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Improved prediction of 10-year risk of severe liver disease in the general population using commonly available biomarkers

Hannes Hagström[1,2] | Jacinth Yan[3] | Mats Talbäck[4] | Anna Andreasson[5,6] | Göran Walldius[4] | Matteo Bottai[3] | Niklas Hammar[4]

[1]Division of Hepatology, Department of Upper GI, Karolinska University Hospital, Stockholm, Sweden

[2]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

[3]Division of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[4]Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[5]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

[6]Department of Psychology, Stress Research Institute, Stockholm University, Stockholm, Sweden

Correspondence
Hannes Hagström, C1:77, Division of Hepatology, Karolinska University Hospital, 141 86 Stockholm, Sweden.
Email: hannes.hagstrom@ki.se

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Summary

Background: Estimating the risk for cirrhosis in the general population is complex. Existing prediction tools are in general unsatisfactory.

Aims: To explore if using commonly available biomarkers can improve the commonly used FIB-4 score in the identification of subgroups at risk of cirrhosis.

Methods: We used laboratory and clinical data on 126,925 individuals aged 35–79 years in Stockholm, Sweden, undergoing health examinations from 1985 to 1996. We used Swedish nationwide registries to ascertain 10-year cumulative incidence of severe liver disease, a composite of diagnoses corresponding to cirrhosis and its complications. We considered combinations of biomarkers associated with severe liver disease to identify subgroups with different risk profiles.

Results: During an average follow-up of 9.3 years, we ascertained 630 incident cases of severe liver disease (0.5%). Age, the FIB-4 score, diabetes or impaired glucose and gamma-glutamyl transferase (gGT) were the most relevant characteristics for classifying risk profiles. Using these factors, we identified 24 groups with a cumulative incidence of severe liver disease at 10 years ranging from 0.2% (age 35–65, low FIB-4, no diabetes or impaired glucose and normal gGT) to 32.1% (age 35–65, high FIB-4, diabetes or impaired glucose and high gGT).

Conclusions: Identification of subjects at increased risk of severe liver disease in the general population using the FIB-4 score can be substantially improved by adding age and specific biomarkers commonly available in the primary care setting. These parameters should be considered for inclusion in the development of future risk prediction models.

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1 | INTRODUCTION

Chronic liver disease is a common cause of morbidity and early mortality, especially in people of working age.[1,2] The panorama of chronic liver disease varies globally, but in many countries the most common liver disease is non-alcoholic fatty liver disease (NAFLD), with an estimated prevalence of 25% globally.[3,4] However, the most common cause of liver *cirrhosis* is alcohol-related liver disease (ALD).[1,5,6] The rate of progression of chronic liver disease varies considerably between individuals, likely affected by both genetic and environmental exposures. The majority of individuals with chronic liver diseases such as NAFLD do not progress to cirrhosis, but rather die from competing causes, such as cardiovascular disease.[7,8] Hence, prediction of clinically relevant liver-related outcomes is important but has proven to be challenging. Non-invasive scores based on simple biomarkers are recommended as a first-line test in primary care to exclude the presence of advanced hepatic fibrosis. We previously showed that these scores could identify some patients who experience liver cirrhosis due to presumed NAFLD, but that these were unsatisfactory because of their low sensitivity and specificity.[9] Some reasons include the following: the scores were designed to be diagnostic tools, not prediction models; the scores were derived from populations with a high proportion of the outcome in question that does not reflect the proportion in primary care where such scores are mostly needed; and small sample sizes increased the risk for model overfitting.[10] There may also be in-person variability of many of the parameters included, as well as technical limitations with inter-lab variability. An additional problem in the field is the separation between NAFLD and ALD. While the diagnosis of NAFLD requires the absence of more than moderate alcohol consumption,[11] these two conditions often coexist.[12,13]

Despite the high prevalence of chronic liver disease, the low rate of outcomes such as decompensated cirrhosis means that large cohorts with adequate follow-up time are vital to construct any prediction tool.

We here used data from a cohort with available liver biochemistry data from the general population with extensive follow-up data. We aimed to explore if parameters commonly available in the primary care setting can be used to improve currently established tools for identification of risk groups with different risk of clinically meaningful liver-related outcomes. Identification of such parameters could then be used in the future development of new or updated current, clinical prediction models.

