LiverRisk score ≥15). All models were compared with FIB4 and APRI scores, two methods used in clinical practice to assess liver fibrosis non-invasively (appendix p 3).[5] 95% CIs were computed with bootstrapping with 2000 random draws. To inspect the calibration of the predictive models, we estimated linear regression models between predicted and observed liver stiffness values with calibration intercept and slopes, and plotted graphical representations.

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	Derivation cohort (n=6357)	Validation cohort 1 (Rotterdam; n=4370)	Validation cohort 2 (LiverScreen; n=3999)	Prognosis cohort (UK Biobank; n=416 200)
Sex				
Female	3352 (52·7%)	1972 (45·1%)	2244 (56·1%)	223 687 (53·7%)
Male	3005 (47·3%)	2398 (54·9%)	1755 (43·9%)	192 513 (46·3%)
Age years	55·1 (11·9)	67·4 (8·2)	57·6 (9·2)	56·6 (8·09)
High alcohol consumption*	2098 (33·0%)	838 (19·2%)	472 (11·8%)	84 828 (20·4%)
BMI, kg/m²	27·1 (5·0)	27·2 (4·0)	27·7 (4·8)	27·4 (4·8)
Waist circumference, cm	92·2 (12·9)	93·1 (12·3)	93·4 (13·6)	90·2 (13·4)
Systolic blood pressure, mm Hg	129 (17)	143 (22)	131 (18)	138 (19)
Diastolic blood pressure, mm Hg	80 (10)	84 (11)	82 (11)	82 (11)
Diabetes†	809 (12·7%)	373 (8·5%)	396 (9·9%)	20 761 (4·9%)
Hypertension	1741 (27·4%)	3389 (77·6%)	2092 (52·3)	126 786 (30·5%)
Glucose, mmol/L	5·75 (1·28)	5·77 (1·22)	5·40 (1·32)	5·12 (1·24)
Creatinine, mg/dL	0·85 (0·22)	0·80 (0·20)	0·81 (0·20)	0·82 (0·21)
Cholesterol, mmol/L	5·39 (1·03)	5·49 (1·10)	5·42 (1·07)	5·69 (1·14)
Cholesterol HDL, mmol/L	1·44 (0·38)	1·50 (0·45)	1·34 (0·35)	1·31 (0·32)
Triglycerides, mmol/L	1·33 (0·94)	1·45 (0·80)	1·31 (0·85)	1·28 (0·57)
Aspartate aminotransferase, IU/L	25 (16)	26 (14)	24 (10)	26 (10)
Alanine aminotransferase, IU/L	26 (18)	21 (14)	24 (15)	24 (14)
Gamma-glutamyltransferase, IU/L	46 (79)	33 (40)	33 (34)	38 (42)
Bilirubin, µmol/L	12·0 (5)	9·4 (6·6)	10·9 (5·4)	9·1 (4·4)
Leucocytes, ×10⁹/L	6·6 (1·8)	7·1 (2·0)	N/A	6·9 (2·1)
Haemoglobin, g/dL	13·7 (2·00)	12·7 (0·74)	11·4 (1·83)	14·1 (1·25)
Platelets, ×1000/µL	245 (61·1)	267 (64·7)	238 (59·7)	253 (60·0)
Liver stiffness, kPa	5·9 (5·8)	5·3 (2·2)	4·9 (1·9)	NA
Ethnicity				
White‡	NA	NA	NA	392 086 (94·2%)

Data are n (%) or mean (SD). NA=not applicable. *Measured as more than 14 (sex-adjusted) standard units of alcohol per week. †Measured as a prevalent diabetes diagnosis at baseline. ‡Classified as White with British, Irish, or any other White background.

