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Evaluating clinical outcomes and prognosis in patients with cirrhosis and portal hypertension: a retrospective observational cohort study

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ABSTRACT

Objective Cirrhosis describes the end-stage of chronic liver disease. Irreversible changes in the liver cause portal hypertension, which can progress to serious complications and death. Only a few studies with small sample sizes have investigated the prognosis of cirrhosis with portal hypertension. We used electronic healthcare records to examine liver-related outcomes in patients with diagnosed/suspected portal hypertension.

Design This retrospective observational cohort study used secondary health data between 1 January 2017 and 3 December 2020 from the TriNetX Network, a federated electronic healthcare records platform. Three patient groups with cirrhosis and diagnosed/suspected portal hypertension were identified ('most severe', 'moderate severity' and 'least severe'). Outcomes studied individually and as a composite were variceal haemorrhage, hepatic encephalopathy, complications of ascites and recorded mortality up to 24 months.

Results There were 13 444, 23 299, and 23 836 patients in the most severe, moderate severity and least severe groups, respectively. Mean age was similar across groups; most participants were white. The most common individual outcomes at 24 months were variceal haemorrhage in the most severe group, recorded mortality and hepatic encephalopathy in the moderate severity group, and recorded mortality in the least severe group. Recorded mortality rate was similar across groups. For the composite outcome, cumulative incidence was 59% in the most severe group at 6 months. Alcohol-associated liver disease and metabolic-associated steatohepatitis were significantly associated with the composite outcome across groups.

Conclusion Our analysis of a large dataset from electronic healthcare records illustrates the poor prognosis of patients with diagnosed/suspected portal hypertension.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cirrhosis causes structural changes in the liver that can result in portal hypertension, which is associated with serious complications such as variceal haemorrhage. Data from small studies suggest that the mortality rate from variceal bleeding may remain high in patients with cirrhosis, despite the prevention and management of varices being a focal point of treatment.

WHAT THIS STUDY ADDS

⇒ Using a large dataset from the TriNetX Database, this retrospective study provides the most robust examination to date of liver-related outcomes in patients with cirrhosis and portal hypertension. At 24 months post-index, the occurrence of at least one of variceal haemorrhage, hepatic encephalopathy, complications of ascites or mortality was considerably more common in patients with (vs without) a documented history of gastro-oesophageal variceal bleeding. High rates of mortality (13–18%) were observed irrespective of variceal bleeding history.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data emphasise the considerable burden of cirrhosis with portal hypertension, despite the availability of modern treatment interventions and the importance of reducing the risk of variceal haemorrhage to improve clinical outcomes.

INTRODUCTION

Cirrhosis describes the end stage of chronic liver disease that is characterised by fibrosis and ultimately results in hepatic failure.[1] Cirrhosis may be compensated, implying a degree of preserved liver function, or decompensated, where the liver is unable to perform vital metabolic, synthetic and storage functions. This progressive condition can lead to significant morbidity, resource-intensive complications, hepatocellular carcinoma and, in the absence of liver transplantation, death. An analysis of the Global Burden of Disease Study 2017 reported over 1.32 million cirrhosis-related deaths globally, which was approximately 2.4% of all deaths worldwide.[2] The aetiology of cirrhosis is

varied; in 2017, the most common, global underlying causes include hepatitis B and C, alcohol-associated liver disease and metabolic-associated steatohepatitis (MASH, formerly referred to as non-alcoholic steatohepatitis), with the latter more commonly the underlying cause than hepatitis B in Latin America, high-income North America and Western Europe.[2] Other causes may be attributed to underlying liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis, haemochromatosis and Wilson's disease.[3]

In cirrhosis, portal hypertension is caused by structural changes in the liver that increase intrahepatic vascular resistance against portal venous flow.[4] Clinically significant portal hypertension, defined as hepatic venous pressure gradient ≥10 mm Hg, eventually leads to serious complications of cirrhosis, such as variceal haemorrhage, ascites, hepatic encephalopathy, portal hypertensive gastropathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary and portopulmonary syndrome, bacteraemia and hypersplenism.[5] In particular, variceal haemorrhage from ruptured gastro-oesophageal varices is most life-threatening. Hence, the treatment of cirrhosis is centred around the prevention and management of varices and variceal haemorrhage, according to the clinical stages of portal hypertension and cirrhosis.[6] Despite the mortality rate of patients with cirrhosis with variceal bleeding declining since the 1960s, the rate remains high, with a study of 178 patients conducted between 2007 and 2010 reporting a 6-week mortality rate of 16%.[7 8]

A limited number of studies with small sample sizes (<350 participants) have investigated the prognosis of cirrhosis with features of portal hypertension.[9–11] Although some development in prognostic markers has occurred,[12] a lack of studies with large datasets, in addition to the range of complications of portal hypertension and varying clinical presentations of the disease, makes designing interventional clinical trials and defining endpoints difficult.[13] There is as yet no regulatory precedence for a relevant composite endpoint in portal hypertension, although the most important endpoints include variceal haemorrhage, worsening or complications of ascites, hepatic encephalopathy and death.[14] In particular, the need for further research on the interactions of prognostic indicators with time of events in the bleeding episodes was highlighted during the Baveno V consensus workshop on portal hypertension.[15] In a 25-year prospective study, the first major clinical event was the development of ascites (33%), followed by variceal haemorrhage (10%), hepatocellular carcinoma (9%), encephalopathy (5%) and finally jaundice (3%) in 377 patients with compensated cirrhosis; however, the occurrence of portal hypertension was not reported.[16]

One way to address the lack of evidence from large patient cohorts relating to the outcomes and prognosis of patients with cirrhosis and portal hypertension is by developing and analysing retrospective datasets based on real-world evidence from healthcare databases. Our analysis used TriNetX, a federated electronic healthcare records platform, to examine liver-related outcomes and the association with other clinical characteristics in patients with diagnosed/suspected portal hypertension followed up to 24 months.

METHODS

Study design

This retrospective observational cohort study used secondary data from the TriNetX Network, a federated electronic healthcare records platform of de-identified health data from approximately 59 healthcare organisations worldwide (ie, 47 in the USA, 6 in the UK and 1 each in Australia, Brazil, Bulgaria, India, Malaysia and Taiwan), between 1 January 2017 and 3 December 2020.

Patient and public involvement

Analyses were based on data from large healthcare networks and there was no direct involvement of patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Patients

Three groups of patients with cirrhosis and diagnosed/suspected portal hypertension were identified, with each group mimicking potential entry criteria for an interventional clinical trial. These groups were given descriptive names ('most severe', 'moderate severity', and 'least severe') based on our preconceptions during study design. Inclusion criteria for each group were as follows: group 1 ('most severe') included patients diagnosed with cirrhosis and gastro-oesophageal varices who had a documented bleeding episode; group 2 ('moderate severity') included patients diagnosed with cirrhosis and gastro-oesophageal varices who had no prior recording of bleeding from oesophageal varices; group 3 ('least severe') included patients diagnosed with cirrhosis and portal hypertension without documented oesophageal varices. A diagnosis of portal hypertension was not required for inclusion in the most severe and moderate severity groups since the combination of a cirrhosis and varices diagnosis suggests portal hypertension is present. Patients ≥18 years of age at the index date (date of first diagnosis relevant to each group) with data available 6 months prior were included. Patients could be included in >1 group and would have different index dates representing different stages of their disease. Exclusion criteria were secondary causes of cirrhosis, including Budd-Chiari syndrome, biliary cirrhosis, granulomatous hepatitis, schistosomiasis, liver transplant, class C cirrhosis and hepatocellular carcinoma.