2 | MATERIALS AND METHODS

2.1 | Study population

We used data from the Swedish Apolipoprotein Mortality Risk (AMORIS) cohort, a general population cohort that underwent clinical examinations with blood sampling between 1985 and 1996.[14] The cohort consists of 812,073 individuals who were either taking part in yearly routine health check-ups through occupational health screening or outpatients in primary or secondary care referred for laboratory testing. No individuals were inpatients at the time of blood sampling. All individuals of the AMORIS cohort were residents of Sweden and predominantly living in Stockholm County (67%) at the time of the blood sampling. During the baseline period (1985–1996), the total population of Stockholm County was about 1.6 million inhabitants. Thus, the AMORIS cohort constituted a large part (about 35%) of the total population of Stockholm County during this time. The AMORIS cohort is presented in greater detail elsewhere,[14] as are our findings from the analysis on currently used non-invasive scores.[9,15]

We excluded study subjects with diagnoses of chronic liver diseases, or diagnoses of drug- or alcohol use disorders, at or before baseline. The ICD codes used to define such diagnoses are listed in Table S1. We also excluded patients with no data on standard liver biochemistry (AST and ALT). Study baseline was defined as the earliest available timepoint where all predictors required to develop the classification were available. Patients who were diagnosed with chronic liver diseases other than NAFLD or the outcome in question (defined below), or drug- or alcohol use disorders, during follow-up were censored. We further censored subjects who emigrated from Sweden, died of causes other than the outcome in question or remained alive without an outcome 10 years after study baseline.

2.2 | Variables at baseline

Information on all biomarkers was derived from the baseline health examinations in 1985–1996. All analyses were conducted on fresh blood serum samples (53% after overnight fasting) at CALAB Medical Laboratories, Stockholm, Sweden using a uniform methodology, described in the Appendix.

2.3 | Variable selection

To select variables for the risk classification, we took a pragmatic approach. Given the large size of the AMORIS cohort and adequate follow-up time for liver-related events to occur, we could derive cumulative incidence of liver-related events across a wide range of subgroups. This approach enabled identification of high-risk subpopulations requiring further evaluation in clinical practice, such as referral to a hepatologist or more advanced non-invasive tests such as elastography.[16]

We balanced the inclusion of parameters based on their availability in primary care, cost, the individual association of the parameters with severe liver disease at 10 years, as presented in Table 2 and when assessed graphically in combination with other parameters, and availability in the AMORIS cohort.

As previously reported,[9] 10-year cumulative incidence of severe liver disease was particularly high in patients with a high FIB-4 in the AMORIS cohort (7.3%), corresponding to an incidence

rate ratio of 27.8 (95% CI: 22.8–34.0) compared to persons with low FIB-4. However, 92.7% of the persons with a high FIB-4 did not develop severe liver disease within 10 years. Considering this known association between the FIB-4 score and liver-related outcomes,[9] its widespread use in the hepatology community, and a finding that platelets strongly correlated with incident severe liver disease, we chose to use the FIB-4 score as a point of departure for further exploration of variables that could be of additional value in the identification of subjects at increased risk of severe liver disease.

It may be difficult to predict events far in the future for instance due to changes in risk factors (e.g. alcohol consumption and development of obesity), and occurrence of competing risks such as cardiovascular events. Further, patients and healthcare providers are more interested in events likely to occur in the more near future. For these reasons, we focused on 10-year cumulative incidence of liver-related events.

We categorised the selected variables with current, widely accepted clinical cut-off values. For the FIB-4 score, however, we used the three established categories (low, intermediate and high risk for advanced liver fibrosis).[17] This categorisation may simplify making clinical decisions.

