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Comorbidity combinations and latent patterns associated with liver-related events in metabolic dysfunction-associated steatotic liver disease

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Abstract

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multisystem condition, yet the relevance of comorbidity composition and co-occurrence to liver-related outcomes is poorly understood. We evaluated associations of comorbidity burden, individual conditions, disease pairs, and latent patterns with liver-related events (LREs).

Methods

We conducted a prospective analysis of 137,607 UK Biobank participants with MASLD. We assessed 51 comorbidities, eligible pairs among 1,275 combinations, and comorbidity patterns identified by latent class analysis. Associations with incident LREs were estimated using multivariable Cox regression.

Results

During a median follow-up of 14.7 years, 9,948 participants developed LREs. Compared with the lowest Charlson Comorbidity Index tertile, the highest tertile had an adjusted hazard ratio (aHR) for LREs of 1.41 (95% CI 1.31–1.51). Compared with no comorbidities, having ≥ 3 comorbidities was associated with an aHR of 1.54 (95% CI 1.43–1.65). Solid organ cancers and diabetes exhibited the strongest associations with LREs. Pairwise analyses identified multiple associations, including hypertension with substance use disorder (aHR 1.51, 95% CI 1.37–1.65), hypertension with solid organ cancers (aHR 1.44, 95% CI 1.31–1.57), diabetes with hyperlipidemia (aHR 1.43, 95% CI 1.27–1.60), and diabetes with depression (aHR 1.40, 95% CI 1.24–1.59). Three classes were identified in addition to a minimal-comorbidity class. Compared with minimal-comorbidity class, psychiatric-respiratory, hypertension-centered metabolic, and cardiovascular-kidney-metabolic classes had aHRs of 1.39, 1.40, and 2.08, respectively.

Conclusion

Comorbidity composition and co-occurrence patterns were associated with LRE risk in MASLD. These findings suggest that multidimensional comorbidity assessment may complement liver-focused risk stratification.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major global health concern, affecting approximately 30 to 40% of adults worldwide.[1] Individuals with MASLD frequently have multiple coexisting chronic conditions, resulting in heterogeneous comorbidity profiles.[2] Liver-related events (LREs) mark clinically meaningful progression of the underlying liver disease and contribute directly to liver-related morbidity and mortality.[3] However, whether LRE risk varies according to the composition, and co-occurrence of comorbidities in MASLD remains poorly understood.

Comorbidity is commonly evaluated using aggregate measures of disease burden, including simple condition counts or weighted indices such as the Charlson Comorbidity Index (CCI).[4] These measures provide an estimate of overall disease burden but reduce complex clinical profiles to a single score.[5] Simple counts assign equal importance to all included conditions, whereas the CCI applies predetermined weights to a restricted set of conditions based on their associations with mortality.[6] Neither approach identifies which conditions coexist; consequently, individuals with the same count or CCI score may have different disease profiles and prognoses.

Analyses of individual comorbidities preserve disease-specific information. Type 2 diabetes,[7] hypertension,[8] cardiovascular disease, and chronic kidney disease have been associated with fibrosis progression, hepatic complications,

or mortality. However, previous studies have often examined a relatively narrow range of prespecified conditions, with a particular emphasis on cardiometabolic diseases.[9] They therefore provide limited insight into the broader comorbidity landscape and do not account for disease co-occurrence.[10] This may be important because noncardiometabolic conditions could also influence hepatic outcomes in MASLD.[11]

To address this gap, we used data from a large population-based cohort to characterize the comorbidity landscape among individuals with MASLD across multiple dimensions, including overall burden, individual conditions, specific disease pairs, and latent comorbidity patterns. We hypothesized that participants with MASLD would show heterogeneous comorbidity profiles, and these profiles would be associated with different risks of LREs. Specifically, we evaluated the associations of baseline comorbidity count, CCI, individual conditions, and comorbidity pairs with subsequent LREs. We further used latent class analysis (LCA) to identify underlying comorbidity patterns and examined their associations with LRE risk. Finally, we compared the prognostic discrimination of burden-based and pattern-based approaches to assess whether comorbidity patterns provided additional information for LRE risk stratification.

Methods

Study design and population

We used data from UK Biobank, a prospective cohort of more than 500,000 participants recruited across the United Kingdom between 2006 and 2010. Baseline sociodemographic, lifestyle, medical, anthropometric and laboratory data were linked to hospital inpatient records, cancer registries, and death registries. All participants provided written informed consent. UK Biobank received approval from the North-West Multi-Centre Research Ethics Committee (21/NW/0157), and data were accessed under application 1164182. After applying the eligibility criteria, 137,607 participants with prevalent MASLD were included (Supplementary Figure S1).