Patient characteristics and outcomes

Demographics (age, race, and ethnicity) and clinical characteristics prior to the index date (aetiology of portal hypertension, presence of comorbidities and antiviral use) were collected. Aetiology of portal hypertension was stratified by diagnostic code into several broad groups,

comprising MASH, alcohol-associated liver disease, autoimmune hepatitis, Wilson's disease, haemochromatosis, chronic viral hepatitis, primary sclerosing cholangitis and other causes.

Outcomes studied individually and as a composite were the first event of gastro-oesophageal varices with bleeding (ie, variceal haemorrhage), hepatic encephalopathy, complications of ascites (spontaneous bacterial peritonitis or hepatorenal syndrome) and recorded mortality for up to 24 months after the index date for each patient in each group.

All diagnostic codes used to define variables in this analysis are provided in online supplemental file 1. These comprise codes from the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), the Logical Observation Identifiers Names and Codes, and the Current Procedural Terminology codelists. Mapping between ICD-10 codes and the previous 9th Revision codes was performed automatically by the TriNetX platform.

Statistical analysis

All statistical analyses were performed using the TriNetX platform advanced analytics feature. The TriNetX platform is live and updates at least daily to reflect subtle changes in patients' data, and patient numbers can differ depending on the run date; therefore, a run date was allocated to each analysis. For any missing data, complete case analysis was used. Kaplan-Meier plots (redrawn using R) were used to describe cumulative incidence of outcomes from the index date in each disease severity group, and to compare aetiology strata within each group. Patients were censored at the occurrence of the relevant outcome, migration from the database, end of study period, 2 years after index date or death. Aetiology strata (ie, patients with a condition vs those without) within each group and the association with the composite outcome were also compared using log-rank tests and Cox proportional hazard models. For Cox proportional hazard models, the proportional hazards assumption was tested using the approach by Grambsch and Therneau[17]; the HR and associated 95% CIs and p values are presented.

RESULTS

Patients

On 17 May 2022, there were approximately 90 million patients in the TriNetX analytics Network. Approximately half a million patients had a diagnosis of cirrhosis in the study period, and approximately one-third of a million additionally met no exclusion criteria. A total of 13 444, 23 299 and 23 836 patients met the criteria for the most severe, moderate severity and least severe groups, respectively (online supplemental figure 1). The mean age at index date was similar between groups, ranging from 63 years of age in the most severe group to 64 years of age in the moderate severity and least severe groups (table 1). The percentage of females was slightly lower in the most severe group (36%) compared with the moderate severity and least severe groups (41% and 43%, respectively). Most participants were white and not Hispanic or Latino, with similar proportions of race and ethnicity across all severity groups (table 1).

The percentage of patients with a portal hypertension diagnosis prior to or at index date was 100% in the least severe group (in line with eligibility criteria), 73% in the most severe group and 58% in the moderate severity group (table 1). Across all severity groups, the most common aetiologies, excluding 'other' aetiologies, were alcohol-associated liver disease (most common in patients with variceal haemorrhage, that is, in the most severe group), chronic viral hepatitis and MASH. The most common comorbidities were type 2 diabetes, neoplasms and alcohol abuse; alcohol abuse was more common in the most severe group (39%) compared with the moderate severity and least severe groups (30% and 31%, respectively). Major depression (22% in the most severe group vs 28% in the least severe group) and heart failure (12% in the most severe group vs 22% in the least severe group) were less common in patients with more severe disease. The distribution of estimated glomerular filtration rate (eGFR) in each group is provided in figure 1; approximately 20–25% of patients had an eGFR <60 mL/min/1.73 m^2 in the previous 6 months, suggestive of chronic kidney disease.[18] Further patient characteristics in each group are presented in table 1 and online supplemental tables 1–3.

Outcomes

The most common individual outcome at 24 months was variceal haemorrhage in the most severe group, whereas recorded mortality and hepatic encephalopathy in the moderate severity group and recorded mortality in the least severe group were the most common (figure 2 and table 2). Of note, recorded mortality in the least severe group (18%) was similar to that of the moderate severity and most severe groups (13% and 18%, respectively), and hepatic encephalopathy was comparable in the least severe and the moderate severity groups (13% and 13%) (figure 2B and D and table 2). For the composite outcome at 6 months, cumulative incidence was 57% in the most severe group, 12% in the moderate severity group and 15% in the least severe group (figure 2A and table 2).

The association of recorded aetiology with the composite outcome in each disease group is given in online supplemental table 4 and Kaplan-Meier plots are shown in online supplemental figure 2, with key results highlighted here. Patients with alcohol-associated liver disease were often male, more likely to be younger and have recorded alcohol abuse (online supplemental tables 1–3), and had a higher incidence of the composite outcome than those without the disease (online supplemental table 4). Across severity groups, the HR (95% CI) was 1.23 (1.18 to 1.28) in the most severe group, 1.50 (1.42 to 1.59) in the moderate severity group and 1.47 (1.40 to 1.55) in the least severe group

Table 1 Patient demographics and clinical characteristics by severity group*

Demographic/clinical characteristic	Group 1 most severe (N=13 444)	Group 2 moderate severity (N=23 299)	Group 3 least severe (N=23 836)
Demographics			
Age, years, mean (SD)	63 (12)	64 (12)	64 (12)
Females, n (%)	4840 (36)	9552 (41)	10 249 (43)
Race, n (%)			
White	9545 (71)	16 309 (70)	17 162 (72)
Black or African American	941 (7)	2563 (11)	2622 (11)
Asian	269 (2)	466 (2)	477 (2)
American Native or Alaska Native	134 (1)	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Unknown	2554 (19)	3961 (17)	3575 (15)
Ethnicity, n (%)			
Not Hispanic or Latino	8604 (64)	15 377 (66)	16 447 (69)
Hispanic or Latino	2151 (16)	2796 (12)	3099 (13)
Unknown	2689 (20)	5126 (22)	4290 (18)
Clinical characteristics			
Portal hypertension, n (%)	9835 (73)	13 500 (58)	23 836 (100)
Aetiology, n (%)			
Other	6044 (45)	10 174 (44)	9976 (42)
Alcohol-associated liver disease	6646 (49)	8578 (37)	7675 (32)
Chronic viral hepatitis	3852 (29)	7180 (31)	6464 (27)
Metabolic-associated steatohepatitis	2018 (15)	3450 (15)	2931 (12)
Autoimmune hepatitis	413 (3)	770 (3)	729 (3)
Haemochromatosis	163 (1)	360 (2)	374 (2)
Primary sclerosing cholangitis	165 (1)	210 (1)	259 (1)
Wilson's disease	43 (0.003)	41 (0.002)	56 (0.002)
Comorbidities, n (%)			
Type 2 diabetes	5292 (39)	8984 (39)	9392 (39)
Neoplasms (all)	4689 (35)	8331 (36)	8398 (35)
Benign neoplasms	3384 (25)	6243 (27)	2744 (12)
Malignant neoplasms	2170 (16)	2659 (11)	3582 (15)
Alcohol abuse	5207 (39)	6965 (30)	7410 (31)
Major depression	3023 (22)	5746 (25)	6668 (28)
Ischaemic heart diseases	2411 (18)	3703 (16)	4696 (20)
Heart failure (all)	1587 (12)	3372 (14)	5198 (22)
Heart failure with preserved ejection fraction	1182 (9)	2095 (9)	3070 (13)
Stroke	921 (7)	1983 (9)	2585 (11)
Heart failure with reduced ejection fraction	351 (3)	907 (4)	1866 (8)
HIV	276 (2)	621 (3)	1115 (5)
Sarcopenia	50 (0.004)	32 (0.001)	50 (0.002)
Antiviral use, n (%)			
Never or >5 years ago	10 732 (80)	18 962 (81)	19 190 (81)
1–5 years ago	1160 (9)	2547 (11)	2325 (10)
In the last year	1313 (10)	2731 (12)	2734 (11)

