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ORIGINAL ARTICLE - HEPATOLOGY (CLINICAL)

Combined Impact of Triglyceride–Glucose Index and Alanine Aminotransferase on Steatotic Liver Disease and Subtypes

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ABSTRACT

Background and Aim: The triglyceride–glucose (TyG) index and alanine aminotransferase (ALT) are emerging biomarkers linked to metabolic disturbances and liver health. Nonetheless, the combined impact of these markers on predicting new-onset steatotic liver disease (SLD) and its metabolic and alcohol-associated subtypes remains unclear. This study aimed to investigate the association of TyG and ALT, individually and combined, in incident SLD in the Korean Genome and Epidemiology Study (KoGES) and UK Biobank cohorts.

Methods: This study utilized data from two large population-based cohorts: KoGES (adults aged 40–69 years from South Korea [2001–2002]) and UK Biobank (participants aged 37–73 years from the United Kingdom [2006–2010]). Participants without baseline SLD were classified into four groups based on TyG index and ALT levels, and the incidence of SLD was compared among these groups to assess risk.

Results: Elevated baseline TyG index and ALT levels were significantly associated with a higher risk of new-onset SLD and its subtypes in both cohorts. The highest HRs and ORs were observed in individuals with both markers elevated (2.39 in KoGES; 3.89 in UK Biobank). Survival analyses confirmed significantly lower survival probabilities in high-risk groups ($p < 0.001$). Predictive accuracy was highest with the combined TyG index + ALT model, outperforming either marker alone ($p < 0.001$).

Conclusions: Elevated combined baseline TyG index and ALT levels were significantly associated with increased risk of SLD and its subtypes. Combined use of these markers may be valuable for early identification and risk stratification of individuals at risk for SLD.

1 | Introduction

Steatotic liver disease (SLD) has emerged as a major global public health concern, affecting approximately 38% of the general population [1]. The increasing SLD prevalence is closely linked to increasing obesity, metabolic disorders, and alcohol consumption. SLD classification has evolved, defining metabolic dysfunction–associated steatotic liver disease (MASLD) as a primary subtype and distinguishing metabolic and alcohol-associated liver disease (MetALD) and alcohol-associated liver disease (ALD) as distinct entities [2]. The clinical spectrum of SLD ranges from simple hepatic steatosis to severe complications, including

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steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma [3]. SLD (particularly MASLD) is associated with an increased risk of systemic conditions, such as cardiovascular disease, chronic kidney disease, and certain extrahepatic cancers, underscoring its broader health implications [4]. Given the increasing SLD burden, early identification of high-risk individuals is crucial for timely intervention and effective disease management.

Although liver biopsy remains the gold standard for diagnosing SLD, its invasiveness, cost, and potential complications limit its widespread use in routine clinical practice [5]. Therefore, noninvasive biomarkers play a pivotal role in identifying individuals at risk for SLD and predicting disease progression. Among emerging biomarkers, the triglyceride–glucose (TyG) index, a surrogate marker of insulin resistance (IR), is linked to hepatic fat accumulation, inflammation, and fibrosis progression [6, 7]. Similarly, alanine aminotransferase (ALT), a widely used indicator of liver injury, is associated with SLD severity and disease progression [8, 9]. However, ALT is a marker of hepatocellular damage and may not fully capture the underlying metabolic dysfunction contributing to SLD development [10]. Given the strong metabolic component of SLD, combining the TyG index with ALT may better assess hepatic injury and metabolic risk.

Although both the TyG index and ALT have been independently implicated in metabolic dysfunction and liver disease, their combined impact on SLD and subtypes (MASLD, MetALD, and ALD) remains underexplored. Considering the increasing SLD prevalence and the need for improved risk stratification, determining whether these markers—individually or in combination—can improve the accuracy of predicting SLD onset is crucial. Therefore, the present study aimed to (1) evaluate the risk of SLD and its subtypes across various groups stratified by the TyG index and ALT levels and (2) determine the predictive value of the TyG index and ALT, individually and in combination, in the development of SLD and its subtypes using biomarker-defined criteria from the Korean Genome and Epidemiology Study (KoGES) and International Classification of Diseases, Tenth Revision (ICD-10) codes from the UK Biobank.

2 | Materials and Methods

Details on the study population, data sources, anthropometric and laboratory measurements, group classification, definitions, and statistical analysis are provided in the eMethods in the Supporting Information.

2.1 | Study Population and Data Source

Data derived from two large population-based prospective cohorts (the KoGES and UK Biobank) were utilized. Ultimately, 6541 participants from KoGES and 344 770 from the UK Biobank were included in the final analysis. Detailed participant selection criteria and exclusion flow are illustrated in Figure 1.

2.2 | Participant Groups According to the TyG Index and ALT Levels

The study population was stratified into four groups according to predefined cut-off values for the TyG index and ALT levels.