Ascertainment of MASLD

MASLD was defined according to the latest international consensus as hepatic steatosis in combination with at least one cardiometabolic risk factor. Hepatic steatosis was assessed using a fatty liver index ≥ 60.[8] Detailed definitions of the cardiometabolic risk factors are provided in the **Supplementary Methods**.

Definition of comorbidities

Comorbidities were ascertained from hospital inpatient records. Conditions were selected based on a Delphi consensus framework for multimorbidity research and the ICD codes were based on a previous MASLD study [2]. Four additional MASLD-relevant metabolic conditions were included, including diabetes, hypertension, hyperlipidemia, and obesity. The final comorbidity set comprised 51 conditions, which were recorded using ICD-10 codes (**Supplementary Table S1)**. Comorbidity count and CCI were quantified using the established coding algorithm (**Supplementary Table S2**).

Outcome and covariates

The outcome was a composite of liver-related events, defined as hospital admissions for ascites, hepatic encephalopathy, portal hypertension, variceal bleeding, hyperbilirubinemia, hepatocellular carcinoma, cirrhosis, hepatic failure, or liver-related mortality, consistent with definitions used in a previous study.[8] The corresponding ICD-10 codes are provided in the **Supplementary Methods**. Participants were followed from enrollment until the first LRE, loss to follow-up, or administrative censoring (December 31, 2023), whichever occurred first.

Baseline covariates included demographic and socioeconomic factors, anthropometric measures, medication use, liver enzymes, glycemic markers, lipid profile, and hepatic, renal and hematologic markers. Variable groupings and extent of missing data are provided in **Supplementary Table S3 and Table S4**. Missing values in covariates were imputed using multiple imputations by chained equations, generating 10 imputed datasets with 10 iterations per dataset. All subsequent analyses were performed separately within each imputed dataset, and estimates were combined using Rubin's rules.

Statistical Analysis

Continuous variables were presented as means with standard deviations or as medians with interquartile ranges (IQRs), as appropriate, and categorical variables as counts with percentages. Group differences were compared using Student's t-test for normal continuous variables, or Mann-Whitney U test for non-normal continuous variables, and chi-square test for categorical variables.

Multivariable Cox proportional hazards regression models were constructed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association of comorbidity count and CCI with the risk of LREs. Sequential models were adjusted for sociodemographic, lifestyle, anthropometric, clinical, biochemical, and medication-related factors, as detailed in the **Supplementary Methods**. For sensitivity analysis, comorbidity count and CCI with LREs were also re-evaluated in the complete-case dataset.

Separate Cox models were fitted to evaluate the associations of individual comorbidities and pairwise comorbidity combinations with LREs risk. In pairwise analyses, A + B was defined as the concurrent presence of both A and B at baseline, with participants without the specific pair (including neither condition, either condition alone, or other comorbidity patterns) serving as the reference group. Model adjustment followed the same strategy, except that covariates constituting the exposure of interest were excluded to avoid overadjustment. To ensure model stability, analyses were performed only when at least 10 outcome events per variable included in the model. To account for multiple comparisons, P values were adjusted using the Benjamini-Hochberg false discovery rate (FDR), and FDR-adjusted P values < 0.05 were considered statistically significant. The proportional hazards assumption was assessed using Schoenfeld residuals.

LCA was performed to identify distinct comorbidity patterns. Participants without comorbidities at baseline (N = 33,497) were classified as the minimal comorbidity group and excluded from LCA because they contribute to limited heterogeneity in comorbidity patterns, in line with a previous study.[12] More detailed methodology is presented in Supplementary Methods.

To evaluate the robustness of the identified comorbidity patterns, LCA was conducted separately in male and female. LCA was repeated using a lower prevalence threshold of 1% for indicator selection.

Statistical analyses were performed using R version 4.3.2. LCA was conducted using the *poLCA* package.

Results

Study population characteristics

The final analysis included 137,607 UK Biobank participants (**Supplementary Figure S1**). During a median follow-up of 14.7 years (IQR 13.79–15.48), 9,948 participants (7.2%) developed LREs. Those with LREs were older, more deprived, had higher BMI and WC and were less likely to have higher education (Table 1). Missing data for baseline variables is reported in **Supplementary Table S3**