*The run date for this analysis was 17 May 2022.

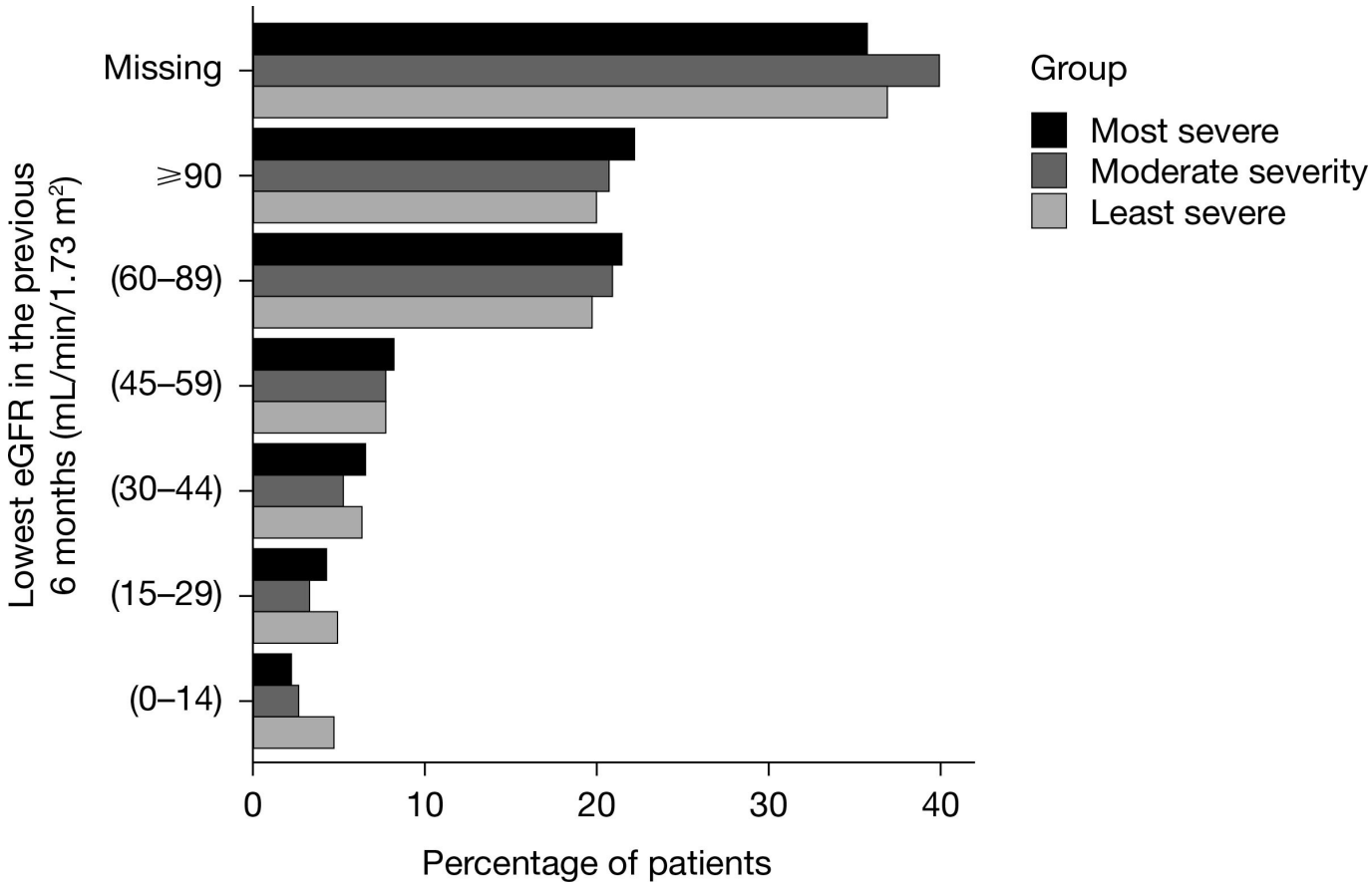

Figure 1 Distribution of eGFR within each group.*† *The run date for this analysis was 7 July 2022. †The lowest recorded eGFR data (recorded in mL/min/1.73 m^2) from 6 months prior to index date were collected for each patient. eGFR, estimated glomerular filtration rate.

(online supplemental table 4). Evidence of violation of the proportional hazards assumption was seen in the most severe group, but the log-rank test, which does not depend on this assumption, showed there was a significant association between alcohol-associated liver disease and the composite outcome across all groups (p≤0.0001).

Patients with either autoimmune or chronic viral hepatitis had a lower rate of the composite endpoint than those without autoimmune or chronic viral hepatitis in the moderate severity and least severe groups (online supplemental table 4). The HR (95% CI) for autoimmune hepatitis was 0.72 (0.61 to 0.85) in the moderate severity group and 0.56 (0.46 to 0.67) in the least severe group, and for chronic viral hepatitis was 0.65 (0.61 to 0.69) in the moderate severity group and 0.63 (0.59 to 0.67) in the least severe group. Patients with autoimmune hepatitis were more often female in the moderate severity group and male in the least severe group than patients with chronic viral hepatitis (online supplemental tables 2 and 3). Some evidence of violation of the proportional hazards assumption was seen in the association of autoimmune hepatitis with the composite outcome in the least severe group but the log-rank test, which does not depend on this assumption, showed a significant association between hepatitis (autoimmune or chronic viral) and the composite outcome in the moderate severity and least severe groups (p≤0.0001) (online supplemental table 4).