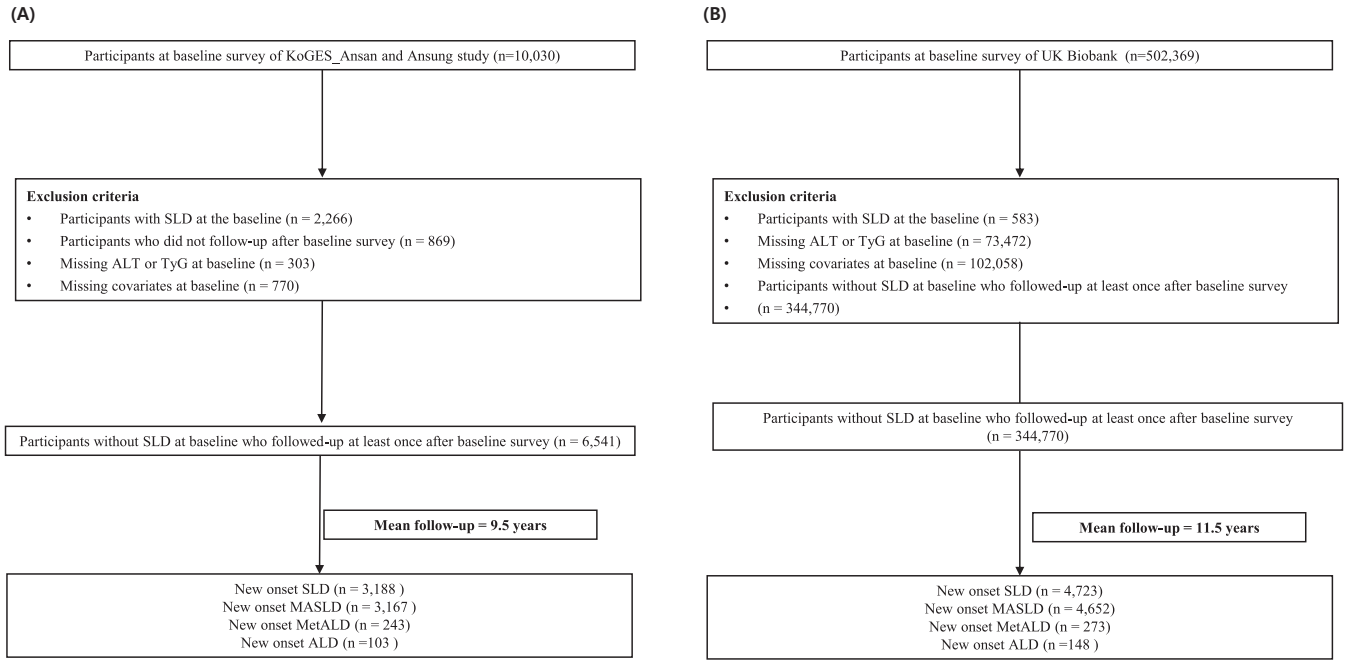

FIGURE 1 | Flow chart of the study population. Participants in the KoGES Ansan–Ansung cohort ($n = 10\,030$) and UK Biobank cohort ($n = 502\,369$) were assessed at baseline. After excluding participants with baseline steatotic liver disease (SLD), missing baseline triglyceride–glucose (TyG) index or alanine aminotransferase (ALT) values, and those without follow-up data, a total of 6541 KoGES participants (mean follow-up: 9.5 years) and 344 166 UK Biobank participants (mean follow-up: 11.5 years) remained eligible for analyses. Incident cases of SLD and its subtypes—metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD)—were identified during follow-up periods in both cohorts.

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The classification thresholds were a TyG index of 8.5 [11, 12] and ALT levels of 30 U/L (males) or 20 U/L (females) [8, 9].

2.3 | Definitions

New-onset SLD was defined as NAFLD-LFS higher than −0.640, irrespective of cardiometabolic risk factors. This category included new-onset MASLD, new-onset MetALD, and new-onset ALD. New-onset MASLD was defined as SLD plus the presence of at least one cardiometabolic risk factor, as per the established MASLD definition. In the UK Biobank dataset, new-onset SLD was defined as SLD diagnosed after baseline assessment (ICD-10: K76.0 or K75.8). New-onset MASLD was defined as an SLD diagnosed after baseline and meeting cardiometabolic criteria.

3 | Results

3.1 | Participant Characteristics

Participants' baseline characteristics by new-onset SLD status in the KoGES and UK Biobank cohorts are summarized in Table 1. In both cohorts, participants with new-onset SLD were older, more often males (UK Biobank), and exhibited higher BMI, WC, and BP levels ($p < 0.001$ for all). Fasting blood sugar, HbA1c, TG, and TyG index levels were significantly elevated, whereas HDL-C levels were lower in the new-onset SLD group ($p < 0.001$). AST and ALT levels were also higher among those with new-onset SLD ($p < 0.001$). In the KoGES, alcohol consumption and smoking status were similar between groups ($p > 0.05$). In the UK Biobank, the new-onset SLD group had lower alcohol intake but higher smoking prevalence ($p < 0.001$). The prevalence of diabetes mellitus, hypertension, dyslipidemia, and MetS was significantly higher in participants with new-onset SLD across both cohorts ($p < 0.001$).

The participants' baseline characteristics according to the presence of new-onset MASLD, MetALD, and ALD in the KoGES and UK Biobank cohorts are presented in Tables S1–S3, respectively. The baseline characteristics of participants from the KoGES and UK Biobank cohorts stratified by elevated ALT and TyG index levels are presented in Tables S4 and S5, respectively.

3.2 | Risk of New-Onset SLD, MASLD, MetALD, and ALD Based on the TyG Index and ALT Status

The distributions of the TyG index and ALT levels of KoGES participants are presented in Figure S1A,B. The association between the TyG index and ALT levels and the adjusted HRs for SLD, analyzed using restricted cubic spline (RCS) models, is shown in Figure S1C,D. The distributions of the TyG index and ALT levels among UK Biobank participants are presented in Figure S2A,B, and their relationship with SLD risk according to the RCS model analysis is shown in Figure S2C,D.

The Kaplan–Meier survival curves for new-onset SLD (Figure 2A), MASLD (Figure 2B), MetALD (Figure 2C), and ALD (Figure 2D) in the KoGES cohort revealed significantly lower survival probability and greater risk of disease onset in participants with higher TyG index and ALT levels, with statistically significant differences among groups ($p < 0.001$).