Table 1
Baseline characteristics of the study population

Variable	Overall, N = 137607[1]	No Event, n = 127659[1]	Event, n = 9948[1]	p-value[2]
Sex				< 0.001
female	48,844.0 (35.5%)	45,059.0 (35.3%)	3,785.0 (38.0%)	
male	88,763.0 (64.5%)	82,600.0 (64.7%)	6,163.0 (62.0%)	
Age	59.0 (51.0, 64.0)	58.0 (51.0, 63.0)	60.0 (54.0, 65.0)	< 0.001
Ethnicity				0.061
non white	7,890.0 (5.7%)	7,362.0 (5.8%)	528.0 (5.3%)	
white	129,717.0 (94.3%)	120,297.0 (94.2%)	9,420.0 (94.7%)	
Education				< 0.001
below high school	43,299.0 (31.5%)	39,537.0 (31.0%)	3,762.0 (37.8%)	
high school or above	94,308.0 (68.5%)	88,122.0 (69.0%)	6,186.0 (62.2%)	
TDI	-1.8 (-3.5, 1.1)	-1.9 (-3.5, 1.0)	-1.3 (-3.2, 1.9)	< 0.001
WC (cm)	103.0 (98.0, 110.0)	103.0 (98.0, 110.0)	105.0 (99.0, 112.0)	< 0.001
BMI (kg/m2)	31.5 (29.2, 34.5)	31.4 (29.1, 34.5)	32.0 (29.5, 35.4)	< 0.001
Smoking				< 0.001
never	64,785.0 (47.4%)	60,829.0 (47.9%)	3,956.0 (40.1%)	
previous	56,179.0 (41.1%)	51,678.0 (40.7%)	4,501.0 (45.6%)	
current	15,793.0 (11.5%)	14,373.0 (11.3%)	1,420.0 (14.4%)	
CCI	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	< 0.001
Diabetes				< 0.001
no	122,754.0 (89.2%)	114,638.0 (89.8%)	8,116.0 (81.6%)	
yes	14,853.0 (10.8%)	13,021.0 (10.2%)	1,832.0 (18.4%)	
Hypertension				< 0.001
no	80,215.0 (58.3%)	75,349.0 (59.0%)	4,866.0 (48.9%)	
yes	57,392.0 (41.7%)	52,310.0 (41.0%)	5,082.0 (51.1%)	
Chronic kidney disease				< 0.001
no	134,307.0 (97.6%)	124,741.0 (97.7%)	9,566.0 (96.2%)	
yes	3,300.0 (2.4%)	2,918.0 (2.3%)	382.0 (3.8%)	
Solid organ cancers				< 0.001
no	127,763.0 (92.8%)	118,883.0 (93.1%)	8,880.0 (89.3%)	

Abbreviations: TDI, Townsend deprivation index; WC, Waist circumference; BMI, Body mass index; CCI, Charlson Comorbidity Index; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; HbA1c, Hemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; eGFR, Estimated glomerular filtration rate; FIB-4, Fibrosis-4 index

Variable	Overall, N = 137607[1]	No Event, n = 127659[1]	Event, n = 9948[1]	p-value[2]
yes	9,844.0 (7.2%)	8,776.0 (6.9%)	1,068.0 (10.7%)	
Depression				< 0.001
no	124,150.0 (90.2%)	115,475.0 (90.5%)	8,675.0 (87.2%)	
yes	13,457.0 (9.8%)	12,184.0 (9.5%)	1,273.0 (12.8%)	
Hyperlipidemia				< 0.001
no	129,618.0 (94.2%)	120,595.0 (94.5%)	9,023.0 (90.7%)	
yes	7,989.0 (5.8%)	7,064.0 (5.5%)	925.0 (9.3%)	
Ischemic heart disease				< 0.001
no	125,423.0 (91.1%)	116,795.0 (91.5%)	8,628.0 (86.7%)	
yes	12,184.0 (8.9%)	10,864.0 (8.5%)	1,320.0 (13.3%)	
Arrhythmia				< 0.001
no	131,901.0 (95.9%)	122,509.0 (96.0%)	9,392.0 (94.4%)	
yes	5,706.0 (4.1%)	5,150.0 (4.0%)	556.0 (5.6%)	
Lipid lowering drugs				< 0.001
no	136,673.0 (99.3%)	126,833.0 (99.4%)	9,840.0 (98.9%)	
yes	934.0 (0.7%)	826.0 (0.6%)	108.0 (1.1%)	
Glucose-lowering drugs				< 0.001
no	134,833.0 (98.0%)	125,216.0 (98.1%)	9,617.0 (96.7%)	
yes	2,774.0 (2.0%)	2,443.0 (1.9%)	331.0 (3.3%)	
ALT (U/L)	27.1 (20.5, 36.7)	27.0 (20.5, 36.3)	29.4 (21.4, 42.6)	< 0.001
AST (U/L)	26.6 (22.7, 32.1)	26.5 (22.6, 31.8)	28.6 (23.4, 37.3)	< 0.001
HbA1c (mmol/mol)	36.6 (33.9, 40.0)	36.5 (33.8, 39.8)	37.5 (34.5, 42.0)	< 0.001
Albumin (g/L)	45.1 (43.3, 46.8)	45.1 (43.4, 46.9)	44.8 (43.0, 46.7)	< 0.001
Total cholesterol (mg/dL)	5.7 (4.8, 6.5)	5.7 (4.9, 6.5)	5.4 (4.6, 6.3)	< 0.001
HDL-C (mmol/L)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	< 0.001
LDL-C (mmol/L)	3.6 (3.0, 4.2)	3.6 (3.0, 4.3)	3.4 (2.8, 4.1)	< 0.001
Platelet count (10^9 cells/L)	247.0 (211.5, 287.0)	247.0 (212.0, 287.0)	242.2 (203.0, 285.2)	< 0.001
Creatinine (umol/L)	75.1 (65.2, 85.2)	75.2 (65.4, 85.2)	73.8 (63.6, 85.0)	< 0.001
Total bilirubin (umol/L)	8.0 (6.4, 10.4)	8.0 (6.4, 10.3)	8.2 (6.4, 10.9)	< 0.001
eGFR (mL/min/1.73 m2)	96.0 (84.9, 102.7)	96.1 (85.0, 102.8)	95.6 (83.8, 102.2)	< 0.001