Table 1: **Baseline characteristics**

Prognostic evaluation

For the prognostic assessment of the models, we calculated the competing risks-adjusted (for non-liver-related events) cumulative incidence functions of liver-related outcomes (hospitalisation, cancer incidence, and death) as a function of four different risk categories (minimal-risk, low-risk, medium-risk, and high-risk) according to the LiverRisk score. ICD-10 codes that we used are shown in the appendix (p 4-6). We also used Cox regression models to estimate the hazard ratios (HRs) of different thresholds of the LiverRisk score. We did several subgroup analyses to assess the sensitivity of the scores with respect to different population characteristics. We did analyses for age groups, presence or absence of diabetes of any type, obesity, alcohol consumption patterns, sex, and ethnicity. We also assessed the association between the continuous LiverRisk score and liver-related and non-liver-related 10-year mortality and hospitalisations with generalised additive models. We also compared the performance of the LiverRisk score with that of the FIB4 and APRI scores. All analyses were done in R (version 4.1.2).

	≥6 kPa	≥10 kPa	≥15 kPa
Derivation cohort			
LiverRisk	0·71 (0·70–0·73)	0·88 (0·86–0·90)	0·95 (0·93–0·97)
FIB-4	0·60 (0·58–0·61)	0·75 (0·72–0·78)	0·85 (0·81–0·89)
APRI	0·63 (0·61–0·65)	0·79 (0·76–0·82)	0·87 (0·83–0·90)
Validation cohort 1 (Rotterdam)			
LiverRisk	0·65 (0·63–0·66)	0·77 (0·72–0·81)	0·82 (0·71–0·92)
FIB-4	0·59 (0·57–0·61)	0·67 (0·62–0·72)	0·73 (0·61–0·84)
APRI	0·60 (0·58–0·61)	0·71 (0·66–0·76)	0·80 (0·71–0·90)
Validation cohort 2 (LiverScreen)			
LiverRisk	0·68 (0·66–0·70)	0·83 (0·78–0·89)	0·83 (0·72–0·94)
FIB-4	0·53 (0·51–0·55)	0·68 (0·61–0·75)	0·78 (0·69–0·88)
APRI	0·59 (0·56–0·61)	0·73 (0·66–0·81)	0·84 (0·74- 0·93)

Data are area under the receiver operating characteristic curve (95% CI). FIB-4=fibrosis-4 index. APRI=aspartate aminotransferase to platelet ratio index.

Table 2: **Discriminatory accuracy of the LiverRisk, FIB-4, and APRI scores in the prediction of liver stiffness at different cutoff values**

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See **Online** for appendix

For more on the **LiverRisk score** see https://www.liverriskscore.com

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Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing, or the decision to submit the report.

Results
We included 14726 participants: 6357 (43·2%) in the derivation cohort, 4370 (29·7%) in the first external validation cohort, and 3999 (27·2%) in the second external validation cohort. The baseline characteristics of participants included in the three cohorts are shown in table 1. Participants from the three cohorts were similar, without imbalance in sex distribution, neither in metabolic factors such as BMI or presence of diabetes or arterial hypertension. Notably, prevalence of alcohol consumption, defined as consumption of more than 14 standard units of alcohol per week, was higher in the derivation cohort, compared with the two validation cohorts.