In the most severe group, patients with MASH in comparison with those without MASH were more often female (52% vs 31%, respectively) and older (mean of 61 years of age vs 56 years of age, respectively), and had a higher incidence of the composite outcome with an HR (95% CI) of 1.17 (1.11 to 1.23) (online supplemental tables 1 and 4). In contrast, in the moderate severity and least severe groups, patients with and without MASH had a similar mean age (online supplemental tables 2 and 3), and patients with MASH had a lower incidence of the composite outcome versus those without MASH (HR (95% CI); moderate severity group: 0.86 (0.79 to 0.93); least severe group: 0.88 (0.77 to 0.90)) (online supplemental table 4). There was evidence of violation of the proportional hazards assumption in all of the MASH models, but the log-rank test, which does not depend on this assumption, showed a significant association between MASH and the composite outcome across all groups (p≤0.0001).

In the moderate severity group, patients with haemochromatosis were more often male and had a lower incidence of the composite outcome (HR (95% CI) 0.72 (0.56 to 0.92); log-rank test p=0.0079) in comparison with those without haemochromatosis (online supplemental

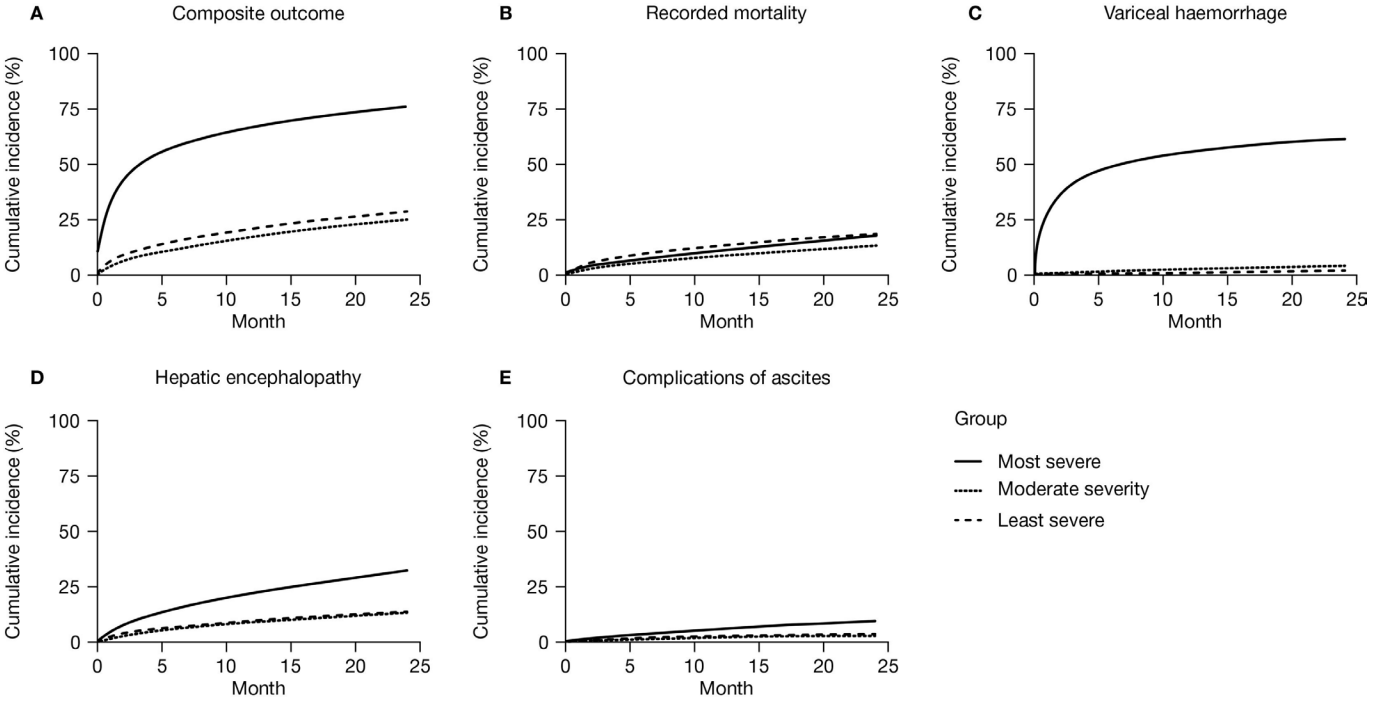

Figure 2 Kaplan-Meier plots of the cumulative incidence in each severity group of (A) first event of composite outcomes of variceal haemorrhage, hepatic encephalopathy, complications of ascites and mortality; (B) recorded mortality; (C) variceal haemorrhage; (D) hepatic encephalopathy and (E) complications of ascites. The analysis run date was 1–8 February 2023. Data are presented with 95% CIs. The Kaplan-Meier plots for the moderate severity group and the least severe group overlap in figure 2D,E.

tables 1 and 2). There was no evidence for an association of Wilson's disease or primary sclerosing cholangitis with the composite outcome (online supplemental table 1). These were also the least prevalent aetiologies (table 1).

DISCUSSION

This is as yet the largest dataset of patients with diagnosed/suspected portal hypertension for which detailed

Table 2 Cumulative incidence of outcomes in each severity group at 3, 6, 12 and 24 months*

Outcome		Kaplan-Meier cumulative incidence, % (95% CI)			
		3 months	6 months	12 months	24 months
Composite outcome	Group 1, most severe	48 (47 to 49)	57 (57 to 58)	67 (66 to 68)	76 (75 to 77)
	Group 2, moderate severity	7.6 (7.3 to 8.0)	12 (11 to 12)	17 (16 to 17)	25 (24 to 25)
	Group 3, least severe	11 (10 to 11)	15 (15 to 15)	21 (20 to 21)	28 (28 to 29)
Recorded mortality	Group 1, most severe	5.0 (4.6 to 5.4)	7.2 (6.7 to 7.7)	11 (10 to 11)	18 (17 to 18)
	Group 2, moderate severity	3.6 (3.4 to 3.8)	5.7 (5.4 to 6.1)	8.5 (8.2 to 8.9)	13 (13 to 14)
	Group 3, least severe	6.6 (6.3 to 6.9)	9.4 (9.0 to 9.8)	13 (13 to 14)	18 (18 to 19)
Variceal haemorrhage	Group 1, most severe	41 (40 to 42)	48 (47 to 49)	55 (54 to 56)	62 (61 to 63)
	Group 2, moderate severity	1.1 (1.0 to 1.2)	1.7 (1.5 to 1.9)	2.5 (2.3 to 2.7)	4.0 (3.7 to 4.3)
	Group 3, least severe	0.4 (0.3 to 0.5)	0.6 (0.5 to 0.7)	1.0 (0.8 to 1.1)	1.7 (1.5 to 1.9)
Hepatic encephalopathy	Group 1, most severe	10 (9.5 to 11)	15 (14 to 16)	22 (21 to 23)	32 (31 to 33)
	Group 2, moderate severity	3.8 (3.5 to 4.0)	5.9 (5.6 to 6.3)	8.8 (8.4 to 9.2)	13 (13 to 14)
	Group 3, least severe	4.8 (4.5 to 5.1)	6.6 (6.3 to 7.0)	9.4 (9.0 to 9.8)	13 (13 to 14)
Complications of ascites	Group 1, most severe	2.5 (2.2 to 2.8)	3.6 (3.3 to 4.0)	5.7 (5.3 to 6.2)	9.7 (9.1 to 10)
	Group 2, moderate severity	0.9 (0.8 to 1.1)	1.6 (1.4 to 1.7)	2.2 (2.0 to 2.5)	3.4 (3.1 to 3.7)
	Group 3, least severe	1.2 (1.1 to 1.4)	1.8 (1.6 to 2.0)	2.6 (2.4 to 2.8)	3.5 (3.2 to 3.8)

Due to limitation of the TriNetX platform, no adjustments have been made for competing risks.
*The run date for this analysis was 1–8 February 2023.

comorbidity and liver outcome data are available. Over 13 000 patients were identified who fit the criteria for the most severe symptoms of portal hypertension, and over 23 000 patients fit each of the other phenotypical criteria. Of note, across all three severity groups, high rates of mortality and morbidity were seen. This is despite the availability of modern interventions, including beta blockade, variceal banding and transjugular intrahepatic portosystemic shunts.[6] Furthermore, more than half of the cumulative incidence of the composite outcome occurred within the first 6 months, emphasising the high unmet need of this patient group.