Abbreviations: TDI, Townsend deprivation index; WC, Waist circumference; BMI, Body mass index; CCI, Charlson Comorbidity Index; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; HbA1c, Hemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; eGFR, Estimated glomerular filtration rate; FIB-4, Fibrosis-4 index

Variable	Overall, N = 137607[1]	No Event, n = 127659[1]	Event, n = 9948[1]	p-value[2]
Triglycerides (mmol/L)	2.2 (1.7, 3.1)	2.2 (1.7, 3.1)	2.2 (1.6, 3.1)	0.4
FIB-4	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	1.3 (1.0, 1.8)	< 0.001

[1]n (%); Median (Q1, Q3)

[2]Pearson's Chi-squared test; Wilcoxon rank sum test

Abbreviations: TDI, Townsend deprivation index; WC, Waist circumference; BMI, Body mass index; CCI, Charlson Comorbidity Index; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; HbA1c, Hemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; eGFR, Estimated glomerular filtration rate; FIB-4, Fibrosis-4 index

Association between comorbidity count and LREs

LRE incidence increased from 4.8% with no comorbidity to 6.8% with 1–2 and 10.4% with ≥ 3 conditions. After full adjustment, ≥ 3 conditions remained associated with LREs (HR 1.54, 95% CI 1.43–1.65; Table 2). Compared with participants without comorbidity, those with ≥ 3 comorbidities had a higher risk of LREs in the unadjusted model (HR 2.37, 95% CI 2.23–2.51; P < 0.001). The association was attenuated but remained evident after full adjustment (HR 1.54, 95% CI 1.43–1.65; P < 0.001) (Table 2).

Table 2
Association between CCI, comorbidity count and LREs occurrence in MASLD population

	Group	LREs/Total (%)	Model 1: HR with 95% CI; P value	Model 2: HR with 95% CI; P value	Model 3: HR with 95% CI; P value	Model 4: HR with 95% CI; P value	Model 5: HR with 95% CI; P value
CCI*	T1	2354/45869 (5.1%)	1.0[Reference]	1.0[Reference]	1.0[Reference]	1.0[Reference]	1.0[Reference]
	T2	3275/45869 (7.1%)	1.44 (1.36–1.52); <0.001	1.25 (1.17–1.33); <0.001	1.22 (1.15–1.30); <0.001	1.19 (1.11–1.27); <0.001	1.20 (1.13–1.28); <0.001
	T3	4319/45869 (9.4%)	2.01 (1.92–2.12); <0.001	1.63 (1.52–1.75); <0.001	1.55 (1.45–1.66); <0.001	1.40 (1.31–1.50); <0.001	1.41 (1.31–1.51); <0.001
Count	0	1613/33497 (4.8%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	1–2	4672/68788 (6.8%)	1.44 (1.36–1.53); <0.001	1.34 (1.27–1.42); <0.001	1.30 (1.23–1.37); <0.001	1.22 (1.15–1.30); <0.001	1.23 (1.15–1.31); <0.001
	≥ 3	3663/35322 (10.4%)	2.37 (2.23–2.51); <0.001	2.00 (1.89–2.13); <0.001	1.84 (1.73–1.96); <0.001	1.56 (1.45–1.67); <0.001	1.54 (1.43–1.65); <0.001

Model 1: Crude Cox model without adjustment; Model 2: Multivariable Cox model adjusted on Age, Sex, Ethnicity, TDI, Education; Model 3: Adjusted based on Model 2 and BMI, WC, Smoking; Model 4: Adjusted based on Model 3 and chronic kidney disease, DM, hypertension; Model 5: Adjusted based on Model 4 and AST, ALT, HbA1c, albumin, total cholesterol, LDL-C, platelet count, triglycerides, eGFR, Total Bilirubin, creatinine, and use of glucose-lowering and lipid-lowering drugs.