Information on the association between each variable and 10-year cumulative incidence of severe liver disease was investigated by visual inspection of the number of events per category in combination with other variables. For instance, we investigated the cumulative incidence of severe liver disease at 10 years for the combination of a high FIB-4 and high age, sex, high triglycerides, high gamma-GT and then added data on impaired glucose. Variables that did not meaningfully affect the cumulative incidence were dropped from the final classification, although this was not formally assessed. The included variables and their cut-offs included age (35–65, or 66–79); diabetes or impaired glucose (defined as a fasting glucose above 6.0 mmol/L or non-fasting glucose above 7.8 mmol/L, or a known diagnosis of type 1 or 2 diabetes recorded in AMORIS through linkage with national registers); elevated gamma-glutamyl transferase (gGT, above 2.0 μkat/L) and FIB-4. We used the age-specific cut-offs proposed by McPherson et al to define subgroups of the FIB-4 score.[18] Low risk was defined as ≤1.3 in patients below 65 years, and ≤2.0 in patients aged 65 or older. Intermediate risk was defined as >1.3 in patients below 65 years, and >2.0 in those 65 or older. High risk was defined as >2.67 for all patients. We also stratified subgroups on sex to investigate if rates of severe liver disease meaningfully differed between men and women.

2.4 | Follow-up

All residents of Sweden have a 10-digit personal identification number that generally does not change with time. This is used in all healthcare contacts and in cross-linkage of data from all national registers. To ascertain outcomes, linkage to nationwide Swedish registers using the personal identification number was performed on hospitalizations, specialised outpatient care (available since 2001), incident cancers and causes of death, from the laboratory test up to a maximum of 10 years of follow-up or an event within 10 years. A description of the registers is available in the Appendix. The overall quality of the registers is considered high, with positive predictive values of >85% for most diagnoses, and >90% for diagnoses related to cirrhosis, except for ascites that frequently occur in non-hepatic disease.[19–22]

2.5 | Primary and secondary outcomes

Our primary outcome was severe liver disease (SLD). This was defined as a composite variable, consisting of diagnoses based on ICD codes corresponding to either compensated or decompensated cirrhosis, hepatocellular carcinoma (HCC) or death from any of these. The use of this definition is in line with a recent expert panel consensus statement.[23] Decompensated liver disease, in turn, was defined as coding for oesophageal varices, hepatorenal syndrome or hepatic encephalopathy. The definitions of these ICD codes are listed in Table S2. Importantly, in contrast to our previous definition of SLD,[9,15] we added diagnosis of alcohol-related cirrhosis (ICD-10: K70.3, ICD-9: 571.2) to the composite outcome. This was done as alcohol consumption is often difficult to estimate in a clinical situation, with studies reporting that 10%–28% of patients with presumed NAFLD might have a high alcohol consumption,[24,25] and because of the additive effect of high alcohol consumption and NAFLD on the risk of development of cirrhosis.[26] Thus, this outcome might better reflect the common scenario in clinical practice where a high alcohol consumption is co-existing with NAFLD. This might be difficult to quantify but an estimation of risk for both alcohol-related and non-alcohol-related cirrhosis is desired. In contrast, our secondary outcome further censored patients with coding for alcohol-related cirrhosis. This approach might better reflect events of cirrhosis that are more likely to be caused by NAFLD. Finally, we specifically examined the 10-year cumulative incidence of the main components of the composite outcome: compensated cirrhosis; decompensated cirrhosis and hepatocellular carcinoma (definitions in Table S2).

2.6 | Statistical analysis

We summarised the features of the variables by showing median and interquartile range for continuous and frequencies and proportions for categorical variables. We calculated the number of people at risk, number of events over the follow-up and cumulative incidence at 10 years to show a picture of overall onset of severe liver disease during follow-up. We also obtained the yearly incidence rate of developing liver disease. The incidence rates between groups were compared by incidence rate ratios with 95% confidence intervals.

To explore to what extent the predictive ability of a FIB-4 score may be improved we selected the three most relevant variables to

jointly create a composite profile of future liver disease risk. The liver disease risk conditional on each composite profile was assessed by the number of people at risk and cumulative incidence rates (with 95% confidence intervals [CI]) in every subgroup to identify subpopulations at a relatively high risk of developing severe liver disease. The risk profile was then coded with different colours and displayed to create a visualisation of the different risk profiles for the subgroups. All analyses were performed in Stata version 17.0 (StataCorp).

2.7 | Ethical considerations

The study was approved by the Regional Ethics Committee in Stockholm (Dnr 2010/1:7).

