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Original Article

Misclassification of Alcohol Use Disorder in MASLD and MetALD: Prevalence, Clinical Characteristics, and Outcomes

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Background/Aims: Within metabolic dysfunction and alcohol-associated liver disease (MetALD), there exists a continuum where the condition can conceptually shift between being metabolic dysfunction-associated steatotic liver disease (MASLD) and alcoholic liver disease. However, alcohol use disorder (AUD) can be included in these diagnoses. The aim of this study was to investigate the prevalence and clinical characteristics of misclassified AUD among patients with MASLD and MetALD.

Methods: The study included a total of 3,362,552 participants from the 2011 to 2012 National Health Screening Program. Steatotic liver disease was defined as having a hepatic steatosis index score of 36 or higher. Significant alcohol intake was calculated on the basis of self-report questionnaire responses. AUD was defined as having received medical care for an alcohol-related condition at least once during the study period. The mean follow-up period for participants was 9.8 years.

Results: MASLD and MetALD prevalence were 23.8% and 1.9%, respectively. AUD was identified in 1.1% (8,481 individuals) of MASLD and 4.7% (2,989 individuals) of MetALD cases. Misclassified AUD was associated with significantly higher all-cause and liver-related mortality. Adjusted hazard ratios for liver-related mortality were 6.53 for AUD misclassified as MASLD and 6.98 for AUD misclassified as MetALD. Extrahepatic cancer mortality risk was also elevated (adjusted hazard ratio: 1.33 in MASLD and 1.44 in MetALD).

Conclusions: A significant number of AUD cases were misclassified as MASLD and MetALD in cross-sectional assessment of alcohol consumption. Patients with AUD misclassified as MASLD or MetALD had higher liver-related mortality than the pure MASLD and MetALD groups. **(Gut Liver, 2025;19:735-745)**

Key Words: Alcohol use disorder; Metabolic dysfunction and alcohol-associated liver disease; Metabolic dysfunction-associated steatotic liver disease; Alcohols; Mortality

INTRODUCTION

Steatotic liver disease (SLD) has been redefined as an umbrella term for fatty liver disease, encompassing metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), and alcoholic liver disease (ALD).[1-3] This updated nomenclature recognizes alcohol intake as a key determinant in categorizing SLD, viewing MASLD, MetALD, and ALD as different points along a continuous disease spectrum rather than as entirely distinct entities.[4]

In many epidemiological studies, alcohol intake has typically been determined through self-reported questionnaires administered only during the index year. Such self-reported assessments are prone to recall bias and underreporting, and may fail to accurately capture past or fluctuating alcohol consumption, potentially leading to misclassification. According to a recent study, a considerable number of patients

with MASLD had a prior diagnosis of ALD or alcohol use disorder (AUD), which was linked to a significantly higher risk of liver-related adverse outcomes.[5] This underscores the importance of capturing alcohol use history comprehensively, as fluctuating alcohol consumption may not be effectively assessed through single-point questionnaire measurements. Thus, accounting for hidden AUD is crucial to properly assess the clinical risks and treatment needs of individuals with MASLD or MetALD.

Recently, Nasr *et al.*[5] investigated the history of ALD or AUD among patients with MASLD in a Swedish hospital cohort. They found that 12% of patients with MASLD had a prior diagnosis of ALD or AUD, with an additional 5% diagnosed with ALD or AUD during follow-up. These results suggest that a substantial number of MetALD or ALD cases may have been misclassified as MASLD. Therefore, careful assessment of alcohol intake in MASLD is essential to determine the true prevalence and long-term outcomes of MetALD. Most epidemiological studies related to MASLD and MetALD currently rely on self-reported alcohol consumption questionnaires from the index year.[6-9] This reliance makes it challenging to rule out the possibility of alcohol intake under-reporting or the inclusion of temporary abstainers in the MASLD category.[10] To accurately evaluate the prevalence, characteristics, and long-term outcomes of MetALD, future research should employ more comprehensive alcohol intake assessments, including past medical history and previous drinking behaviors.

Therefore, we aimed to determine the prevalence, characteristics, and their long-term clinical outcomes among concurrent history of AUD in patients with MASLD and those with MetALD using a large-scale cohort.

MATERIALS AND METHODS

1. Study design

The study was a retrospective cohort study using the 2011 to 2012 National Health Screening Program provided by the Korea National Health Insurance Service (NHIS). This study was conducted in accordance with the STROBE Statement. The Institutional Review Board of Hanyang University Hospital approved the study (IRB number: 2024-01-042). The requirement for informed consent was waived because we used anonymized data provided by the NHIS database according to the Personal Data Protection Act guidelines.