Abbreviations: CCI, Charlson Comorbidity Index; LREs, liver-related events; MASLD, metabolic dysfunction-associated steatotic liver disease; HR, hazard ratio; CI, confidence interval; TDI, Townsend deprivation index; BMI, body mass index; WC, waist circumference; DM, diabetes mellitus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated Glomerular filtration rate

* CCI was categorized into tertiles using cut points of 1 and 2, corresponding to scores of 0–1, 2, and ≥ 3, respectively.

No significant multicollinearity was detected among covariates, with all variance inflation factors below 5 (**Supplementary Table S5**). Assessment of the proportional hazards assumption is reported (**Supplementary Table S6**). Robust findings are presented in completed-case dataset (**Supplementary Table S7**).

Association between CCI and LREs

The incidence of LREs increased across CCI tertiles (T1: 5.1%, T2: 7.1%, T3: 9.4%). The highest versus lowest tertile remained associated after full adjustment (HR 1.41, 95% CI 1.31–1.51; Table 2), with consistent complete-case findings (Supplementary Table S10). Multicollinearity and proportional hazards assumption tests are presented in **Supplementary Tables S8 and S9**, respectively. The findings remained robust in completed-case analyses (**Supplementary Table S10**).

Associations of individual comorbidities and comorbidity combinations with LREs

The most prevalent individual comorbidities were hypertension (57,392; 41.7%), chronic respiratory disease (22,239; 16.2%), asthma (18,574; 13.5%), and diabetes (14,853; 10.8%). The most prevalent airs are diabetes with hypertension (N = 10,736; 7.8%), chronic respiratory disease with hypertension (N = 9,235; 6.7%), and hypertension with ischemic heart disease (N = 8,754; 6.4%). Detailed results for other combinations are presented in **Supplementary Table S11**.

Solid organ cancers showed the strongest association with LRE (HR 1.48, 95% CI 1.39–1.58). Among cardiometabolic conditions, diabetes demonstrated the strongest association (HR 1.39, 95% CI 1.29–1.49), followed by chronic kidney disease (HR 1.30, 95% CI 1.16–1.45), hyperlipidemia (HR 1.24, 95% CI 1.16–1.34), hypertension (HR 1.19, 95% CI 1.14–1.24), ischemic heart disease (HR 1.19, 95% CI 1.12–1.27), and arrhythmia (HR 1.15, 95% CI 1.05–1.25). Significant associations were also observed for several respiratory and neuropsychiatric conditions, including chronic obstructive pulmonary disease (COPD) (HR 1.37, 95% CI 1.24–1.50), asthma (HR 1.18, 95% CI 1.12–1.25), depression (HR 1.30, 95% CI 1.22–1.38), anxiety (HR 1.21, 95% CI 1.10–1.32), substance use disorder (HR 1.31, 95% CI 1.22–1.41), and connective tissue disease (HR 1.32, 95% CI 1.23–1.41) (all BH-adjusted $P < 0.05$). Estimates from the unadjusted and sequentially adjusted models are presented in **Supplementary Table S11**.

Comorbidity pairs were also associated with marked differences in LRE risk. After full adjustment, the strongest associations were observed for hypertension with substance use disorder (HR 1.51, 95% CI 1.37–1.65), asthma with depression (HR 1.48, 95% CI 1.32–1.67), hypertension with solid organ cancers (HR 1.44, 95% CI 1.31–1.57), diabetes with hyperlipidemia (HR 1.43, 95% CI 1.27–1.60), and diabetes with depression (HR 1.40, 95% CI 1.24–1.59) (all BH-adjusted $P < 0.05$). Overall, cardiometabolic combinations consistently showed elevated LRE risk, while combinations involving respiratory, psychological, or behavioral disorders also remain independently associated with adverse outcomes, supporting the importance of disease co-occurrence beyond individual comorbidities. The results from unadjusted and other adjusted models for pairwise comorbidities are provided in **Supplementary Table S12**.

Identification of distinct comorbidity patterns

LCA identified three distinct comorbidity patterns in addition to a minimal comorbidity class. Class 1 comprised 61,660 participants (44.8%), followed by Class 2 (29,562; 21.5%), Class 3 (12,888; 9.4%), and minimal comorbidity class (33,497; 24.3%) (Fig. 2A). The comorbidities overexpressed in each latent class relative to the overall study population were illustrated in Fig. 2B.