3 | RESULTS

In total, 126,925 persons from the AMORIS cohort with available FIB-4 data were available for inclusion. Table 1 describes the baseline characteristics of this population. During a follow-up of a mean of 9.3 years, we ascertained 630 incident cases of severe liver disease (0.5%). The 10-year risk of severe liver disease varied considerably between subgroups of biochemical and clinical variables. For instance, the cumulative incidence of severe liver disease at 10 years was 0.42% for those with a normal glucose, while it was 1.58% for persons with impaired glucose. Similarly, the cumulative incidence was 0.36% for persons with normal gGT, compared with 4.97% for persons with an elevated gGT. Other variables did not meaningfully discriminate between categories of risk. For instance, the cumulative incidence of severe liver disease for those with an AST/ALT ratio of <0.8 was 0.47% compared to 0.53% for those with a ratio of more than 1.0. Numbers of outcomes at 10 years, incidence rates and incidence rate ratios for increased versus normal variables are reported in Table 2.

When combining variables, a clear differentiation of risk was found. For instance, 10-year cumulative incidence of severe liver disease within the high FIB-4 subgroup differed from 2.5% to 32.1% depending on other characteristics. Based on four simple variables (FIB-4, gGT, age and glucose) 24 different subgroups were created, with 10-year cumulative incidence of severe liver disease ranging from 0.0% to 32.1%. Many of the identified subgroups were small, with number of exposed individuals less than 100. The cumulative incidence of severe liver disease at 10 years for this combination of variables together with their 95% confidence intervals is presented in Table 3. This information was further used to design a risk heat map (Figure 1), visualising the differences in risk based on these variables.

3.1 | Subgroup analyses

The risk for liver cirrhosis might differ between men and women. Therefore, we repeated the analysis for men and women, separately.

TABLE 1 Baseline characteristics of the cohort

	N with data	Median (IQR) or *N* (%)
Descriptive characteristics at baseline		
Age, years (median, IQR)	126,925 (100%)	52 (43–62)
Sex, male (*n*, %)	126,925 (100%)	56,038 (44.2%)
FIB-4 score (median, IQR)	126,925 (100%)	0.86 (0.64–1.19)
FIB-4 low (*n*, %)	112,405	112,405 (88.6%)
FIB-4 intermediate (*n*, %)	12,773	12,773 (10.1%)
FIB-4 high (*n*, %)	1747	1747 (1.4%)
AST (μkat/L, median, IQR)	126,925 (100%)	0.34 (0.28–0.42)
ALT (μkat/L, median, IQR)	126,925 (100%)	0.36 (0.26–0.52)
gGT (μkat/L, median, IQR)	124,437 (98.0%)	0.34 (0.23–0.54)
Glucose (mmol/L, median, IQR)	119,851 (94.4%)	4.90 (4.50–5.40)
Impaired glucose (*n*, %)	119,851 (94.4%)	8508 (6.7%)
Platelets (10^9/L, median, IQR)	126,925 (100%)	258 (219–301)
Cholesterol, mmol/L (median, IQR)	119,286 (94.0%)	5.70 (5.00–6.50)
Triglycerides, mmol/L (median, IQR)	119,099 (93.8%)	1.10 (0.80–1.70)
Mean follow-up (years)	126,925 (100%)	9.25
Person-years at risk	126,925 (100%)	1,174,024

Abbreviations: ALT, alanine aminotransferase; AST, asparate aminotransferase; gGT, gamma-glutamyltransferase; IQR, interquartile range.

However, no meaningful gender differences of risk were found (Table S3).

When we restricted the outcome to exclude patients with alcohol-related cirrhosis, the cumulative incidence of severe liver disease at 10 years was generally lower. However, the findings were similar in relation to the primary analysis. The cumulative incidence of severe liver disease using this definition is presented in Table S4.

The cumulative incidence of compensated cirrhosis; decompensated cirrhosis and HCC all followed the same pattern as the main analysis, with a clear differentiation of risk across the examined subgroups although with differing cumulative incidence. The estimates of the cumulative incidence and the corresponding "heat-maps" are presented in Tables S5–S7 and Figures S1–S3.