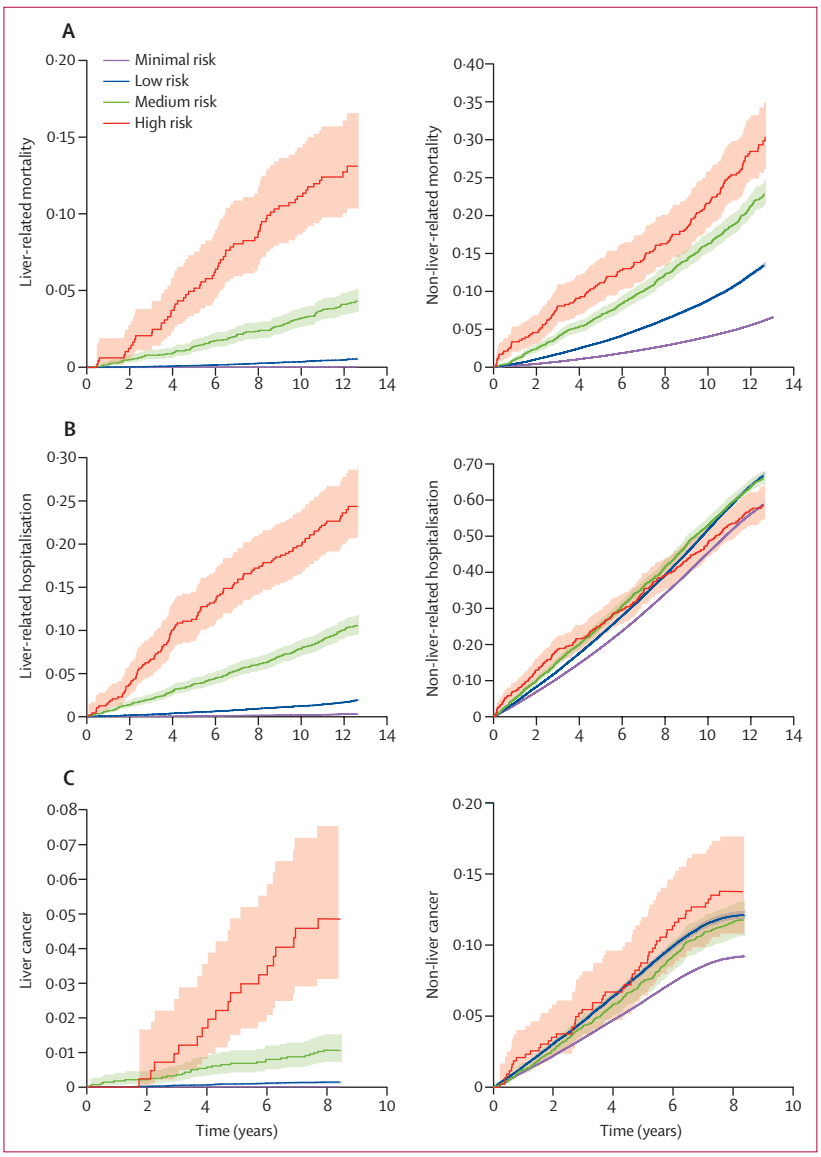

Figure 1: **Cumulative incidence of liver-related and-non-liver related events by LiverRisk score groups**
Cumulative probability of (A) liver-related and non-liver-related mortality, (B) liver-related and non-liver-related hospitalisation, and (C) liver cancer and non-liver cancer in 416 200 participants from the prognostic cohort categorised into risk groups according to LiverRisk score (minimal risk <6, low risk 6–10, medium risk >10–15, and high risk >15). Shaded areas represent 95% CIs.

In the derivation cohort, the four different models developed had very high accuracy in predicting liver stiffness either as continuous or categorical measurements using cutoff values of 6, 10, and 15 kPa (appendix pp 7, 11). Findings were highly consistent in the two validation cohorts, albeit accuracy was slightly lower compared with that of the derivation cohort (appendix p 8). Calibration results of the four models in the validation cohorts are shown in the appendix (pp 12–14). Out of the four models assessed, the linear regression model (LiverRisk score) was selected because of the better calibration and simpler model interpretation (appendix pp 12–14). Variables included in the LiverRisk score were age, sex, fasting glucose, cholesterol, AST, ALT, GGT, and platelet count. The accuracy of the LiverRisk score in predicting liver stiffness was superior to that of standard non-invasive fibrosis tests FIB-4 or APRI for the different cutoffs used (table 2).

We included 416 200 participants who met the inclusion criteria in the prognostic cohort (table 1). We excluded 3471 patients with a diagnosis of liver disease before enrolment, 541 with a diagnosis of viral hepatitis at baseline or at any point during follow-up, and 86 263 with incomplete laboratory variables. We calculated the LiverRisk score for each participant using their entry variables and analysed the score's association with liver-related mortality, first liver-related hospitalisation, and liver cancer during follow-up. During a median follow-up of 12·08 years (IQR 11·34–12·79), 28 627 (6·9%) of 416 200 participants died, of whom 596 (2·1% of all deaths) died because of liver disease.