By 24 months, the cumulative endpoint of variceal haemorrhage, complications of ascites, hepatic encephalopathy or mortality had occurred in over 75% of patients in the most severe group, that is, those who had a documented episode of variceal bleeding. Also of note in this group is the higher prevalence of alcohol-associated liver disease compared with the less severe groups (49% vs 37% and 32%). Furthermore, the cumulative event incidence for variceal haemorrhage alone was over 60%. The increased burden of variceal haemorrhage is matched by a larger increase in episodes of hepatic encephalopathy versus the other two groups. This may be due to increased ammonia load related to recurrent variceal haemorrhage.[19]

Recorded mortality was broadly similar across all three severity groups, suggesting that a higher burden of bleeding in the most severe group did not translate into increased mortality and/or that deaths occurred for reasons other than bleeding in the moderate severity and least severe groups. It is possible that variceal haemorrhage was present but undiagnosed or unrecorded in some patients in the moderate severity and least severe groups. There may also be differences in comorbidities within the three groups which account for these differences.

Patients with MASH and those with alcohol-associated liver disease were more likely to suffer from the composite outcome across portal hypertension aetiological groups than those without these conditions. In alcohol-associated liver disease, this may reflect poor compliance with surveillance endoscopy, low levels of compliance with beta blocker use or ineffectiveness of prophylactic variceal banding. In MASH, this may be related to underlying disease aetiology and limited current options to control disease drivers such as weight loss and insulin resistance.

Although prevalence of primary sclerosing cholangitis was low in this cohort, there was an increased incidence of variceal haemorrhage over time. One explanation for this could be progression of cirrhosis over time. Overall, the relatively low number of patients with Wilson's disease, haemochromatosis and primary sclerosing cholangitis meant that statistical power was limited with respect to evaluating outcomes.

Limitations of our study include those of a real-world data study, namely the risk of confounding variables influencing results; therefore, causal language has been avoided. Although we considered including presence of ascites as an inclusion criterion for our three groups of severity, we reasoned that mild ascites may be poorly recorded in electronic healthcare record databases, particularly as very early disease requires ultrasound to confirm the diagnosis. It is therefore possible that a small number of patients classified in group 3 with the mildest disease may actually already have features of decompensation. With regard to acute bleeding, two I85 codes were used to confirm the diagnosis. It is expected where attached to a hospital episode they would describe a new acute event, although it is possible they may be repeated from a previous one. It seems that our data do in fact represent the true event rate for variceal haemorrhage, being in the range described in the review by Garcia-Tsao and Bosch.[12] Another limitation was that ICD codes for MASH have limited sensitivity and specificity, which limits the comparisons between aetiologies. Furthermore, the majority of patients were white, which means that the study population may not be representative of diverse patient populations. In addition, while TriNetX captures the majority of patient deaths, as it is strongly enriched for mortality in a healthcare setting, mortality recording is incomplete, particularly in non-healthcare settings. For this reason, the number of deaths due to all causes may have been underestimated in the analysis. Finally, due to the limitations of the TriNetX platform, we were not able to take into account non-proportional hazards (except by reference to the log-rank test, which does not rely on this assumption) or use competing risks methods to better study individual outcomes. We hope that the impact of competing risks is limited, given the relatively short follow-up period of our study and the fact that individuals are censored once an event has occurred.

Our analysis of data from a large collection of electronic healthcare records represents robust evidence on the outcomes and mortality of patients with diagnosed/suspected portal hypertension. Despite use of beta blockers and surveillance endoscopy with variceal banding in modern care, morbidity and mortality remain high both in patients with more and less severe disease states, that is, those with and without variceal haemorrhage. A renewed effort is required to manage patients with portal hypertension using existing treatment strategies but also by developing new therapies, particularly with respect to reducing the risk of variceal haemorrhage and worsening of ascites.

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Contributors Conception or design of the study—NHCL, SJK, PRH, VERP, PJG, and PA. Acquisition, analysis, or interpretation of data—NHCL, SJK, SC, SA, DMB, PRH, VERP, PJG, and PA. Edit and review of the manuscript—NHCL, SJK, SC, SA, DMB, PRH, VERP, PJG, and PA. PA is responsible for the overall content of the manuscript and is acting as guarantor.

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Competing interests NHCL was employed by AstraZeneca during the majority of her contributions. SJK is an employee of and owns shares in AstraZeneca. SC is an employee of ZS and worked as a contractor for AstraZeneca. SA is an employee of ZS and worked as a contractor for AstraZeneca. DMB is an employee of and owns shares in AstraZeneca. PRH was employed by AstraZeneca during the majority of his contributions and owned shares in AstraZeneca at the time the work was conducted. VERP is an employee of and owns shares in AstraZeneca. PJG is an employee of and owns shares in AstraZeneca. PA is an employee of and owns shares in AstraZeneca.

Patient consent for publication Not required.

Ethics approval No ethics approval was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data underlying the findings described in this manuscript may be obtained in accordance with the data licensing agreement between AstraZeneca and TriNetX.

