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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.

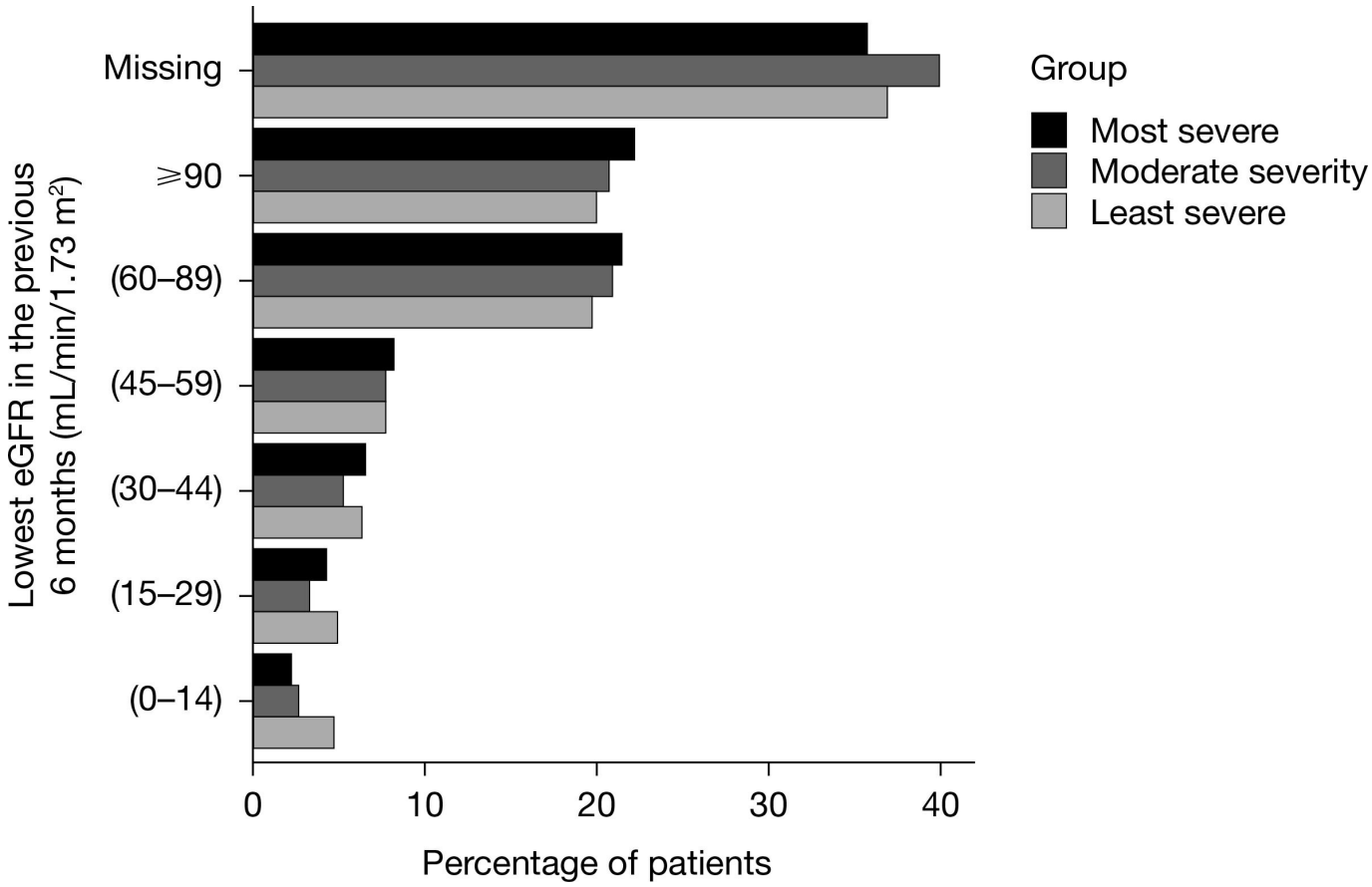

Figure 1 Distribution of eGFR within each group.*† *The run date for this analysis was 7 July 2022. †The lowest recorded eGFR data (recorded in mL/min/1.73 m^2) from 6 months prior to index date were collected for each patient. eGFR, estimated glomerular filtration rate.