We estimated the competing risks-adjusted cumulative incidence of liver-related mortality for four groups (minimal-risk, low-risk, medium-risk, and high-risk groups) according to selected cutoff values of LiverRisk score (6, 10, and 15; figure 1A). 359 713 (86·4%) participants were in the minimal-risk group, 52 845 (12·7%) in the low-risk group, 3157 (0·8%) in the medium-risk group, and 485 (0·1%) in the high-risk group. We found a strong association between LiverRisk score groups and the probability of liver-related death, with participants in the low-risk, medium-risk, and high-risk groups having a progressively higher probability of liver-related death at 12 years of follow-up compared with those in the minimal-risk group (figure 1A).

We found a progressive increase in HRs of liver-related mortality according to risk groups, with participants in the high-risk group having an HR of 471 (95% CI 347–641) for liver-related mortality compared with those in the minimal-risk group (figure 2A). The score was highly specific in predicting liver-related mortality, yet it was also associated with an increased HR of non-liver-related death, but the effect was lower compared with that of

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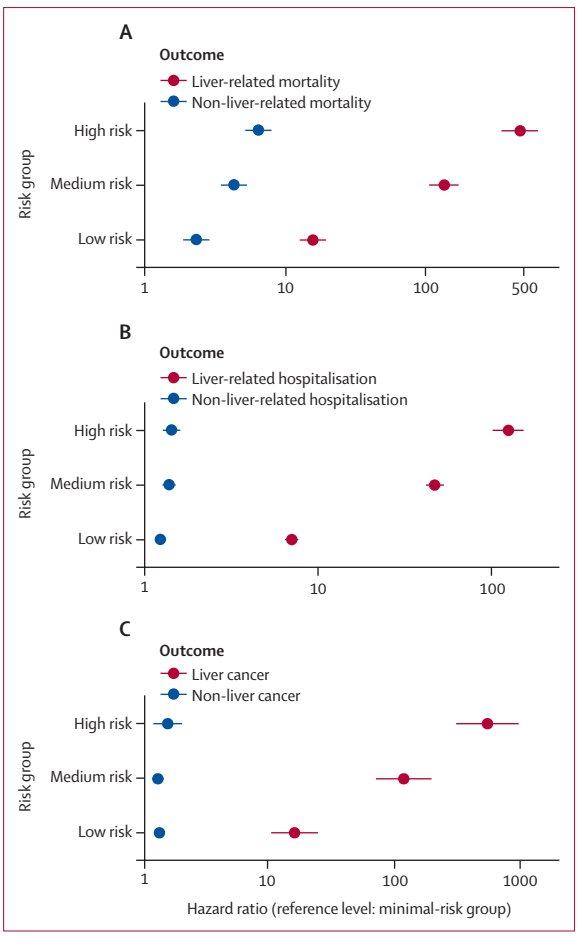

Figure 2: **Hazard ratios of liver-related and-non-liver related events by LiverRisk score groups**
Hazard ratios (Cox proportional hazards) competing risks results of liver-related and non-liver-related mortality (A), first liver-related and first non-liver related hospitalization (B), and liver cancer and non-liver cancer (C) in the 416 200 participants from the prognostic cohort categorised according to LiverRisk score (minimal risk <6, low risk 6–10, medium risk >10–15, and high-risk >15). Wings represent 95% CIs.