4 | DISCUSSION

We found that it is possible to improve on the commonly used FIB-4 score by adding biomarkers commonly available in the primary care setting to identify subjects at increased risk of severe liver disease within 10 years. Subgroups of patients with distinct risk profiles were identified, with risk estimates ranging from 0.0% to 32.1%. Most subgroups with a clinically relevant high risk were small. Only 1.3% of

TABLE 2 Outcomes at 10 years follow-up separate for the investigated predictors

Subgroup	*N* in subgroup	N outcomes at 10 years (cumulative)	Cumulative incidence (%)	CIRR	Incidence rate/1000 PY (with 95% CI)	IRR (95% CI)
FIB-4						
Low	112,405	391	0.35%	1.0 (ref)	0.37 (0.34–0.41)	1.0 (ref)
Intermediate	12,773	111	0.87%	2.5	0.97 (0.81–1.17)	2.60 (2.11–3.21)
High	1747	128	7.33%	21.1	10.38 (8.73–12.35)	27.82 (22.79–33.96)
Impaired glucose						
No	111,343	455	0.41%	1.0 (ref)	0.44 (0.40–0.48)	1.0 (ref)
Yes	8508	117	1.38%	3.4	1.59 (1.33–1.91)	3.64 (2.97–4.46)
gGT						
Normal	120,919	436	0.36%	1.0 (ref)	0.39 (0.35–0.43)	1.0 (ref)
High	3518	175	4.97%	13.8	6.42 (5.54–7.45)	16.57 (13.90–19.75)
Age						
35–65	103,611	437	0.42%	1.0 (ref)	0.45 (0.41–0.49)	1.0 (ref)
≥66	23,314	193	0.83%	2.0	0.99 (0.86–1.14)	2.22 (1.87–2.63)
Sex						
Female	70,887	304	0.43%	1.0 (ref)	0.46 (0.41–0.51)	1.0 (ref)
Male	56,038	326	0.58%	1.4	0.64 (0.58–0.71)	1.40 (1.20–1.64)
AST						
Normal	121,178	422	0.35%	1.0 (ref)	0.37 (0.34–0.41)	1.0 (ref)
High	5747	208	3.62%	10.4	4.42 (3.86–5.06)	11.81 (10.00–13.94)
ALT						
Normal	118,499	462	0.39%	1.0 (ref)	0.42 (0.38–0.46)	1.0 (ref)
High	8426	168	1.99%	5.1	2.26 (1.94–2.64)	5.38 (4.51–6.42)
AST/ALT ratio						
<0.8	47,521	224	0.47%	1.0 (ref)	0.50 (0.44–0.58)	1.0 (ref)
0.8–0.99	29,279	139	0.47%	1.0	0.51 (0.43–0.60)	1.01 (0.82–1.25)
≥1.0	50,125	267	0.53%	1.1	0.58 (0.52–0.66)	1.15 (0.96–1.37)
Triglycerides						
Normal	91,154	390	0,43%	1.0 (ref)	0.46 (0.41–0.51)	1.0 (ref)
High	27,945	179	0,64%	1,5	0.70 (0.61–0.81)	1.53 (1.28–1.83)
Total cholesterol						
Normal	110,274	532	0,48%	1.0 (ref)	0.52 (0.48–0.57)	1.0 (ref)
High	9012	38	0,42%	0,9	0.46 (0.33–0.63)	0.88 (0.63–1.22)

Note: See "methods" text for definitions of normal/high categories.

Abbreviations: ALT, alanine aminotransferase; AST, asparate aminotransferase; CI, confidence interval; CIRR, cumulative incidence rate ratio; gGT, gamma-glutamyltransferase; IQR, interquartile range; IRR, incidence rate ratio.

persons in this cohort were classified as having a 10-year risk of severe liver disease above 5%. Although 5% is an arbitrary figure, this suggests that using such a classification in primary care would not lead to over-referral due to many false positive cases. Importantly, we found that the risk for severe liver disease varies considerably within categories of the FIB-4 score. For instance, the 10-year cumulative incidence of severe liver disease was only 2.5% for persons with high FIB-4 that were above 65 years old, had a normal glucose and normal gamma-GT. In contrast, we found that some patients with a low or intermediate FIB-4 score had a high cumulative incidence of severe liver disease at 10 years. For instance, patients with a low FIB-4 but aged above 65 years, with high gGT and impaired glucose had a 10-year risk of 13%. To better define which risk cut-off that should be used, further evaluations should be performed.