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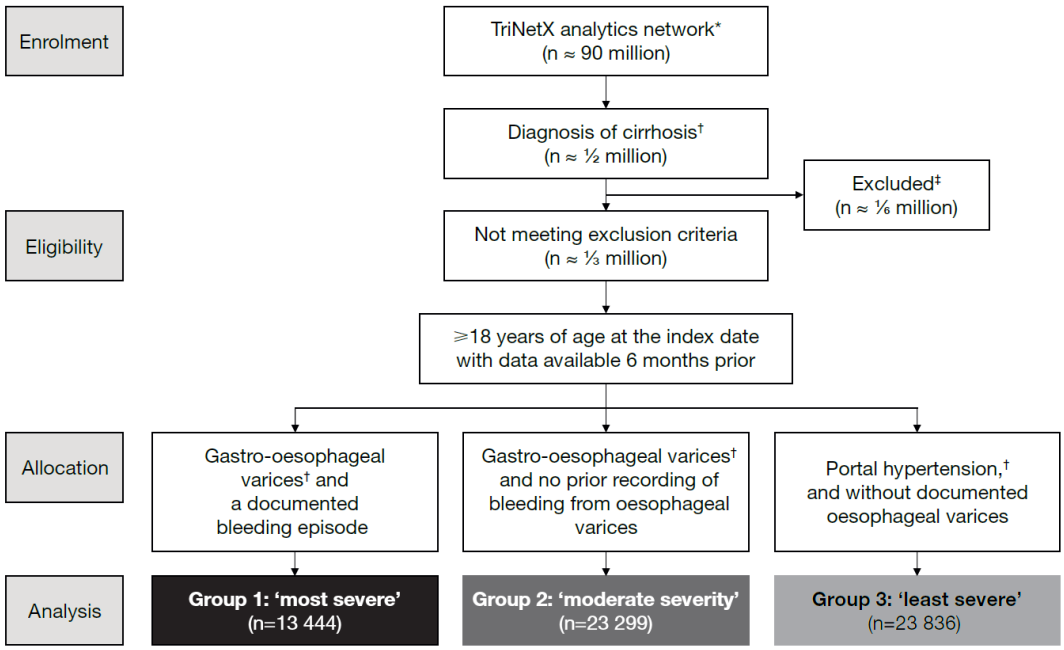
SUPPLEMENTARY INFORMATION

Figure S1 Flow diagram of patient participation

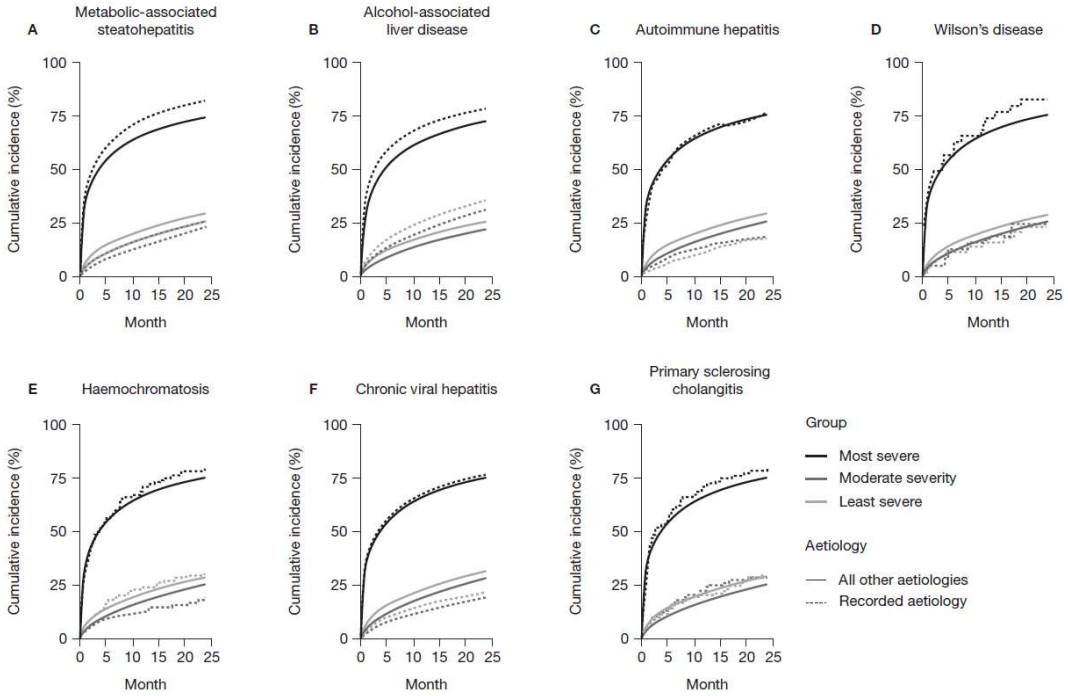


*Data were collected on 17 May 2022.

†Diagnosis during the study period (1 January 2017 to 3 December 2020).

‡Exclusion criteria were secondary causes of cirrhosis, including Budd–Chiari syndrome, biliary cirrhosis, granulomatous hepatitis, schistosomiasis, liver transplant, Class C cirrhosis and hepatocellular carcinoma.

Figure S2 Kaplan–Meier plots of the cumulative incidence in each severity group and aetiology of the first event of composite outcomes of variceal haemorrhage, hepatic encephalopathy, complications of ascites and recorded mortality for (A) metabolic-associated steatohepatitis; (B) alcohol-associated liver disease; (C) autoimmune hepatitis; (D) Wilson's disease; (E) haemochromatosis; (F) chronic viral hepatitis and (G) primary sclerosing cholangitis



The dashed line indicates the recorded aetiology and the solid line indicates all other aetiologies.

The Kaplan–Meier plots for all other aetiologies in the moderate severity group and recorded aetiology in the least severe group overlap in figure S2A.

Table S1 Patient characteristic by aetiology in Group 1, most severe*

Demographic/clinical characteristic	MASH		Alcohol-associated liver disease		Autoimmune hepatitis		Wilson's disease		Haemochromatosis		Chronic viral hepatitis		Primary sclerosing cholangitis	
	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with
N	10 942	1859	6462	6339	12 400	401	12 758	43	12 657	144	9226	3575	12 655	146
Females (%)	31	52	45	23	33	59	34	37	34	22	37	28	34	36
Age, years, mean (SD)	55.8 (11.7)	61.2 (11.0)	59.4 (12.0)	53.7 (10.7)	56.7 (11.6)	52.9 (15.3)	56.6 (11.7)	50.1 (13.6)	56.6 (11.7)	57.3 (11.6)	57.0 (12.6)	55.5 (9.1)	56.6 (11.7)	51.0 (16.5)
Race (%)														
White	73	83	74	74	74	63	74	79	74	81	76	68	74	76
Black or African American	7	2	7	7	7	10	7	23	7	6	5	11	7	8
Asian	2	1	2	1	2	2	2	0	2	6	1	3	2	6

American Native or Alaska Native	1	1	1	2	1	2	1	23	1	6	2	1	1	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	2	0	0	0	0	0	0	0	0
Unknown	17	13	16	16	16	21	16	23	16	10	16	17	16	11
Ethnicity (%)														
Not Hispanic or Latino	61	70	65	59	62	68	62	76	62	79	61	64	62	75
Hispanic or Latino	15	14	14	17	15	13	15	23	15	7	15	16	15	7
Unknown	24	16	21	24	23	19	23	23	23	14	24	20	23	18
Portal hypertension, n	7451	1537	4260	4728	8689	299	8953	35	8874	114	6382	2606	8875	113
Recorded aetiology of cirrhosis, n														

Metabolic-associated steatohepatitis	0	1929	1515	414	1864	65	1923	10	1890	39	1815	114	1919	10
Autoimmune hepatitis	343	65	308	100	0	408	403	10	401	10	349	59	387	21
Chronic viral hepatitis	3406	97	1866	1637	3446	57	3498	10	3462	41	0	3503	3488	15
Alcohol-associated liver disease	5814	382	0	6196	6099	97	6174	22	6135	61	4559	1637	6158	38
Wilson’s disease	37	10	21	22	38	10	0	43	36	10	38	10	41	10
Haemochromatosis	107	35	81	61	135	10	135	10	0	142	101	41	141	10
Primary sclerosing cholangitis	135	10	107	38	124	21	143	10	144	10	131	14	0	145
Other	4093	1047	2715	2425	4870	270	5116	24	5063	77	3520	1620	5057	83
Comorbidities, n														
Alcohol abuse	4589	212	506	4295	4737	64	4782	19	4749	52	3445	1356	4775	26