Table 2 presents the HRs (95% CIs) for new-onset SLD, MASLD, MetALD, and ALD in the KoGES cohort, and the ORs (95% CIs) for these outcomes in the UK Biobank cohort, according to the TyG index and ALT levels. In both cohorts, the risk of new-onset SLD and MASLD progressively increased from Groups 2–4, with Group 4 (high TyG index and high ALT levels) showing the highest risk. In KoGES, the HRs for SLD were 1.64 (Group 2), 1.67 (Group 3), and 2.39 (Group 4) and for MASLD were 1.66 (Group 2), 1.66 (Group 3), and 2.40 (Group 4) ($p < 0.001$) after adjusting for confounders. In the UK Biobank, the ORs for SLD were 1.49 (Group 2), 2.63 (Group 3), and 3.65 (Group 4) and for MASLD were 1.59 (Group 2), 2.75 (Group 3), and 3.89 (Group 4) ($p < 0.001$). The associations were even stronger for new-onset MetALD and ALD, particularly in Group 4, where in KoGES, the HRs for MetALD and ALD were 4.16 (95% CI: 2.78–6.25) and 4.44 (95% CI: 2.44–8.10), respectively ($p < 0.001$). Group 3 also showed a significant increase in risk, with HRs of 2.44 for MetALD (95% CI: 1.33–4.48) and 4.21 for ALD (95% CI: 2.01–8.82) ($p < 0.001$). Similarly, in the UK Biobank, Group 4 exhibited the highest risk for MetALD (OR: 3.53, 95% CI: 2.33–5.37) and ALD (OR: 7.78, 95% CI: 3.85–15.75) ($p < 0.001$), whereas Group 3 also exhibited significantly increased risks (OR: 2.26 for MetALD and OR: 7.37 for ALD, $p < 0.001$). Sensitivity analyses using multiple imputation for missing covariates yielded results consistent with the primary analyses in both cohorts (Table S6).

3.3 | Association of the TyG Index and ALT Levels With New-Onset Liver Disease Across Subgroups in the KoGES and UK Biobank

Subgroup analysis stratified by sex, age, and BMI in the KoGES cohort revealed that participants in Group 4, characterized by higher TyG index and ALT levels, exhibited an increased risk of developing new-onset SLD, MASLD, MetALD, and ALD across all subgroups (Figure S3). The associations remained statistically significant in both males and females, participants aged < 60 and ≥ 60 years, and individuals with BMI < 25 and $\geq 25\,kg/m^2$. Irrespective of subgroup classification, the risk of new-onset liver disease progressively increased from Groups 2 to 4, with Group 4 showing the highest HRs across all conditions ($p < 0.001$) (Figure S3). These findings indicate a consistent dose-dependent relationship between the TyG index, ALT levels, and liver disease risk. A similar subgroup analysis of the UK Biobank cohort (Figure S4) yielded comparable results, further reinforcing the robustness of these associations across populations.

3.4 | Comparative Accuracy of the TyG Index, ALT, and Their Combination in Predicting the Incidence of Liver Diseases in the KoGES and UK Biobank

The accuracy of the TyG index, ALT, and their combination in predicting the incidence of SLD, MASLD, MetALD, and ALD

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TABLE 1 | Baseline characteristics of all participants according to the presence of new-onset SLD in the KoGES and UK Biobank.

Characteristic	KoGES			UK Biobank		
	Nondeveloped SLD ($N=3353$)	New-onset SLD ($N=3188$)	*p* value	Nondeveloped SLD ($N=340\,047$)	New-onset SLD ($N=4723$)	*p* value
Age, years	51.4 ± 9.2	51.9 ± 8.5	0.037	56.3 ± 8.1	56.9 ± 7.9	< 0.001
Sex, *n* (%)			0.062			< 0.001
Male	1618 (48.3%)	1464 (45.9%)		163 712 (48.1%)	2398 (50.8%)	
Female	1735 (51.7%)	1724 (54.1%)		176 335 (51.9%)	2325 (49.2%)	
BMI, kg/m^2	23.0 ± 2.7	25.0 ± 2.7	< 0.001	27.3 ± 4.7	31.1 ± 5.4	< 0.001
WC, cm	77.9 ± 7.8	83.5 ± 7.6	< 0.001	90.1 ± 13.3	100.5 ± 13.6	< 0.001
SBP, mmHg	115.7 ± 16.9	121.6 ± 17.4	< 0.001	137.6 ± 18.5	140.5 ± 18.1	< 0.001
DBP, mmHg	76.7 ± 10.8	80.8 ± 10.9	< 0.001	82.2 ± 10.1	84.5 ± 10.2	< 0.001
Alcohol consumption, *n* (%)	1624 (48.4%)	1564 (49.1%)	0.631	314 818 (92.6%)	4142 (87.7%)	< 0.001
Smoking, *n* (%)	863 (25.7%)	805 (25.3%)	0.672	34 568 (10.2%)	690 (14.6%)	< 0.001
MET-hour/week	23.8 ± 14.7	24.4 ± 14.9	0.124	44.4 ± 45.3	40.0 ± 45.5	< 0.001
FBS, mmol/L	86.4 ± 11.0	90.1 ± 16.8	< 0.001	91.9 ± 21.6	101.4 ± 37.8	< 0.001
HbA1c, % (mmol/mol)	5.5 ± 0.4 (37 ± 4)	5.7 ± 0.7 (39 ± 8)	< 0.001	5.4 ± 0.6 (36 ± 7)	5.8 ± 0.9 (40 ± 10)	< 0.001
hs-CRP, mg/dL	0.2 ± 0.5	0.2 ± 0.6	< 0.001	0.2 ± 0.4	0.4 ± 0.5	< 0.001
Platelet count, $\times 10^9$/L	260.2 ± 60.5	268.6 ± 62.6	< 0.001	252.0 ± 59.5	251.2 ± 65.3	0.404
AST, U/L	23.0 ± 7.5	23.8 ± 8.0	< 0.001	26.1 ± 10.0	33.4 ± 19.1	< 0.001
ALT, U/L	18.2 ± 8.3	21.5 ± 10.2	< 0.001	23.4 ± 13.8	35.4 ± 25.0	< 0.001
TC, mg/dL	192.1 ± 33.3	199.8 ± 35.4	< 0.001	220.0 ± 43.9	211.6 ± 48.6	< 0.001
TG, mg/dL	113.5 ± 62.0	149.6 ± 96.1	< 0.001	153.4 ± 89.6	197.6 ± 110.1	< 0.001
HDL-C, mg/dL	53.1 ± 12.1	48.8 ± 10.8	< 0.001	56.1 ± 14.8	49.7 ± 14.0	< 0.001
LDL-C mg/dL	116.3 ± 30.9	121.1 ± 34.2	< 0.001	137.5 ± 33.4	132.8 ± 36.1	< 0.001
NAFLD-LFS	−2.2 ± 0.7	−1.8 ± 0.7	< 0.001			
TyG index	8.4 ± 0.5	8.7 ± 0.5	< 0.001	8.7 ± 0.6	9.0 ± 0.6	< 0.001
Diabetes mellitus, *n* (%)	120 (3.6%)	242 (7.6%)	< 0.001	16 244 (4.8%)	808 (17.1%)	< 0.001
Hypertension, *n* (%)	615 (18.3%)	1027 (32.2%)	< 0.001	88 465 (26.0%)	2134 (45.2%)	< 0.001
Dyslipidemia, *n* (%)	760 (22.7%)	1278 (40.1%)	< 0.001	57 139 (16.8%)	1480 (31.3%)	< 0.001
MetS, *n* (%)	181 (5.4%)	590 (18.5%)	< 0.001	111 861 (32.9%)	2896 (61.4%)	< 0.001

Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; DBP, diastolic blood pressure; FBG, fasting blood glucose; FIB-4, Fibrosis-4 Index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NAFLD-LFS, nonalcoholic fatty liver disease-liver fat score; SBP, systolic blood pressure; SLD, steatotic liver disease; TG, triglycerides; TyG index, triglyceride–glucose index; WC, waist circumference.

in the KoGES cohort, as evaluated using Harrell's C-index and Heagerty's iAUC, is presented in Table 3. The ALT + TyG index group consistently exhibited the highest predictive accuracy across all liver disease categories, with significantly higher C-index and iAUC values compared with the ALT or TyG index alone ($p < 0.001$ for most comparisons). The TyG index group alone demonstrated

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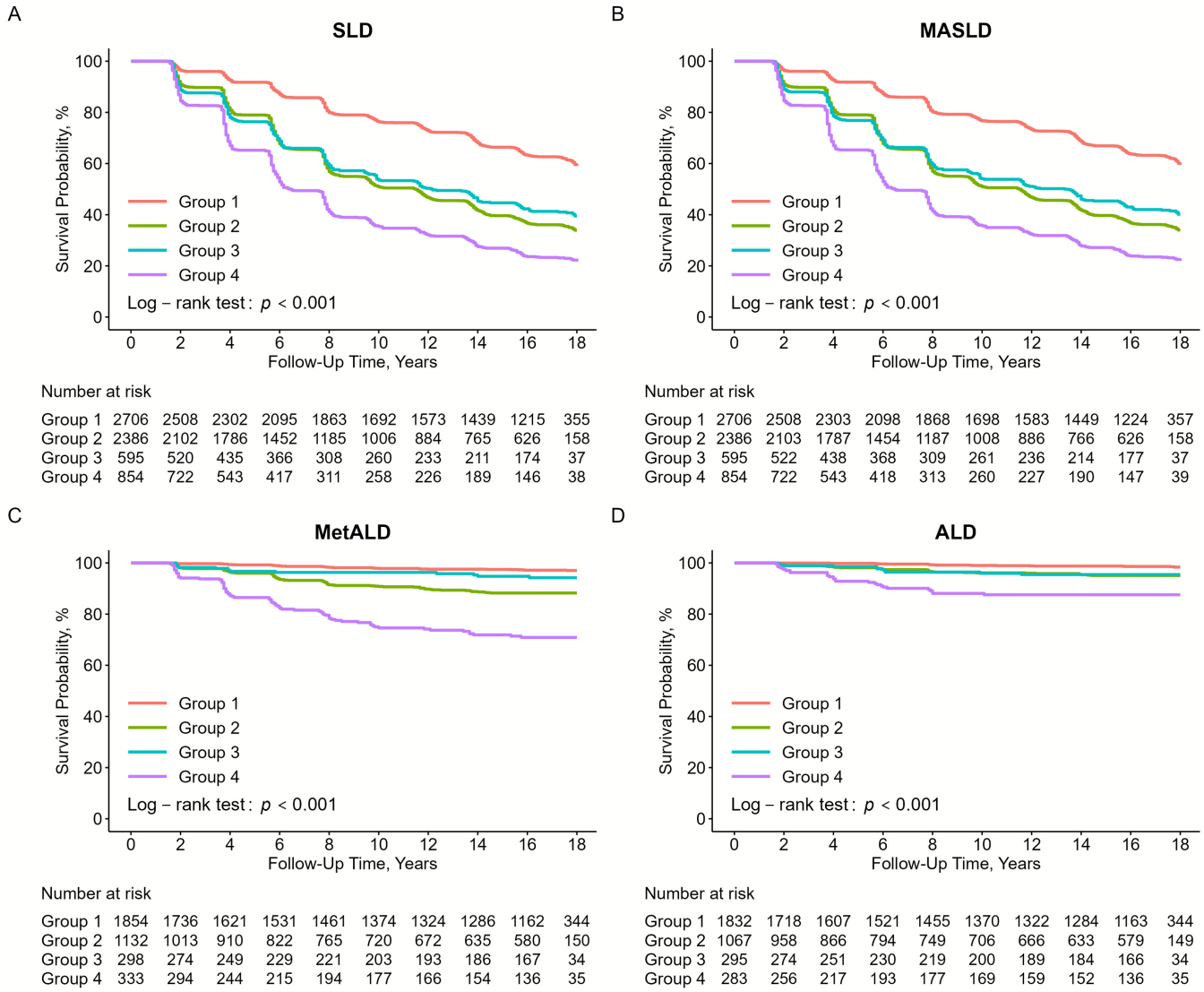