Collectively, this implies that our results could be a starting point for the development of better risk prediction tools in the general population, or a formal re-calibration of the FIB-4 score to serve as a risk prediction model. The findings could also inform models of care, where a first-line test in the general population, such as the FIB-4, is generally recommended.[27] Our findings make it clear that it is possible to improve the FIB-4 score, thus hopefully saving healthcare resources and increasing case-finding of patients at risk for severe

TABLE 3 Numbers of exposed per subgroup, cumulative incidence of severe liver disease at 10 years of follow-up together with 95% confidence intervals

			Impaired glucose			No impaired glucose		
			N exposed	*N* outcome	Cumulative incidence (%)	*N* exposed	*N* outcome	Cumulative incidence (%)
Cumulative incidence (%) of severe liver disease at 10 years								
gGT high	Age 66–79	FIB-4 High	33	6	29.10 (13.78–54.94)	92	10	22.69 (12.00–40.45)
		FIB-4 Intermediate	27	2	13.73 (3.55–45.32)	57	0	0
		FIB-4 Low	66	5	12.99 (5.52–28.91)	249	6	3.55 (1.58–7.86)
gGT normal	Age 66–79	FIB-4 High	88	8	12.45 (6.26–23.92)	650	12	2.53 (1.43–4.46)
		FIB-4 Intermediate	184	4	2.77 (1.02–7.41)	1840	10	0.67 (0.36–1.25)
		FIB-4 Low	1993	21	1.32 (0.86–2.03)	15,554	83	0.61 (0.49–0.75)
gGT high	Age 35–65	FIB-4 High	68	14	32.05 (19.47–49.80)	242	45	25.41 (19.44–32.80)
		FIB-4 Intermediate	150	13	10.66 (6.28–17.80)	505	27	7.41 (5.13–10.65)
		FIB-4 Low	283	6	2.62 (1.18–5.76)	1409	27	2.20 (1.51–3.19)
gGT normal	Age 35–65	FIB-4 High	54	3	6.00 (1.97–17.53)	346	16	5.53 (3.42–8.88)
		FIB-4 Intermediate	680	6	1.03 (0.46–2.27)	8523	32	0.40 (0.28–0.57)
		FIB-4 Low	4734	28	0.64 (0.44–0.93)	81,085	183	0.24 (0.21–0.28)

Abbreviations: CI, confidence interval; gGT, gamma-glutamyltransferase; IQR, interquartile range.

FIGURE 1 Heat map of 10-year cumulative incidence of severe liver disease using the four selected predictors. gGT, gamma-glutamyltransferase. *Group contained 57 persons and no events

			FIB-4 Low	FIB-4 Intermediate	FIB-4 High
gGT high	Impaired glucose	age ≥66	12.99	13.73	29.10
		age 35-65	2.62	10.66	32.05
	No Impaired glucose	age ≥66	3.55	0.00*	22.69
		age 35-65	2.20	7.41	25.41
gGT normal	Impaired glucose	age ≥66	1.32	2.77	12.45
		age 35-65	0.64	1.03	6.00
	No Impaired glucose	age ≥66	0.61	0.67	2.53
		age 35-65	0.24	0.40	5.53

liver-related events. A formal development of future risk prediction models could consider use of the investigated parameters in this study.

We deliberately included alcohol-related cirrhosis as a possible endpoint in our composite outcome. This differs from our previous studies, the argument being that it is difficult to assess alcohol consumption and misclassification between NAFLD and ALD is common, and that patients with NAFLD-cirrhosis are in our clinical experience sometimes misclassified as having ALD-cirrhosis. Also, while separate diagnoses, these conditions often coexist and interact.[28,29] Excluding alcohol-related cirrhosis renders the population "immune" to this endpoint, which might lead to reduced clinical applicability of a risk-prediction system. However, we did exclude persons with obvious alcohol misuse at or before baseline, based on ICD-coding for alcohol-related liver disease without cirrhosis, or drug- or alcohol use disorders. Therefore, it is likely that the cohort is representative of persons in the general population with some degree of alcohol consumption but excludes the heaviest drinkers.

This is highlighted by that gGT was an important contributor to the classification system. Gamma-glutamyl transferase is a marker of several biological processes, but among others is affected by alcohol consumption, although the sensitivity and specificity for this is low.[30] In this study, it is likely that high levels of gamma-GT are associated with alcohol consumption for most patients, although some might have elevated levels due to factors such as cholestasis or be increased as a result of NAFLD. Nevertheless, our sensitivity analysis where alcohol-related cirrhosis was excluded produced similar results as the main analyses.