Type 2 diabetes	3537	1343	3048	1832	4737	143	4863	17	4813	67	3755	1125	4845	35
Major depression	2275	543	1219	1599	2733	85	2802	16	2775	43	1984	834	2795	23
Sarcopenia	29	16	15	30	44	10	45	0	44	10	34	11	44	10
Human immunodeficiency virus	218	30	154	94	242	10	247	10	244	10	112	136	247	10
Heart failure (all)	1104	337	780	661	1397	44	1437	10	1422	19	1104	337	1428	13
Heart failure with preserved ejection fraction	731	285	512	504	976	40	1014	10	999	17	755	261	1004	12
Heart failure with reduced ejection fraction	249	79	178	150	322	10	326	10	323	10	244	84	326	10
Ischaemic heart diseases	1682	540	1243	979	2156	66	2212	10	2191	31	1713	509	2203	19

Stroke	666	197	463	400	828	35	859	10	845	18	656	207	856	10
Neoplasms (all)	3512	819	2347	1984	4172	159	4311	20	4268	63	3035	1296	4264	67
Benign neoplasms	2475	603	1638	1440	2961	117	3059	19	3031	47	2152	926	3034	44
Malignant neoplasms	1655	406	1154	907	1976	85	2051	10	2021	40	1453	608	2026	35
Anti-viral use, n														
Never or >5 years ago	9489	1641	5451	5679	10784	346	11094	36	11011	119	8597	2533	11003	127
1–5 years ago	378	60	284	154	421	17	437	10	431	10	173	265	433	10
In the last year	1075	158	727	506	1195	38	1227	10	1215	18	456	777	1219	14

*The run date for this analysis was 14–22 December 2022.

MASH, metabolic-associated steatohepatitis; SD, standard deviation; w/o, without.

Table S2 Patient characteristic by aetiology in Group 2, moderate severity*

Demographic/clinical characteristic	MASH		Alcohol-associated liver disease		Autoimmune hepatitis		Wilson's disease		Haemochromatosis		Chronic viral hepatitis		Primary sclerosing cholangitis	
	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with
N	19 561	3404	14 510	8455	22 201	764	22 925	40	22 601	354	15 859	7106	22 756	209
Females (%)	38	60	47	30	40	71	41	47	41	28	44	34	41	43
Age, years, mean (SD)	64 (12)	66 (11)	66 (12)	62 (11)	64 (11)	62 (15)	64 (12)	52 (17)	64 (12)	64 (11)	64 (13)	64 (9)	64 (11)	60 (15)
Race (%)														
White	67	81	68	71	70	63	69	80	69	75	73	60	69	64
Black or African American	13	3	12	10	11	15	11	25	12	6	7	22	11	12
Asian	2	1	2	1	2	2	2	0	2	3	1	3	2	4

American Native or Alaska Native	0	1	1	1	0	1	1	0	0	0	1	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	18	14	17	17	17	19	17	25	17	16	18	15	17	21
Ethnicity (%)														
Not Hispanic or Latino	63	76	66	64	65	70	65	85	65	82	65	67	65	80
Hispanic or Latino	13	11	12	14	13	13	13	25	13	4	12	13	13	6
Unknown	24	13	22	22	22	17	22	25	22	14	23	20	22	14
Portal hypertension, n	10 799	2231	7888	5122	12 559	451	12982	28	12 781	229	8962	4048	12 870	140
Recorded aetiology of cirrhosis, n														

Metabolic-associated steatohepatitis	0	3459	2888	571	3339	120	3452	10	3386	73	3243	216	3441	18
Autoimmune hepatitis	652	116	639	117	0	756	750	10	744	12	652	104	724	32
Chronic viral hepatitis	6902	207	4940	2169	7006	103	7107	10	7016	93	0	7109	7089	20
Alcohol-associated liver disease	7819	503	0	8322	8212	110	8313	10	8203	119	6211	2111	8292	30
Wilson’s disease	26	10	24	10	26	10	0	28	26	10	26	10	28	0
Haemochromatosis	287	73	238	122	347	13	357	10	0	360	267	93	357	10
Primary sclerosing cholangitis	191	18	179	30	177	32	209	0	206	10	189	20	0	209
Other	7780	1956	6536	3200	9224	512	9711	25	9548	198	6350	3386	9602	134
Comorbidities, n														
Alcohol abuse	6452	335	1354	5433	6728	59	6779	10	6672	115	4858	1929	6750	37

Type 2 diabetes	6654	2333	6556	2431	8727	260	8976	11	8841	146	6773	2214	8931	56
Major depression	4682	1069	3444	2307	5595	156	5739	12	5638	113	3879	1872	5700	51
Sarcopenia	25	10	15	17	34	10	34	10	35	0	28	10	34	10
Human immunodeficiency virus	552	77	453	176	598	31	627	10	621	10	278	351	614	15
Heart failure (all)	2757	622	2222	1157	3288	91	3374	10	3333	46	2470	909	3352	27
Heart failure with preserved ejection fraction	1629	467	1357	739	2036	60	2093	10	2065	31	1488	608	2072	24
Heart failure with reduced ejection fraction	757	153	599	311	890	20	909	10	892	18	665	245	904	10
Ischaemic heart diseases	2940	803	2485	1258	3663	80	3739	10	3673	70	2825	914	3680	30

Stroke	1626	351	1279	698	1911	66	1974	10	1933	44	1439	538	1951	26
Neoplasms (all)	6744	1549	5566	2727	8005	288	8279	14	8151	152	5619	2674	8193	100
Benign neoplasms	4990	1224	4113	2101	5993	221	6204	10	6200	114	4021	2193	6142	72
Malignant neoplasms	2170	478	1816	832	2558	90	2644	10	2591	57	1987	661	2608	40
Anti-viral use, n														
Never or >5 years ago	15 991	3006	11 580	7417	18 342	655	18 958	39	18 731	266	14 507	10	18 821	176
1–5 years ago	2275	305	1918	662	2515	65	2580	0	2511	69	787	1793	2562	18
In the last year	2460	278	2021	717	2683	55	2738	0	2676	62	829	1909	2723	15

*The run date for this analysis was 18–23 May 2022.

MASH, metabolic-associated steatohepatitis; SD, standard deviation; w/o, without.