Class 1 represented a psychiatric-respiratory phenotype, characterized by enrichment of asthma (25.7% vs 13.5%), chronic respiratory disease (31.5% vs 16.2%), anxiety (7.5% vs 3.9%), depression (18.5% vs 9.8%), and substance use disorder (11.4% vs 6.4%), while cardiometabolic comorbidities, including diabetes, hypertension, ischemic heart disease, and hyperlipidemia, remained less common than in the overall cohort. Participants were relatively younger and had lower HbA1c, higher total cholesterol and LDL-C, and higher eGFR than the overall cohort (Fig. 2C, 2D **and Supplementary Table S13**).

Class 2 represented a hypertension-centered metabolic phenotype, defined by universal hypertension and a higher prevalence of diabetes, whereas the prevalence of other comorbidities remained similar to that of the overall cohort. Participants in this class displayed intermediate biological characteristics, including older age, greater central obesity, higher HbA1c and FIB-4, as well as reduced total cholesterol, LDL, and eGFR compared with Class 1 and overall population (Fig. 2C, 2D **and Supplementary Table S13**).

Class 3 represented an cardiovascular-kidney-metabolic (CKM) phenotype with extensive vascular comorbidity, characterized by a significantly higher prevalence of ischemic heart disease (71.3% vs 8.9%), stroke (11.9% vs 2.4%), arrhythmia (20.5% vs 4.1%), chronic kidney disease (10.4% vs 2.4%), diabetes (36.1% vs 10.8%), hyperlipidemia (58.7% vs 5.8%), obesity (16.5% vs 6.1%), and COPD (9.2% vs 2.9%). Participants were older, more socioeconomically deprived, less educated, more likely to have a history of smoking, and exhibited the highest CCI, HbA1c and FIB-4, together with the lowest eGFR and albumin, consistent with widespread multisystem impairment (Fig. 2C, 2D **and Supplementary Table S13**).

These comorbidity patterns exhibited distinct risks of LREs. During follow-up, 4.8%, 7.3%, 7.8%, and 11.9% of participants in the minimal comorbidity class and Class 1–3, respectively, developed LREs. Compared with the minimal comorbidity class, the fully adjusted hazard ratios for LREs were 1.39 (95% CI 1.31–1.47), 1.40 (95% CI 1.31–1.49), and 2.08 (95% CI 1.93–2.23) for Class 1, Class 2, and Class 3, respectively (all P < 0.001; Table 3). Cumulative incident curves showed clear separation of LRE risk across the four classes, with Class 3 exhibiting the significantly highest cumulative incidence of LREs (**Supplementary Figure S2**; log-rank P < 0.001).

Table 3
Association between comorbidity patterns and LREs occurrence in MASLD population

	Group	LREs/Total (%)	Model 1: HR with 95% CI; P value	Model 2: HR with 95% CI; P value	Model 3: HR with 95% CI; P value
Comorbidity patterns	Minimal comorbidity	1613/33497 (4.8%)	1.0[Reference]	1.0[Reference]	1.0[Reference]
	Class 1	4502/61660 (7.3%)	1.57 (1.48–1.66); <0.001	1.45 (1.37–1.54); <0.001	1.39 (1.31–1.47); <0.001
	Class 2	2296/29562 (7.8%)	1.68 (1.57–1.79); <0.001	1.48 (1.39–1.58); <0.001	1.40 (1.31–1.49); <0.001
	Class 3	1537/12888 (11.9%)	2.86 (2.66–3.06); <0.001	2.29 (2.13–2.46); <0.001	2.08 (1.93–2.23); <0.001
Model 1: Crude Cox model without adjustment					
Model 2: Multivariable Cox model adjusted on Age, Sex, Ethnicity, TDI, Education					
Model 3: Further adjusted for BMI, WC, and Smoking, eGFR, and Total bilirubin					
Abbreviations: LREs, liver-related events; MASLD, metabolic dysfunction-associated steatotic liver disease; HR, hazard ratio; CI, confidence interval; TDI, Townsend deprivation index; BMI, body mass index; WC, waist circumference					

Model fit statistics supported a three-class latent class solution. Although CAIC, BIC, and aBIC decreased with increasing numbers of latent classes, the reduction in BIC was most pronounced between one and three classes and plateaued thereafter (**Supplementary Table S14 and Figure S3**). Therefore, the three-class solution was selected by considering statistical fit, model parsimony, and clinical interpretability. The average posterior probability was 0.84, indicating good classification accuracy. Compared with comorbidity count and the CCI, latent comorbidity patterns consistently yielded lower AIC and BIC values (**Supplementary Table S15**). Similar comorbidity patterns were identified in male and female participants, supporting the robustness of the optimal latent class solution (**Supplementary Table S16-S18**).