(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

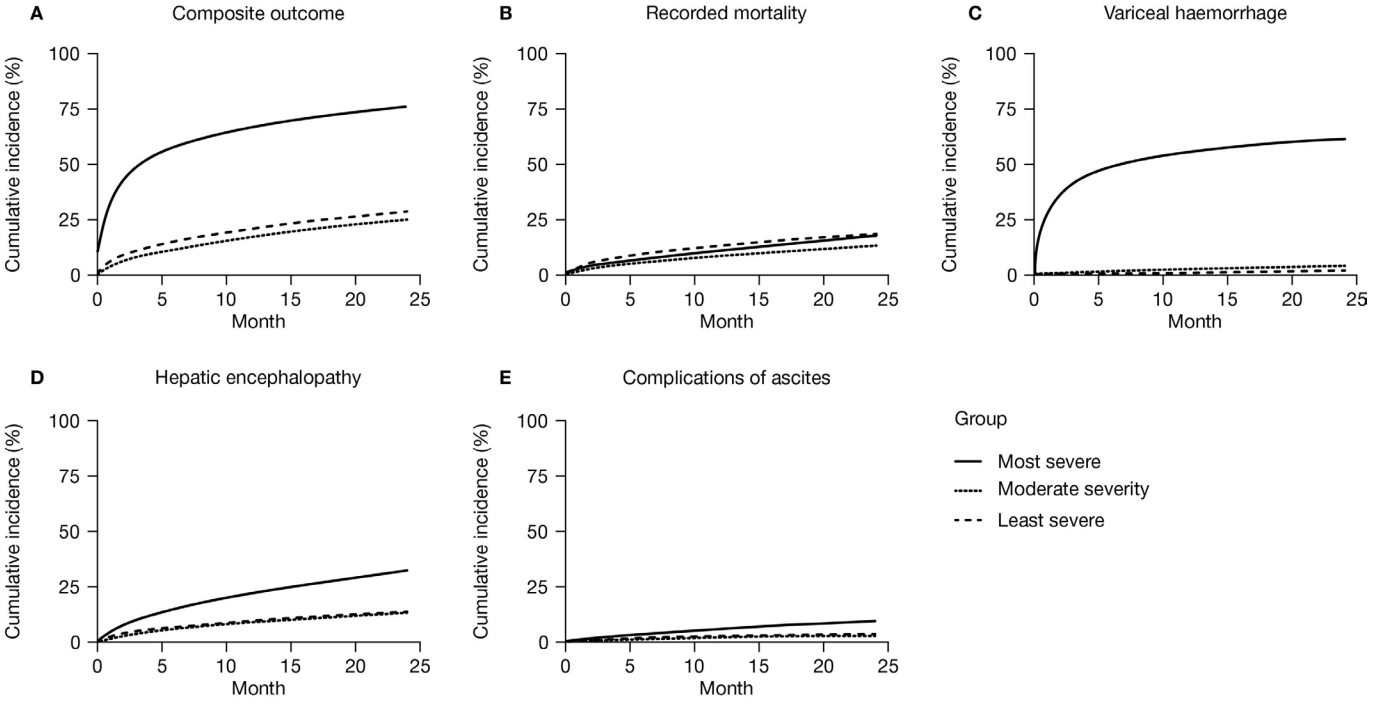

Figure 2 Kaplan-Meier plots of the cumulative incidence in each severity group of (A) first event of composite outcomes of variceal haemorrhage, hepatic encephalopathy, complications of ascites and mortality; (B) recorded mortality; (C) variceal haemorrhage; (D) hepatic encephalopathy and (E) complications 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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