Table S3 Patient characteristic by aetiology in Group 3, least severe*

Demographic/clinical characteristic	MASH		Alcohol-associated liver disease		Autoimmune hepatitis		Wilson's disease		Haemochromatosis		Chronic viral hepatitis		Primary sclerosing cholangitis	
	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with	w/o	with
N	20 516	2891	15 860	7547	22 684	723	23 351	56	23 046	361	17 037	6370	23 150	257
Females (%)	41	60	47	33	42	29	43	41	43	38	45	37	43	44
Age, years, mean (SD)	64 (12)	64 (12)	65 (12)	61 (11)	64 (12)	61 (15)	64 (12)	52 (16)	64 (12)	62 (12)	64 (13)	63 (9)	64 (12)	60 (16)
Race (%)														
White	70	81	71	72	72	68	72	76	72	75	75	62	72	70
Black or African American	12	3	12	9	11	13	11	17	11	8	8	21	11	12
Asian	2	1	2	1	2	2	2	17	2	3	1	3	2	3

American Native or Alaska Native	1	1	1	1	0	1	0	0	0	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	15	13	14	17	15	16	15	17	15	13	16	14	15	14
Ethnicity (%)														
Not Hispanic or Latino	66	79	70	64	68	72	68	73	68	81	68	69	68	87
Hispanic or Latino	14	12	13	14	13	16	14	17	14	8	13	14	14	6
Unknown	20	9	17	22	19	22	18	17	18	11	19	17	18	7
Portal hypertension, n	21 193	2925	16 288	7830	23 384	734	24 062	56	23 747	371	17 587	6531	23 859	259
Recorded aetiology of cirrhosis, n														

Metabolic-associated steatohepatitis	0	2696	2328	368	2575	121	2680	16	2647	49	2509	187	2674	22
Autoimmune hepatitis	594	125	619	90	0	734	697	12	688	21	621	88	653	56
Chronic viral hepatitis	6327	204	4827	1704	6441	90	6523	10	6448	83	0	6531	6504	27
Alcohol-associated liver disease	7395	435	0	7830	7737	93	7816	14	7708	122	6126	1704	7789	41
Wilson’s disease	40	16	42	14	44	12	0	56	43	13	48	10	55	10
Haemochromatosis	315	56	249	122	350	21	358	13	0	371	288	83	369	10
Primary sclerosing cholangitis	233	26	218	41	202	57	258	10	257	10	232	27	0	259
Other	8323	1654	7291	2686	9490	487	9942	35	9768	209	6890	3087	9797	180
Comorbidities, n														
Alcohol abuse	7048	331	1926	5453	7290	89	7365	14	7250	129	5484	1895	7336	43

Type 2 diabetes	7533	1888	7264	2157	9152	269	9400	21	9280	141	7366	2055	9326	95
Major depression	5722	959	4329	2352	6488	193	6660	21	6576	105	4722	1959	6605	76
Sarcopenia	42	10	29	21	48	10	50	0	48	10	29	21	49	10
Human immunodeficiency virus	948	175	918	205	1023	100	1109	14	1103	20	621	502	1087	36
Heart failure (all)	4501	690	3863	1328	5087	104	5181	10	5104	87	4111	1080	5150	41
Heart failure with preserved ejection fraction	2524	540	2256	808	2983	81	3058	10	3001	63	2432	6441	3024	40
Heart failure with reduced ejection fraction	1647	218	1419	446	1839	26	1864	10	1836	29	1528	337	1855	10
Ischaemic heart diseases	3990	705	3471	1224	4587	108	4689	10	4628	67	3732	963	4651	44

Stroke	2219	372	1882	709	2506	85	2579	12	2538	53	1989	602	2560	31
Neoplasms (all)	7095	1278	6194	2179	8097	276	8352	21	8215	158	6115	2258	8237	136
Benign neoplasms	2231	467	1976	722	2602	96	2690	10	2651	47	1913	785	2657	41
Malignant neoplasms	3108	517	2775	850	3504	121	3612	13	3546	79	2850	775	3546	79
Anti-viral use, n														
Never or >5 years ago	16 937	2463	12 634	6767	18 807	594	19 354	47	19 140	260	15 435	3965	19 197	203
1–5 years ago	2071	292	1850	513	2284	79	2361	10	2308	55	1040	1323	2335	28
In the last year	2504	266	2175	595	2696	74	2766	10	2698	72	1089	1681	2738	32

*The run date for this analysis was 18–24 May 2022.

MASH, metabolic-associated steatohepatitis; SD, standard deviation; w/o, without.

Table S4 Association of aetiologies (patients with versus those without a condition) with the composite outcome*

Measure	MASH	Alcohol-associated liver disease	Autoimmune hepatitis	Wilson's disease	Haemochromatosis	Chronic viral hepatitis	Primary sclerosing cholangitis
Group 1, most severe							
Number of patients with the condition, n	1969	6577	408	46	155	3774	154
Number of patients without the condition, n	11 241	6724	12 802	13 164	13 055	9457	13 056
Log-rank test, chi-squared value	31.93	103.972	0.008	0.055	0.191	0.746	0.182
Log-rank test, p value	<0.0001	<0.0001	0.9302	0.8144	0.6619	0.3878	0.6697
Proportional hazards, chi-squared value	12.88	1.362	0.02	0.305	0.021	2.066	5.959

Proportional hazards, p value	0.0003	0.0007	0.8873	0.5806	0.8845	0.1506	0.0146
HR (95% CI)	1.167 (1.106–1.232)	1.232 (1.183–1.282)	1.005 (0.897–1.126)	1.043 (0.745–1.461)	0.961 (0.799–1.155)	1.02 (0.976–1.066)	1.039 (0.868– 1.243)
Group 2, moderate severity							
Number of patients with the condition, n	3529	8591	780	40	360	7180	209
Number of patients without the condition, n	19 804	14 742	22 553	23 293	22 973	16 153	23 124
Log-rank test, chi-squared value	14.618	213.638	14.5	0.014	7.059	182.513	1.644
Log-rank test, p value	0.0001	<0.0001	0.0001	0.9045	0.0079	<0.0001	0.1998
Proportional hazards, chi-squared value	18.079	1.114	1.195	0.121	0.018	0.996	4.874
Proportional hazards, p value	<0.0001	0.2912	0.2742	0.7277	0.8941	0.3183	0.0273

HR (95% CI)	0.858 (0.794–0.928)	1.504 (1.424–1.59)	0.721 (0.609–0.854)	0.961 (0.5–1.848)	0.715 (0.558–0.917)	0.645 (0.605–0.687)	1.188 (0.913–1.546)
Group 3, least severe							
Number of patients with the condition, n	2977	7730	721	55	373	6464	251
Number of patients without the condition, n	20 871	16 118	23 127	23 793	23 475	17 384	23 597
Log-rank test, chi-squared value	19.771	210.762	40.599	0.796	0.51	207.095	0.002
Log-rank test, p value	<0.0001	<0.0001	<0.0001	0.3724	0.4751	<0.0001	0.961
Proportional hazards, chi-squared value	5.918	1.345	2.927	0.022	0.955	0.187	0.443
Proportional hazards, p value	0.0015	0.2462	0.00871	0.8809	0.3284	0.6657	0.5059

HR (95% CI)	0.883 (0.769–0.903)	1.474 (1.399–1.554)	0.555 (0.462–0.667)	0.765 (0.423–1.382)	1.074 (0.884–1.305)	0.63 (0.591–0.671)	1.006 (0.789–1.283)

*The run date for this analysis was 25 May 2022.

CI, confidence interval; HR, hazard ratio; MASH, metabolic-associated steatohepatitis.