FIGURE 2 | Kaplan–Meier survival curves for new-onset steatotic liver disease (SLD), metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD). Kaplan–Meier survival curves for incident (A) new-onset SLD, (B) new-onset MASLD, (C) new-onset MetALD, and (D) new-onset ALD. Participants were classified into four groups according to the baseline triglyceride–glucose (TyG) index and alanine aminotransferase (ALT) levels: Group 1, TyG index < 8.5 and ALT < 30 U/L (males) or < 20 U/L (females); Group 2, TyG index ≥ 8.5 and ALT < 30 U/L (males) or < 20 U/L (females); Group 3, TyG index < 8.5 and ALT ≥ 30 U/L (males) or ≥ 20 U/L (females); and Group 4, TyG index ≥ 8.5 and ALT ≥ 30 U/L (males) or ≥ 20 U/L (females). Group 1 exhibited the highest survival probability, whereas Group 4 exhibited the lowest survival probability. Between-group differences were statistically significant (log-rank test, $p < 0.001$).

better predictive performance than the ALT group, but the combined ALT + TyG index model further improved accuracy. The difference between ALT alone and ALT + TyG index was statistically significant for all conditions ($p < 0.001$), indicating that the combination of the TyG index and ALT provides superior risk stratification for liver disease incidence.

The accuracy of the TyG index, ALT, and their combination in predicting SLD, MASLD, MetALD, and ALD incidence in the UK Biobank cohort, as examined using the age- and sex-adjusted AUC analysis, is presented in Table S7. The ALT + TyG index group demonstrated the highest AUC values across all liver disease categories, indicating superior predictive performance to ALT or TyG index alone. The ALT group alone showed higher predictive accuracy than the TyG index group, but combining ALT and the TyG index further improved prediction, particularly for SLD (AUC: 0.686), MASLD (AUC: 0.692), MetALD (AUC: 0.695), and ALD (AUC: 0.758). The differences between the TyG index alone and ALT + TyG index were statistically significant across all conditions ($p < 0.001$).

4 | Discussion

In this study, we comprehensively assessed the combined and individual predictive impacts of the TyG index and ALT levels on incident SLD and its subtypes, including MASLD, MetALD, and ALD. Our findings clearly indicated that elevated TyG index and ALT levels significantly increased the risk of developing SLD and its subtypes. Notably, individuals in the highest risk

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TABLE 2 | Association of combined triglyceride–glucose index (TyG) and alanine aminotransferase (ALT) levels with incident SLD and subtypes in KoGES and UK Biobank cohorts.

	HR (95% CIs)		HR (95% CIs)		HR (95% CIs)		HR (95% CIs)	
KoGES	**Unadjusted**	***p* value**	**Model 1**	***p* value**	**Model 2**	***p* value**	**Model 3**	***p* value**
New-onset SLD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	2.22 (2.04–2.42)	< 0.001	2.22 (2.04–2.42)	< 0.001	1.91 (1.75–2.08)	< 0.001	1.64 (1.50–1.80)	< 0.001
Group 3	2.02 (1.78–2.30)	< 0.001	1.96 (1.73–2.23)	< 0.001	1.69 (1.49–1.93)	< 0.001	1.67 (1.47–1.90)	< 0.001
Group 4	3.39 (3.06–3.76)	< 0.001	3.48 (3.14–3.87)	< 0.001	2.69 (2.41–2.99)	< 0.001	2.39 (2.14–2.67)	< 0.001
New-onset MASLD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	2.25 (2.07–2.45)	< 0.001	2.26 (2.07–2.46)	< 0.001	1.93 (1.77–2.11)	< 0.001	1.66 (1.52–1.82)	< 0.001
Group 3	2.02 (1.77–2.29)	< 0.001	1.96 (1.72–2.23)	< 0.001	1.69 (1.48–1.92)	< 0.001	1.66 (1.46–1.90)	< 0.001
Group 4	3.43 (3.09–3.81)	< 0.001	3.53 (3.18–3.92)	< 0.001	2.71 (2.43–3.01)	< 0.001	2.40 (2.15–2.69)	< 0.001
New-onset MetALD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	4.41 (3.10–6.26)	< 0.001	3.28 (2.30–4.67)	< 0.001	2.38 (1.65–3.41)	< 0.001	1.85 (1.26–2.71)	0.002
Group 3	2.10 (1.15–3.82)	0.016	2.86 (1.57–5.23)	< 0.001	2.36 (1.29–4.33)	0.005	2.44 (1.33–4.48)	0.004
Group 4	12.33 (8.53–17.83)	< 0.001	8.38 (5.78–12.15)	< 0.001	5.18 (3.53–7.62)	< 0.001	4.16 (2.78–6.25)	< 0.001
New-onset ALD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	3.51 (2.09–5.89)	< 0.001	2.56 (1.52–4.31)	< 0.001	2.02 (1.19–3.45)	0.01	1.72 (0.98–3.03)	0.057
Group 3	3.28 (1.59–6.76)	0.001	4.60 (2.23–9.50)	< 0.001	3.63 (1.74–7.57)	< 0.001	4.21 (2.01–8.82)	< 0.001
Group 4	9.99 (5.74–17.40)	< 0.001	6.84 (3.92–11.94)	< 0.001	4.73 (2.67–8.37)	< 0.001	4.44 (2.44–8.10)	< 0.001
UK Biobank	OR (95% CIs)		OR (95% CIs)		OR (95% CIs)		OR (95% CIs)	
	Unadjusted		Model 1		Model 2		Model 3	
New-onset SLD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	2.13 (1.92–2.37)	< 0.001	2.07 (1.86–2.30)	< 0.001	1.53 (1.38–1.71)	< 0.001	1.49 (1.34–1.66)	< 0.001
Group 3	3.15 (2.76–3.59)	< 0.001	3.17 (2.78–3.61)	< 0.001	2.66 (2.33–3.04)	< 0.001	2.63 (2.30–3.00)	< 0.001

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TABLE 2 | (Continued)