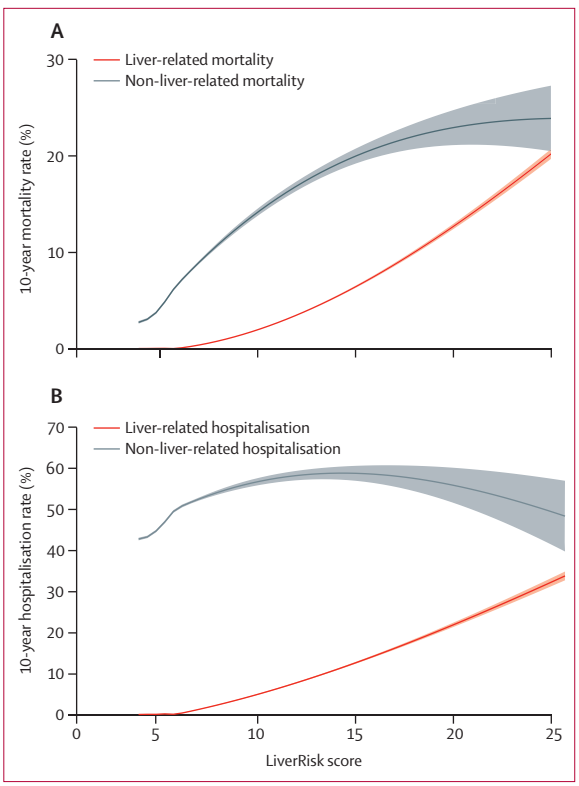

Figure 3: **10-year liver-related and non-liver related mortality and hospitalisation estimates as a function of LiverRisk score**
10-year mortality (A) and first hospitalisation (B) estimates as a function of LiverRisk score, GAM smoothed estimates.

liver-related death (HR 2·29 [2·23–2·36] comparing high-risk and minimal-risk groups).

10-year liver-related mortality estimates increased markedly after the LiverRisk score reached a value of approximately 10, whereas non-liver-related mortality increased initially and then plateaued at around a LiverRisk score of 20 (figure 3). The significance of the LiverRisk score in predicting liver-related mortality persisted across different subpopulations, such as age groups, alcohol consumption, diabetes status, sex, ethnicity, and obesity status (appendix pp 9, 15–20)

FIB-4 and APRI scores also predicted liver-related mortality in the cohort, but their accuracy was lower than that of the LiverRisk score (figure 4; appendix pp 20–21). The LiverRisk score also outperformed the fibrotic NASH index, a score that includes AST, HDL cholesterol, and HbA_{1c}, which has been reported to predict liver fibrosis in people with non-alcoholic fatty liver disease (appendix p 23).

During a median follow-up of 12 years, 2438 (0·6%) of 416 200 participants had at least one liver-related hospitalisation. LiverRisk score groups were associated with progressively increased risk of liver-related hospitalisation but not with risk of non-liver related hospitalisation (figure 1B). The HRs of liver-related hospitalisation were 47 (95% CI 42–53) in the medium-risk group and 126 (102–154) in the high-risk group compared with participants in the minimal-risk group (figure 2B). The significance of the LiverRisk score in predicting first liver-related hospitalisation persisted across different subpopulations categorised by age, alcohol consumption, diabetes status, sex, ethnicity, and obesity status (appendix pp 24–29).

The incidence of liver cancer was also associated with LiverRisk score groups. 182 (<0·1%) of 416 200 participants developed hepatocellular carcinoma during a median follow-up of 8·03 years (IQR 7·48–8·67), with participants in the high-risk group having a cumulative probability of 4·4% of developing liver cancer at 8 years of follow-up, whereas participants in the two lower-risk groups had a very small probability of incident liver cancer (minimal-risk group <0·1% and low-risk group 0·1%), and medium

