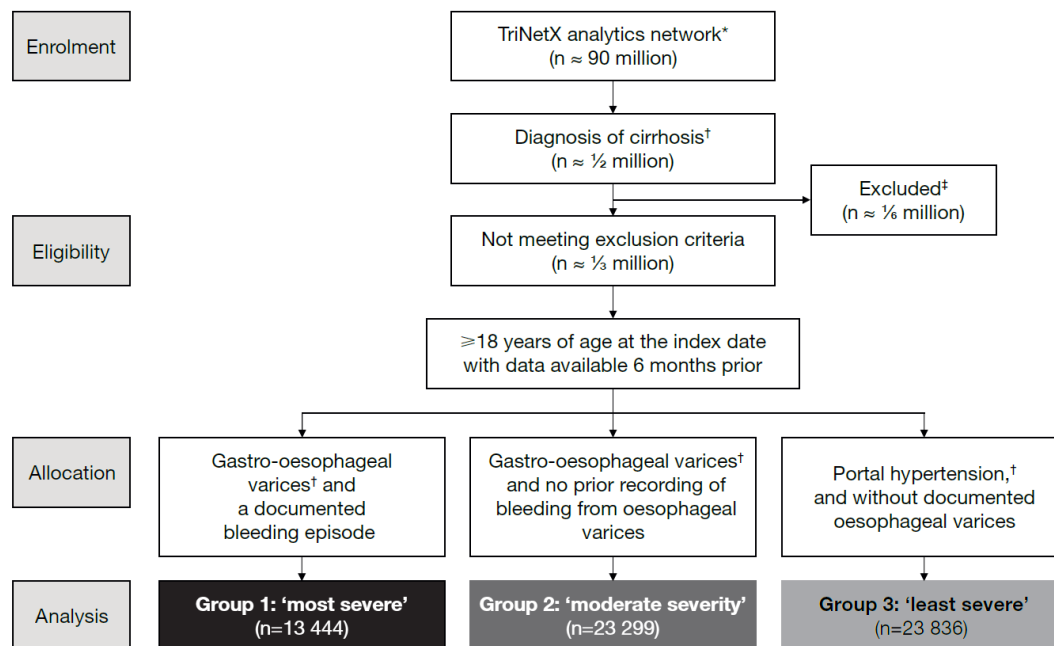


SUPPLEMENTARY INFORMATION

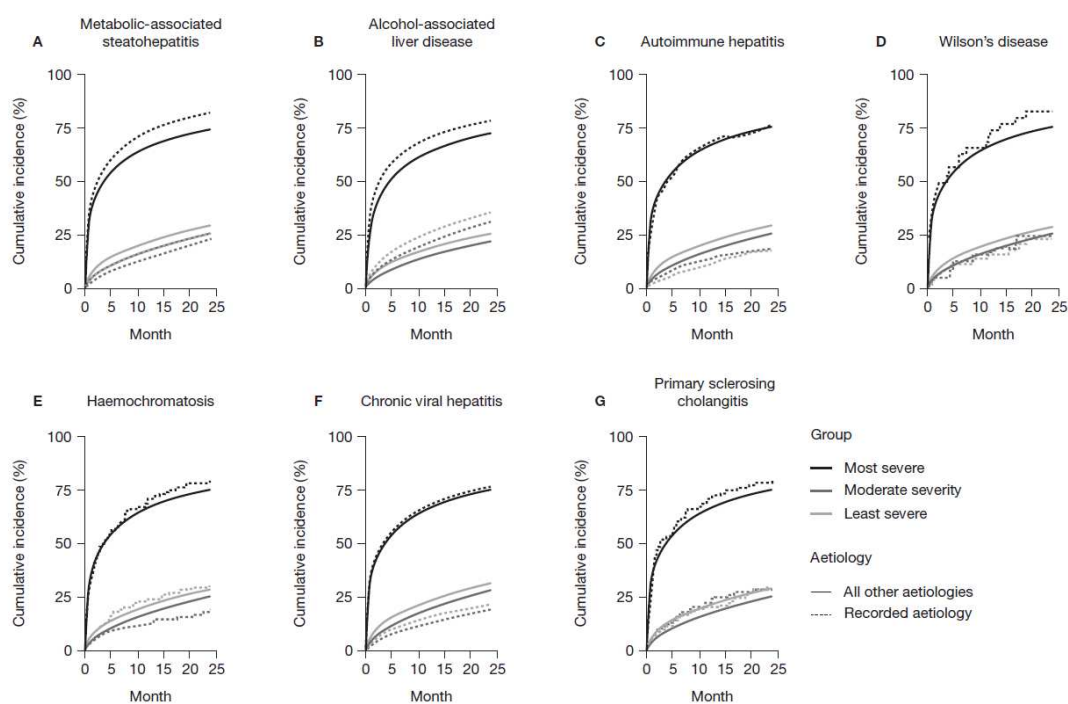
Figure S1 Flow diagram of patient participation

*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
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
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
<i>Group 1, most severe</i>							
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)
<i>Group 2, moderate severity</i>							
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)
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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	1.474	0.555	0.765	1.074	0.63	1.006
	(0.769–0.903)	(1.399–1.554)	(0.462–0.667)	(0.423–1.382)	(0.884–1.305)	(0.591–0.671)	(0.789–1.283)

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

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