KoGES	HR (95% CIs) Unadjusted	*p* value	HR (95% CIs) Model 1	*p* value	HR (95% CIs) Model 2	*p* value	HR (95% CIs) Model 3	*p* value
Group 4	6.49 (5.88–7.16)	< 0.001	6.38 (5.78–7.04)	< 0.001	3.88 (3.51–4.30)	< 0.001	3.65 (3.29–4.04)	< 0.001
New-onset MASLD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	2.30 (2.06–2.56)	< 0.001	2.22 (1.99–2.48)	< 0.001	1.63 (1.46–1.82)	< 0.001	1.59 (1.42–1.78)	< 0.001
Group 3	3.31 (2.89–3.78)	< 0.001	3.33 (2.91–3.81)	< 0.001	2.78 (2.43–3.19)	< 0.001	2.75 (2.40–3.14)	< 0.001
Group 4	7.05 (6.37–7.81)	< 0.001	6.91 (6.24–7.66)	< 0.001	4.15 (3.74–4.61)	< 0.001	3.89 (3.50–4.33)	< 0.001
New-onset MetALD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	2.30 (1.51–3.50)	< 0.001	2.00 (1.31–3.06)	0.001	1.66 (1.08–2.56)	0.02	1.62 (1.05–2.49)	0.028
Group 3	2.54 (1.45–4.46)	0.001	2.70 (1.54–4.73)	< 0.001	2.34 (1.33–4.11)	0.003	2.26 (1.29–3.98)	0.005
Group 4	5.93 (3.97–8.86)	< 0.001	5.54 (3.71–8.28)	< 0.001	3.84 (2.53–5.82)	< 0.001	3.53 (2.33–5.37)	< 0.001
New-onset ALD								
Group 1	Ref		Ref		Ref		Ref	
Group 2	2.84 (1.36–5.94)	0.005	2.33 (1.11–4.88)	0.025	1.97 (0.94–4.15)	0.074	1.93 (0.91–4.06)	0.085
Group 3	7.42 (3.36–16.39)	< 0.001	8.37 (3.78–18.52)	< 0.001	7.65 (3.45–16.98)	< 0.001	7.37 (3.32–16.36)	< 0.001
Group 4	12.14 (6.11–24.12)	< 0.001	11.01 (5.54–21.88)	< 0.001	8.35 (4.13–16.87)	< 0.001	7.78 (3.85–15.75)	< 0.001

Note: Model 1: Age and sex. Model 2: Age, sex, BMI, smoking, alcohol consumption, and METS. Model 3: Age, sex, BMI, smoking, alcohol consumption, METS, hypertension, diabetes mellitus, and dyslipidemia. Group 1: TyG < 8.5 and ALT < 30 (males) or ALT < 20 (females). Group 2: TyG ≥ 8.5 and ALT < 30 (males) or ALT < 20 (females). Group 3: TyG < 8.5 and ALT ≥ 30 (males) or ALT ≥ 20 (females). Group 4: TyG ≥ 8.5 and ALT ≥ 30 (males) or ALT ≥ 20 (females).

group (Group 4) exhibited the highest HRs for incident MASLD, MetALD, and ALD in both cohorts, underscoring the combined importance of metabolic dysfunction and hepatic injury in disease pathogenesis.

ALT, a well-established biomarker of hepatocellular injury clinically used to assess liver disease severity [10], catalyzes the conversion of L-alanine and 2-oxoglutarate into pyruvate and L-glutamate, playing a crucial role in hepatic energy metabolism [8, 9, 13]. Elevated ALT levels reflect oxidative stress, inflammation, and lipotoxicity-induced damage in hepatocytes, contributing to liver disease progression [13, 14]. Additionally, elevated ALT levels are linked to systemic metabolic disturbances, including IR, dyslipidemia, and chronic low-grade inflammation, all of which exacerbate metabolic dysfunction and liver disease [15, 16]. A population-based study reported a 1.7-fold higher risk of cardiovascular mortality and 2.2-fold higher risk of all-cause mortality in men with ALT levels ≥ 40 U/L than in those with ALT levels < 20 [17] Regular ALT monitoring can be useful in predicting SLD risk and progression [13], guiding treatment decisions, and informing lifestyle interventions. Although ALT is a valuable clinical marker, its levels may not always accurately reflect the severity of chronic liver disease observed in biopsies [18], and some patients with Metabolic Associated Fatty Liver Disease (MAFLD) may exhibit normal ALT levels, posing challenges for early detection [19].

The TyG index, a surrogate marker of IR, reflects metabolic dysfunction that contributes to hepatic fat accumulation, inflammation, and the progression of fibrosis. IR plays a central role in SLD development by promoting hepatic de novo lipogenesis, impairing β-oxidation, and reducing very-low-density lipoprotein secretion [20]. The TyG index captures an imbalance between glucose metabolism and lipid homeostasis, leading to increased hepatic TG accumulation [21]. Elevated insulin levels in IR states further exacerbate hepatic lipid deposition by upregulating sterol regulatory element-binding protein-1c, a key transcription factor involved in lipogenesis [22]. Additionally,

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TABLE 3 | Comparison of predictive accuracy for SLD, MASLD, MetALD, and ALD incidence among the groups based on TyG index and ALT status in the KoGES using time-dependent receiver operating characteristic analysis.