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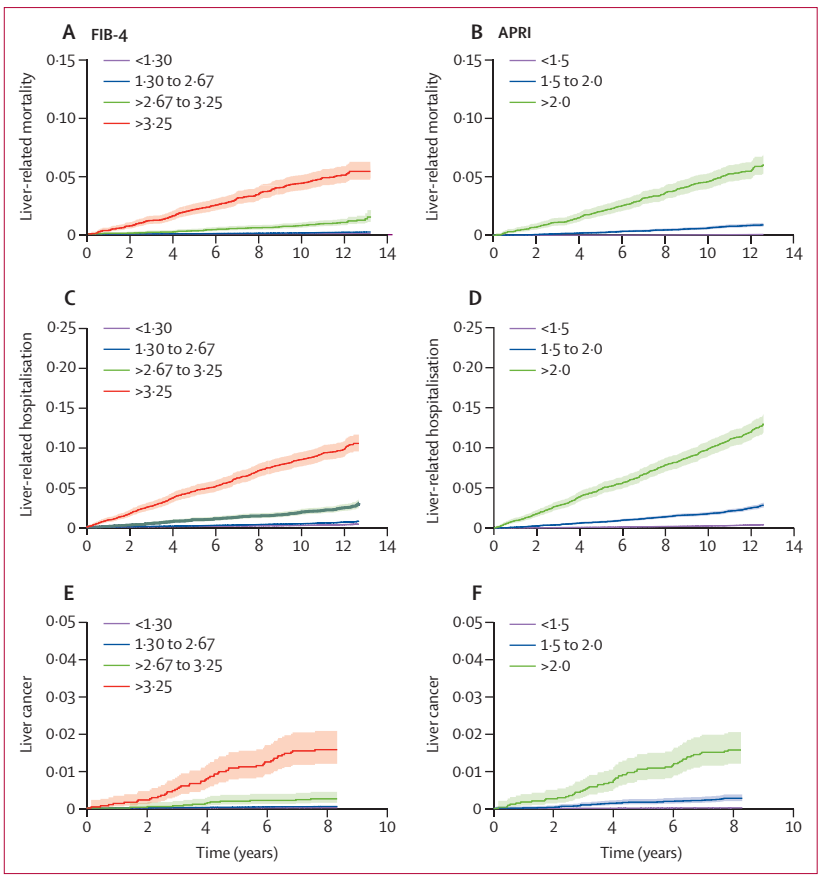

Figure 4: **Cumulative incidence of liver-related events as a function of FIB-4 and APRI**
Cumulative probability of liver-related mortality (A and B), liver-related hospitalisation (C and D), and liver cancer (E and F) in 416 200 participants from the prognostic cohort categorised according to FIB-4 (A, C, and E) and APRI scores (B, D, and F). FIB-4=fibrosis-4 index. APRI=aspartate aminotransferase to platelet ratio index.

For the **online calculator** see https://www.liverriskscore.com

risk 1·0% (figure 1C, 2C). FIB-4 and APRI also predicted liver-related hospitalisation and incident liver cancer in the cohort, but their accuracy was lower than that of the Liver Risk score (figure 4; appendix pp 9, 21).

Discussion

We report on a novel score, the LiverRisk score, which predicts the degree of liver stiffness and future liver-related outcomes in an adult general population without known liver disease. The LiverRisk score is composed of eight variables—age and sex as well as six laboratory variables (fasting glucose, cholesterol, AST, ALT, GGT, and platelet count), all of which are easily available in standard laboratory investigations worldwide—and can be calculated with an online calculator. The LiverRisk score is similar to scores widely used to assess risk profiles in chronic diseases, such as cardiovascular risk scores,[27] and appears to be quite specific for liver-related outcomes.

The proposed LiverRisk score is effective in identifying individuals at risk for liver-related mortality and liver-related hospitalisation as well as liver cancer and allows categorisation of individuals into four groups with markedly different risks of liver-related outcomes. As for liver-related mortality, very few participants from minimal-risk and low-risk groups died because of liver disease compared with 4·1% of participants in the medium-risk group, and 12·9% of those in the high-risk group. This finding corresponds to very high hazard ratios of liver-related mortality in the high-risk group and in the medium-risk group as compared with in the minimal-risk group.

The accuracy of the LiverRisk score in predicting long-term liver-related outcomes was better than that of FIB-4 or APRI scores. This finding is probably related to the fact that the FIB-4 and APRI scores were derived from smaller cohorts of patients with chronic hepatitis C with high prevalence of liver fibrosis,[5] whereas the LiverRisk score was derived from a larger, non-selected, population-based cohort with low prevalence of liver fibrosis, representative of the general population. The dependent variable used for the development of the LiverRisk score was liver stiffness assessed by transient elastography, a measurement that provides a good estimate of presence and severity of hepatic fibrosis.[5] The LiverRisk score was accurate for diagnosis of increased liver stiffness in the derivation cohort as well as in two independent validation cohorts, including more than 14 000 participants from the general population. Therefore, the prognostic value of the LiverRisk score is likely to be related to its capacity to identify liver fibrosis early. Evidence suggests that liver fibrosis is a strong predictor of liver-related complications and death, both in non-alcoholic fatty liver disease and alcohol-associated liver disease.[28,29] Of note and at variance with other studies assessing the value of some scores in the prediction of future clinical events in cohorts of people with non-alcoholic fatty liver disease,[30] our study was done in population-based cohorts of adults and therefore is not selective for any specific cause of liver disease.