Discussion

To our knowledge, this is the first study to evaluate the prognostic relevance of comorbidity in MASLD across aggregate burden measures, individual conditions, disease pairs, and data-driven patterns. Higher comorbidity count and CCI were associated with increased risk of liver-related events (LREs), but risk also varied according to the composition and co-occurrence of conditions. Latent class analysis (LCA) identified three clinically distinct phenotypes, of which the cardiovascular-kidney-metabolic (CKM) class had the highest risk. These findings suggest that comorbidity composition provides information that is not captured by aggregate burden alone.

Both comorbidity count and CCI showed graded associations with LRE risk, consistent with previous studies linking greater comorbidity burden to mortality in MASLD and NAFLD.[2, 15] However, counts assign equal importance to clinically heterogeneous conditions, whereas CCI uses fixed weights derived primarily from mortality associations. Neither measure identifies which conditions coexist. This limitation was illustrated by the psychiatric-respiratory and hypertension-centered metabolic classes, which had similar adjusted HRs for LREs (1.39 and 1.40, respectively) despite marked differences in age, adiposity, glycemic status, renal function, FIB-4, and disease composition. These findings do not establish equivalence between the classes but show that similar levels of risk may arise from clinically different comorbidity profiles.

LCA complemented the burden-based measures by identifying patterns spanning psychiatric, respiratory, metabolic, cardiovascular, and renal conditions. The psychiatric-respiratory class was younger and had a relatively favourable conventional metabolic profile, whereas the hypertension-centered metabolic class was older and had greater central adiposity and poorer glycemic status. Their numerically similar LRE risks suggest that conventional metabolic characteristics may not capture all dimensions of liver-related vulnerability. Comorbidity patterns may therefore complement, rather than replace, count- or CCI-based assessment.

The CKM class represented a subgroup with extensive multisystem disease, poorer glycemic and renal profiles, higher FIB-4, and lower albumin. Participants in this class had approximately twice the risk of LREs compared with those in the minimal-comorbidity group (HR 2.08, 95% CI 1.93–2.23). This phenotype broadly resembles the CKM framework, which emphasizes the interrelationship between metabolic risk, kidney disease, and cardiovascular disease.[13] A prior study similarly reported a higher risk of LRE among individuals with MASLD at advanced CKM stages (HRs 1.98, 95% CI 1.25–3.13).[14] However, because we did not apply predefined CKM criteria, our findings should not be interpreted as independent validation of that framework. The association may reflect shared systemic pathways, more advanced underlying liver disease, or residual confounding.

Diabetes was the most consistent cardiometabolic correlate of LRE risk across the individual-condition, pairwise, and latent-class analyses. This finding is consistent with previous evidence linking type 2 diabetes to hepatic decompensation in NAFLD.[15] Insulin resistance and hyperglycemia may promote lipotoxicity, inflammation, and profibrotic signaling, thereby accelerating fibrosis progression.[16] Chronic kidney disease was also independently associated with LREs and contributed to the highest-risk class, consistent with the shared metabolic, vascular, and inflammatory pathways between MASLD and kidney disease.[17] Hypertension showed a modest individual association but was frequently present in higher-risk pairs. Because the pairwise models did not formally test statistical interaction, these findings indicate risk associated with co-occurrence rather than a synergistic effect between conditions.

The respiratory and neuropsychiatric findings extend the analysis beyond conventional cardiometabolic comorbidity. COPD was independently associated with LRE, whereas the broader chronic respiratory disease was not. The broader category may have combined disorders with heterogeneous etiologies and systemic consequences, thereby attenuating condition-specific associations.[18] COPD is associated with systemic inflammation, oxidative stress, physical limitation, and vascular and metabolic abnormalities, which overlap with pathways implicated in MASLD progression.[18–20] Similarly, the psychiatric-respiratory class and the associations of depression, anxiety, and substance use disorder suggest that neuropsychiatric and behavioral health may represent an underrecognized dimension of risk in MASLD. Notably, the elevated

risk in this phenotype persisted despite younger age and a comparatively favorable metabolic profile. Smoking, sleep disturbance, physical inactivity, diet, treatment adherence, and engagement with preventive care are possible explanations, [21] but but these mechanisms were not directly assessed and require further investigation.