	SLD		MASLD		MetALD		ALD	
	Harrell's C index	Heagerty's iAUC	Harrell's C index	Heagerty's iAUC	Harrell's C index	Heagerty's iAUC	Harrell's C index	Heagerty's iAUC
ALT group, (1)	0.595 (0.584, 0.605)	0.579 (0.569, 0.593)	0.595 (0.585, 0.605)	0.580 (0.568, 0.593)	0.792 (0.767, 0.816)	0.796 (0.770, 0.819)	0.818 (0.784, 0.852)	0.818 (0.786, 0.848)
TyG index group, (2)	0.620 (0.610, 0.630)	0.612 (0.601, 0.624)	0.622 (0.612, 0.632)	0.614 (0.603, 0.627)	0.812 (0.789, 0.834)	0.814 (0.789, 0.837)	0.815 (0.782, 0.847)	0.814 (0.778, 0.842)
ALT + TyG index group, (3)	0.643 (0.633, 0.652)	0.632 (0.621, 0.646)	0.644 (0.635, 0.654)	0.635 (0.624, 0.649)	0.826 (0.804, 0.849)	0.830 (0.806, 0.852)	0.843 (0.812, 0.874)	0.840 (0.808, 0.867)
Difference (1, 2)	−0.025 (−0.037, −0.013)	−0.032 (−0.045, −0.020)	−0.027 (−0.039, −0.015)	−0.035 (−0.048, −0.021)	−0.020 (−0.038, −0.002)	−0.018 (−0.036, −0.000)	0.003 (−0.027, 0.033)	0.004 (−0.022, 0.030)
Difference (1–3)	−0.048 (−0.057, −0.039)	−0.053 (−0.063, −0.045)	−0.049 (−0.058, −0.040)	−0.055 (−0.066, −0.046)	−0.035 (−0.048, −0.022)	−0.034 (−0.047, −0.021)	−0.025 (−0.042, −0.008)	−0.021 (−0.039, −0.007)
Difference (2, 3)	−0.023 (−0.028, −0.018)	−0.020 (−0.029, −0.015)	−0.022 (−0.028, −0.017)	−0.020 (−0.030, −0.015)	−0.015 (−0.023, −0.007)	−0.016 (−0.026, −0.008)	−0.028 (−0.048, −0.008)	−0.025 (−0.045, −0.010)
p value: (1) vs. (2)	< 0.001	< 0.001	< 0.001	0.002	0.032	0.024	0.837	0.607
p value: (1) vs. (3)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.004	< 0.001
p value: (2) vs. (3)	< 0.001	0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001

Abbreviations: ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; iAUC, integrated area under the receiver operating characteristic curve; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; SLD, steatotic liver disease; TyG index, triglyceride–glucose index. All values were adjusted for age and sex.

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IR induces mitochondrial dysfunction and oxidative stress, leading to hepatocellular damage, inflammation, and fibrosis progression [23]. This supports the role of IR in SLD pathogenesis, as reflected by the TyG index. Our findings align with those of previous studies reporting a close relationship between the TyG index and hepatic fat accumulation, suggesting its utility as a noninvasive metabolic biomarker for SLD screening [6, 7].

The TyG index and ALT can independently predict new-onset fatty liver disease. In a large cohort, the risk of NAFLD was significantly higher in the high TyG group, with an HR of 1.67 in males and 2.06 in females [24]. Furthermore, a meta-analysis of 17 studies involving approximately 120000 participants confirmed the TyG index as a strong predictor of incident NAFLD, reporting an OR of 6.00 (95% CI 4.12–8.74) and an HR of 1.70 (95% CI 1.28–2.27) in the high group compared to the low group [25]. These results demonstrate that the TyG index consistently predicts incident NAFLD across multiple cohorts, as supported by meta-analytic evidence.

ALT was also confirmed as an independent predictor. In a study cohort, even when ALT levels were within the normal range, higher levels increased the risk of new-onset NAFLD [26]. In another population cohort, long-term exposure to elevated-normal ALT within the normal range was linearly associated with the risk of developing MAFLD [27].

This suggests that ALT is not merely a marker of liver damage but can also predict the long-term development of MASLD.

However, evidence on the combined effect of these two markers in predicting incident fatty liver disease has been limited. Interestingly, our study revealed differences in the predictive performance of these biomarkers between the two cohorts. The TyG index exhibited stronger predictive value for SLD risk in the KoGES, whereas ALT was a more robust predictor in the UK Biobank. This discrepancy may be attributable to ethnic differences in metabolic health and liver disease susceptibility. As indicated in previous studies, East Asians exhibit a higher predisposition to metabolic dysfunction than Western populations [28, 29].

A key finding of our study is that combining the TyG index and ALT improves SLD risk prediction beyond either biomarker alone. The C-index and iAUC values demonstrate that the combined model offers superior predictive performance that remains significant across different follow-up periods. Therefore, incorporating both metabolic and hepatic markers enhances risk stratification, providing clinicians with a more comprehensive tool for identifying high-risk individuals. Our findings are consistent with studies emphasizing multimodal risk assessment, particularly in conditions with overlapping metabolic and hepatic components, such as SLD.

The findings of this study have several important clinical implications. In both cohorts, models combining the TyG index and ALT demonstrated modest yet consistent improvements in predictive discrimination compared with models incorporating either marker alone. Although the absolute gains in the C-index were small, their consistency across populations suggests a meaningful complementary contribution of metabolic and hepatic markers to risk stratification in clinical settings. Given the strong association between the TyG index, ALT, and the risk of steatotic liver disease, routine assessment of these biomarkers may support early risk stratification in primary care settings. Their combined use as a simple, low-cost first-line screening tool could help identify individuals at higher metabolic risk who may benefit from prioritized imaging evaluation (e.g., ultrasound) or early targeted lifestyle interventions. In this way, the TyG-ALT combination may serve as a practical gatekeeping step to enhance the efficiency of existing screening strategies rather than replace them. Furthermore, the highest risk population may benefit from targeted interventions, such as aggressive lifestyle modifications, metabolic control, and hepatoprotective treatments. Moreover, integrating both metabolic (TyG index) and hepatic (ALT) markers into existing SLD prediction models may enhance their accuracy, improving clinical decision-making. These findings emphasize the importance of a more comprehensive strategy that incorporates metabolic and hepatic risk factors to prevent and manage SLD, thereby reducing the disease burden at both the individual and population levels. The cutoff values were predefined a priori based on previous studies to enhance clinical interpretability and comparability; notably, they were also close to the empirical distribution of the study population (approximately the median for the TyG index and the upper quartile for ALT) [11, 12]. Further studies are warranted to explore whether population-specific or fully data-driven thresholds could further optimize risk prediction across diverse populations. The strengths of our study include its robust design, which uses two large, well-established prospective cohorts, enabling comprehensive validation and generalizability of the findings across diverse populations. The extensive follow-up periods provided sufficient power to capture new-onset SLD and its subtypes, and the stratified analyses across multiple metabolic and hepatic biomarkers enhanced our understanding of disease risk stratification.