The LiverRisk score reported here is applicable for general use in clinical practice worldwide because of its simplicity, use of laboratory variables that are readily available, and fairly low cost. The LiverRisk score could be used by general practitioners and nurses for opportunistic screening of liver fibrosis among patients seen in primary care with metabolic risk factors for chronic liver disease or chronic alcohol consumption. Such use might allow subsequent correction of causal factors, which might then prevent disease progression and improve prognosis. The LiverRisk score might also be applied as a tool for population screening by automatically embedding the score into standard laboratory analyses performed for periodic controls in patients with chronic conditions, in hospitals or health centres, or in regular health check-ups. Hence, further studies are needed to explore the use of LiverRisk score in population screening. The score can also be used for

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risk prediction in individuals and might be useful to empower individuals to change their lifestyle and behaviour to decrease the potential future risk of severe liver disease.[7,8] Finally, the LiverRisk sore can also be helpful to inform local policy makers and health authorities about liver disease risks in the population for which they are responsible.

This study has some limitations. First, the prognostic value of the LiverRisk score was assessed in a large cohort but assessment was retrospective by calculating the value of the score for each participant at entry into the cohort and then assessing liver-related hospitalisations and liver-related death during follow-up using ICD-10 codes. Although the cohort meets relevant standards of quality with respect to data collection, the prognostic value of the LiverRisk score should ideally be tested with prospective collection of data. However, since most participants included in the different cohorts were White, whether these findings apply similarly to all ethnic groups remains to be established.

In summary, we report the development and validation of the LiverRisk score that predicts future development of liver-related outcomes in the general population. The calculation of the LiverRisk score is based on simple demographic and laboratory parameters and can therefore be easily applicable to clinical practice in most countries. The LiverRisk score might be useful for predicting risk in individuals and help them to modify risk factors for liver disease as well as for screening for liver diseases at the population level. Future studies are needed to investigate the effect of the use of the LiverRisk score and document cost-effectiveness of screening, which might eventually help reduce the large burden of liver diseases in the world.

Contributors

MS-B and PG conceived the idea for the study with input from FS-B, AJ, MT, IG, EP, IGr, RJdK, LC, AK, FL, and PSK, and were responsible for the decision to submit the manuscript. MS-B designed the study, accessed and verified the data, developed the database, undertook statistical analyses and interpretation, and drafted and revised the manuscript. FS-B accessed and verified the data, developed the database, undertook statistical analyses, interpreted the data, and drafted and revised the manuscript. AJ, MT, IGr, EP, GP, IG, LC, SP, LaVK, MR, DR, JMP, JMS, and EAT acquired data, interpreted the data, and drafted and revised the manuscript. ING, MG-R, RH, JH, MF, CE, AM, PS, AM, SD, MT, AM, ATM, JP, EB, MJ, AS, MC, JG-G, RMM, PT, JMN, AT, CF, AL, AA, HJdK, FC, MM, PNN, RH, AMA, PA, RJdK, THK, PG, VW-SW, NF, LC, AK, FL, and PSK interpreted the data and contributed to manuscript drafting and revision. PG designed the study, accessed and verified the data, and drafted and revised the manuscript.