Age was also a relevant contributor to the classification of risk groups. It has previously been shown that FIB-4 performs poor in persons above 65, why we opted to use age-stratified cut-offs for the FIB-4 score.[18] Finally, impaired fasting glucose or a diagnosis of diabetes was included. Diabetes is a well-known risk factor for development of both NAFLD and cirrhosis.[31,32] However, many patients might not have a recorded diagnosis in specialised care, making it possible for us to identify such patients. Therefore, we selected

to also include glucose levels to capture those with an elevated fasting glucose, which might also capture those with prediabetes. This showed that patients with diabetes or elevated glucose had a higher risk of liver disease, supporting active evaluation of liver disease in this population.

The need for an improved risk prediction model for use in primary care is high. In our exploratory analyses, we used only data that is inexpensive and routinely available in primary care. Our findings suggest that an updated or new risk prediction model does not need to be expensive or use patented serum tests. There are few models of care implemented for patients with NAFLD, and most include the use of some versions of a non-invasive score such as FIB-4.[27] A more granular classification as exampled here could therefore be superior for use in future developments of models of care.

Strengths of the study include the large cohort, derived from a general population setting. This allows for a reduced risk for selection bias and high external validity. The biomarkers were determined based on fresh blood using a well-documented and consistently applied methodology from a single clinical laboratory. The use of validated, population-based registers minimises loss to follow-up and enables all outcomes to be captured to a high degree. Outcomes were selected to be captured with a very high probability by our methodology.[22]

Limitations include the historical setting of the cohort that might not be fully representative of today's society with a higher prevalence of obesity and NAFLD. We did not externally validate the findings, since this is not a study developing a new prediction model, rather we argue that these exploratory findings should be considered in future model development. In contrast to our previous examination of the predictive capacity of the FIB-4 score,[9] the definition of the composite outcome differs slightly in that we here included cases with ALD cirrhosis but did not include ascites as part of the composite outcome, since a recent validation study showed a low positive predictive value for this in a general population.[22]

The cohort was relatively homogenous regarding ethnicity with 85% being born in Sweden and results may not be generalizable to other countries with a different genetic composition. Data on alcohol biomarkers such as phosphatidyl ethanol, or questionnaire data, was not available. We did not have access to modern biomarkers, such as Pro-C3,[33] however such biomarkers are unlikely to be commonly available in a primary care setting, thereby limiting its usefulness. Another limitation is that we did not assess if changes in these risk groups over time, such as transitioning from one group to another, is further associated with risk for severe liver disease. This should be a topic for further studies. Finally, while the cohort is large, most of the subgroups with a high risk were small and estimates might be imprecise. For instance, there were only 57 persons in the subgroup with intermediate FIB-4, no impaired glucose, high gGT and age 66 or older. This small subgroup had no events, which is likely due to the small sample, and should be interpreted carefully although it likely matters little for the identification of the included parameters defining the subgroups.

5 | CONCLUSION

Using simple biomarkers routinely available in primary care, we found that risk classification for the estimation of 10-year probability of severe liver disease can be substantially improved on top of the established FIB-4 score. This information should be considered for inclusion in future risk prediction models.

AUTHORSHIP

Guarantor of article: HH and NH.

All authors approved the final version of the article, including the authorship list.

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AUTHOR CONTRIBUTIONS

Hannes Hagström: Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Jacinth Yan:** Formal analysis (lead); investigation (equal); visualization (lead); writing – review and editing (equal). **Mats Talbäck:** Data curation (lead); formal analysis (equal); investigation (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Anna Andreasson:** Methodology (equal); writing – review and editing (equal). **Göran Walldius:** Methodology (equal); writing – review and editing (equal). **Matteo Bottai:** Formal analysis (equal); methodology (lead); supervision (equal); writing – review and editing (equal). **Niklas Hammar:** Conceptualization (equal); funding acquisition (supporting); investigation (equal); methodology (equal); supervision (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

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ORCID

Hannes Hagström https://orcid.org/0000-0002-8474-1759
Jacinth Yan https://orcid.org/0000-0002-2217-6977
Anna Andreasson https://orcid.org/0000-0003-0203-7977

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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