Nevertheless, this study has some limitations. First, SLD diagnosis relied on noninvasive measures rather than liver biopsies or advanced imaging methods, potentially leading to misclassification of liver disease severity or subtype. Because imaging data and Gamma-glutamyl transpeptidase (GGT) values were unavailable in the KoGES cohort, the NAFLD-LFS was the only validated indicator available for predicting steatosis in this study. Although the NAFLD-LFS is a validated score widely used in many studies, its components include glucose, triglycerides, and the AST/ALT ratio, which may partially overlap with our exposure variables (TyG and ALT), raising concerns of potential circular reasoning. However, in the UK Biobank cohort, SLD was defined using ICD-10 codes, and this limitation was mitigated through cross-cohort validation, as consistent results were observed across both cohorts. Accordingly, further studies incorporating imaging modalities, such as ultrasound, CT, or MRI, along with histological confirmation through liver biopsy, are warranted to externally validate the predictive performance of the combined TyG and ALT model and establish its clinical utility. Second, in the UK Biobank cohort, differences in the timing of SLD diagnosis and the assessment of cardiometabolic criteria used to define MASLD could have led to misclassification or an underestimation of the true association between metabolic dysfunction and SLD incidence. Third, despite rigorous adjustments, residual confounding from unmeasured factors, such as

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dietary intake or genetic predispositions, may remain. Lastly, differences in definitions and diagnostic criteria between the two cohorts could introduce variability in disease classification, potentially affecting the consistency of results. Nonetheless, the study's large-scale, prospective nature, and validation in two independent cohorts strengthen the reliability and applicability of our findings.

In conclusion, our study demonstrated that elevated TyG index and ALT levels were independently and synergistically associated with an increased risk of new-onset MASLD and that their combined assessment showed superior predictive accuracy. Integrating the TyG index and ALT into MASLD screening and prediction models may improve early detection and targeted management, reducing the SLD burden. Future studies should be conducted to validate our findings across diverse populations or to explore the impact of interventions that address both metabolic dysfunction and liver injury.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Information about the KoGES dataset and data-sharing procedures can be found on the National Research Institute of Health's website, under the Korea Disease Control and Prevention Agency, Ministry of Health and Welfare, Korea.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Density plot and nonlinear association between baseline ALT, TyG, and MASLD risk in the KoGES. Restricted cubic spline analyses of the nonlinear association between baseline ALT, TyG, and MASLD on a continuous scale in the KoGES. HRs are indicated by solid lines, whereas 95% CIs are denoted by shaded areas. Adjusted for age, sex, BMI, smoking, alcohol consumption, METS, HTN, DM, and DYS. **Figure S2:** Density plot and nonlinear association between baseline ALT, TyG, and MASLD risk in the UK Biobank. Restricted cubic spline analyses of the nonlinear association between baseline ALT, TyG, and MASLD on a continuous scale in the UK Biobank. HRs are indicated by solid lines, whereas 95% CIs are denoted by shaded areas. Adjusted for age, sex, BMI, smoking, alcohol consumption, METS, HTN, DM, and DYS. **Figure S3:** Forest plots showing adjusted hazard ratios (HRs) with 95% CIs for the development of (A) new-onset steatotic liver disease (SLD), (B) metabolic dysfunction-associated steatotic liver disease (MASLD), (C) metabolic and alcohol-associated liver disease (MetALD), and (D) alcohol-associated liver disease (ALD) in the KoGES Ansan–Ansung cohort, stratified by baseline triglyceride–glucose (TyG) index and alanine aminotransferase (ALT) levels. Hazard ratios were adjusted for age, sex, body mass index (BMI), smoking status, alcohol consumption, physical activity, and additional clinical covariates. Group 1 (TyG index <8.5 and ALT <30 U/L [males] or <20 U/L [females]) served as the reference group. Higher HRs indicate an increased risk for developing incident SLD and its subtypes. **Figure S4:** Subgroup analysis of new-onset SLD, MASLD, MetALD, and ALD risk by triglyceride–glucose (TyG) index and alanine aminotransferase (ALT) status in the UK Biobank. Odd ratios (ORs) and 95% CIs for new-onset SLD, MASLD, MetALD, and ALD based on the TyG index and ALT status in the UK Biobank cohort are presented. Analyses are stratified by age, sex, and body mass index (BMI). (A) New-onset SLD, (B) new-onset MASLD, (C) new-onset MetALD, (D) new-onset ALD. ORs are represented by solid points, with 95% CIs shown as error bars. All models are adjusted for age, sex, BMI (when not a stratification factor), smoking, alcohol consumption, metabolic equivalent of task score, hypertension, diabetes mellitus, and dyslipidemia. **Table S1:** Baseline characteristics of all participants according to the presence of new-onset MASLD in the KoGES and UK Biobank. **Table S2:** Baseline characteristics of all participants according to the presence of new-onset MetALD in the KoGES and UK Biobank. **Table S3:** Baseline characteristics of all participants according to the presence of new-onset ALD in the KoGES and UK Biobank. **Table S4:** Baseline characteristics of all participants in the KoGES stratified by elevated TyG and ALT levels. **Table S5:** Baseline characteristics of all participants in the UK Biobank stratified by elevated TyG and ALT levels. **Table S6:** Sensitivity analysis using multiple imputation for missing covariates in the KoGES and UK Biobank cohorts. **Table S7:** Comparison of predictive accuracy for SLD, MASLD, MetALD, and ALD incidence among TyG and ALT status groups in the UK Biobank using age- and sex-adjusted AUC analysis.

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