Declaration of interests

PN reports grants from Novo Nordisk and has received consulting fees from Novo Nordisk, Boehringer Ingelheim, Gilead, Intercept, Poxel Pharmaceuticals, Bristol Myers Squibb (BMS), Pfizer, Sun Pharma, Madrigal and GSK. He also reports honoraria as a speaker for Novo Nordisk and AiCME; upport for attending meetings from for Novo Nordisk; and participation on an advisory board for Novo Nordisk, Boehringer Ingelheim, Gilead, Intercept, Poxel Pharmaceuticals, BMS, Pfizer, Sun Pharma, Madrigal, and GSK. AK reports grants from EU Horizon 2020, Novo Nordisk Foundation, Danish National Research Foundation, Region of Southern Denmark; royalties or licenses from Gyldendal; has served as speaker for Norgine, Siemens and Nordic Bioscience; patents from Region of Southern Denmark and University of Southern Denmark; has participated in advisory boards for Norgine and Siemens; has been Vice Secretary European Association for the Study of The Liver (EASL); and received other services from Norgine, Siemens and Echosens. LC has served as speaker for Echosens and Nordic Bioscience; and received consulting fees from Echosens, Madrigal, MSD, Novo Nordisk, Pfizer and Sagimet. LaC reports a grant from Gilead, has received consulting fees from Echosens, Madrigal, MSD, Novo Nordisk, Pfizer and Sagimet; and payment as a speaker for Echosens and Novo Nordisk. AMA reports a grant from Novo Nordisk, Pfizer, and Target Pharma; and has received consulting fees from Novo Nordisk. RJdK reports a grant from GSK, Gilead, Janssen, Inventiva, and Echosens; has served as speaker for Abbvie, Gilead, and Echosens; and has received consulting fees from Abbvie and Gilead. NF has received consulting fees from Gilead. PGa has served as speaker for Bayer, Adaptimmune, Sirtex, Lilly, Roche and Ipsen; and received consulting fees from Bayer, Boston Scientific, AstraZeneca, Adaptimmune, BMS, Eisai, MSD, Sirtex, Lilly, Roche, Guerbet, and Ipsen. IGr participated in advisory boards for GE healthcare; and has served as speaker for Roche and Siemens. ING reports a grant from Gilead. RuH served as speaker for the American Gastroenterological Association and was a manuscript reviewer for *GUT*; reports support for lectures at the University of Navarra, Pamplona, Spain; and was an external advisor for LiverHope 2020. He also participated in the Steering committee of AASLD-ACLF Special interest Group and Practice Guidelines Committee of AGA. PK reports a grant from Sequana; royalty for UpToDate; honorarium as an Associate Editor for *Gastroenterology*; and support for attending meeting of EASL and INASL. TK served as speaker for Gilead; has received consulting fees from Albireo and MSD; was a board member at Biomed Alliance; and reports a relationship of stock or stock option with Ultimovacs. JMP reports grants from the European Commission (EFPIA IMI2 853966-2 ISCIII PI19/01898, EFPIA IMI2 777377 ISCIII PI22/01770, and H2020 847989) and Ajuntament de Barcelona-Fundació La Caixa; served as speaker for Novartis, Novo Nordisk, and FLS; and received consulting fees from Boehringer-Ingelheim, MSD, and Novo Nordisk. He also received support from Rubió and NovoNordisk. SP reports a grant from the European Association for the Study of the Liver and the Italian Ministry of Health; received consulting fees from Protein Plasma Therapeutics Assocation and Resolution Therapeutics; and served as speaker for Grifols. 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DR received honoraria as speaker from Gilead and Abbvie; and received support for meetings and travel from Gilead and AbbVie. PG has received research funding from Gilead, Mallinckrodt, Grifols, and Ferring. PG has consulted or attended advisory boards for Grifols SA, Ferring Pharmaceuticals, Gilead, Intercept, Martin Pharmaceuticals, Promethera, Sequana, RallyBio, SeaBeLife Merck Sharp and Dohme (MSD), and Behring; and received speaking fees from Pfizer. RMM has received honoraria as speaker from

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Data sharing

Data from this manuscript can be requested by qualified researchers. Before the use of the data, proposals need to be approved by all partners of the LiverScreen Consortium and a data sharing agreement will need to be signed. Approval will depend on the scientific value of the proposal, compatibility with the original patient consent, and data protection legislation.

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