Our findings have several clinical implications for the management of MASLD. First, current approaches to MASLD risk assessment focus primarily on liver fibrosis and established cardiometabolic risk factors. Our results suggest that the assessment of multimorbidity in MASLD may benefit from moving beyond simple disease counts toward recognition of clinically meaningful disease combinations and patterns.[22] Patients with coexisting cardiovascular, renal, and metabolic disease may warrant careful assessment of liver fibrosis and closer longitudinal surveillance, even when the individual conditions are already being managed within other specialties.[23] The psychiatric-respiratory class suggests that reliance on conventional metabolic indicators alone could overlook noncardiometabolic vulnerability. Comorbidity profiles should complement rather than replace established liver risk assessments such as FIB-4 and liver stiffness measurement. More broadly, the prominence of cardiometabolic, renal, respiratory, and neuropsychiatric comorbidities highlights an integrated, multidisciplinary approach to MASLD care.[24]

This study benefited from a large population-based cohort, long-term follow-up and assessment of comorbidity, using several complementary approaches. LCA provided a data-driven approach for identifying patterns of disease co-occurrence. However, several limitations should be acknowledged. First, UK Biobank participants are subject to healthy-volunteer selection and were recruited within a single country, which may limit generalizability. Second, hepatic steatosis was ascertained using the fatty liver index rather than imaging or histology, which potentially resulted in misclassification of MASLD. Third, comorbidities and latent-class membership were assessed at baseline and treated as time-fixed. Incident conditions, changes in disease severity, and transitions between class were therefore not captured. Fourth, as an observational study, residual confounding and reverse causation and ascertainment bias cannot be fully excluded despite extensive multivariable adjustment. Therefore, the observed associations should not be interpreted as causal. Fifth, the proportional hazards assumption was not satisfied for the main exposures, and the reported HRs should therefore be interpreted as average associations over the follow-up period. Finally, competing risks were not formally modelled. Because death may preclude the occurrence of an LRE, cumulative incidence may have been overestimated, although the cause-specific hazard estimates remain interpretable as etiological associations under the assumptions of the Cox model.

In conclusion, LRE risk in MASLD was associated with both comorbidity burden and the composition of co-occurring conditions. CKM, psychiatric-respiratory, and hypertension-centered metabolic profiles identified clinically distinct groups, including groups with similar LRE risk despite different underlying disease structures. External studies should determine whether incorporating comorbidity patterns into established liver-risk pathways improves prediction or clinical decision-making.

Abbreviations

Abbreviation	**Full term**
aBIC	adjusted Bayesian information criterion
AIC	Akaike information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIC	Bayesian information criterion

BMI
body mass index
CAIC
consistent Akaike information criterion
CCI
Charlson Comorbidity Index
CI
confidence interval
CKM
cardiovascular-kidney-metabolic
COPD
chronic obstructive pulmonary disease
DM
diabetes mellitus
eGFR
estimated glomerular filtration rate
FDR
false discovery rate
FIB-4
fibrosis-4 index
HbA1c
hemoglobin A1c
HDL-C
high-density lipoprotein cholesterol
HR
hazard ratio
ICD-10
International Classification of Diseases, 10th Revision
LCA
latent class analysis
LDL-C
low-density lipoprotein cholesterol
LRE
liver-related event
MASLD
metabolic dysfunction-associated steatotic liver disease
O/E
observed-to-expected ratio
SMDs
standardized mean differences
TDI
Townsend deprivation index
WC
waist circumference

Declarations

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Conflicts of interest

Apichat Kaewdech received research grants or support from Roche, Roche Diagnostics, and Abbott Laboratories, and honoraria from Roche, Roche Diagnostics, Abbott Laboratories, and Esai. However, these roles do not present any conflict of interest concerning the content of this work. The other authors have no relevant conflict of interest to declare. All other authors disclose no potential conflicts of interest.

Statement of whether data

The individual-level data used in this study were obtained from the UK Biobank under Application No. 1164182 and cannot be shared directly by the authors because of data-use restrictions. These data are available to eligible researchers through the UK Biobank Access Management System (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

Analytic materials

The analytic methods are described in the manuscript and Supplementary Methods.

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Code availability

All the codes and relevant materials for the models and algorithms presented in our study were available at the repository https://github.com/Bingqing-Yang/Comorbidity-analysis-in-MASLD.

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Apichat Kaewdech received research grants or support from Roche, Roche Diagnostics, and Abbott Laboratories, and honoraria from Roche, Roche Diagnostics, Abbott Laboratories, and Esai. However, these roles do not present any conflict of interest concerning the content of this work. The other authors have no relevant conflict of interest to declare. All other authors disclose no potential conflicts of interest.

Author contributions

Jiandong Zhou, Karen Tu, David Ka Ki Wong, Bianca Bingqing Yang contributed to conceptualization and methodology. Jiandong Zhou performed data extraction and data preprocessing. Bianca Bingqing Yang contributed to statistical analysis and drafted the manuscript. All authors contributed to revising the manuscript. Jiandong Zhou and David Ka Ki Wong supervised the study. All authors proofread, reviewed, and approved the final version of the manuscript.

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