2. Characteristics of database

The NHIS offers a free biennial health screening for Korean adults, targeting regional household heads, workplace insurance members, dependents aged 20 or older, and medical welfare recipients aged 20 to 64, as mandated by Article 52 of the National Health Insurance Act. This program facilitates early disease detection, with participation rates of 72.6% and 72.9% in 2011 to 2012. It includes anthropometric measurements, blood and urine tests, lifestyle questionnaires, and personal and familial medical histories. Additionally, the NHIS database provides medical records, diagnosis dates, and data coded using the International Classification of Diseases, 10th Revision (ICD-10). Mortality information, including cause and date of death, is linked to Statistics Korea via de-identified IDs.

3. Study population

Fig. 1 shows flowchart of the study population. Among the 3,391,478 Koreans who participated in the National Health Screening Program during the index year (2011 to 2012), a total of 864,271 participants were finally included applying the following exclusions: (1) individuals who aged <19 years (n=228); (2) those with viral hepatitis (n=190,683); (3) missing alcohol intake information (n=8,531); (4) excessive alcohol intake (n=74,437); (5) missing data to calculate hepatic steatosis index (HSI) (n=847); (6) those who were dead before 2013 (n=19,320); (7) those with cryptogenic SLD (n=103,440); and (8) those without SLD (n=2,128,721). Participants were classified into MASLD without AUD (n=792,407), AUD misclassified as MASLD (n=8,481), MetALD without AUD (n=60,394), and AUD misclassified as MetALD (n=2,989).

4. Definition of MASLD, MetALD, and AUD

SLD was defined as an HSI of 36 or higher, which is a well-validated, noninvasive method for identifying hepatic steatosis. MASLD was defined as (1) the presence of SLD, (2) alcohol intake <30 g/day for men and <20 g/day for women, and (3) at least one of the cardiometabolic risk factors. MetALD was defined using the same criteria as MASLD, except that it included moderate alcohol consumption, defined as 30–60 g/day for men and 20–50 g/day for women. AUD was defined by ICD-10 codes F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70.0–K70.4, K70.9, K85.2, K86.0, X45, X65, or Y15 during the 2011 to 2012.

5. Misclassification of MASLD and MetALD

Self-reported alcohol consumption was used as the basis for classifying individuals as MASLD or MetALD. However, cases with medical records indicating a diagnosis of AUD during the index year were defined as AUD misclassified as MASLD or MetALD.

6. Outcomes setting

The primary outcome measure was liver-related mortal-

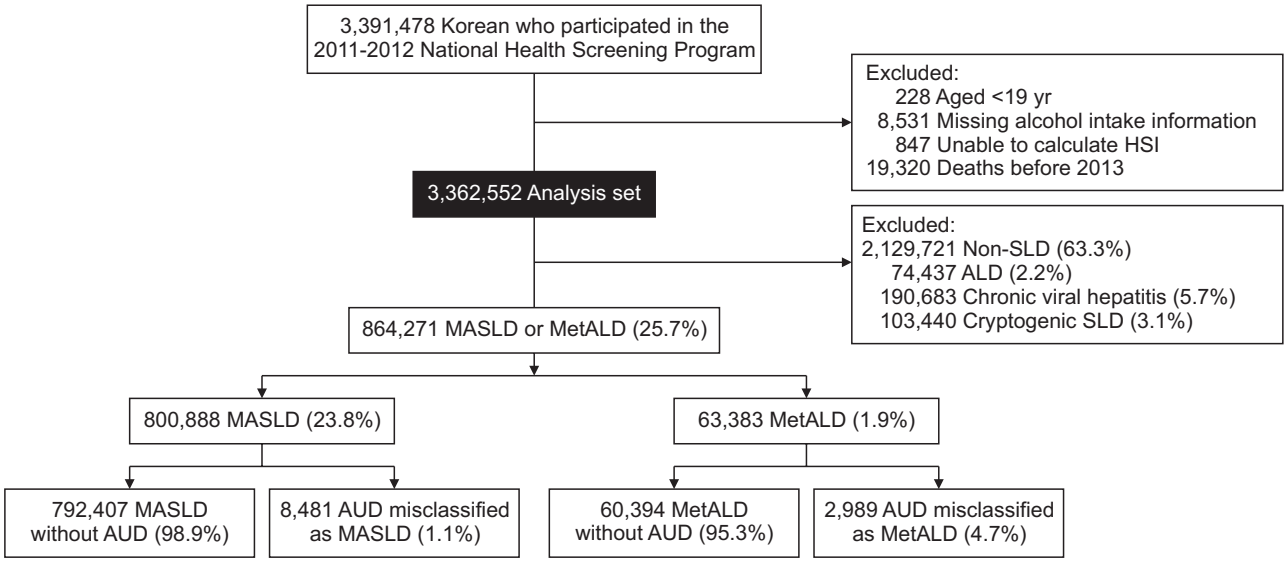


Fig. 1. Flowchart of the study population selection. HSI, hepatic steatosis index; SLD, steatotic liver disease; ALD, alcoholic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; AUD, alcohol use disorder.

ity. Liver-related mortality included death due to hepatocellular carcinoma (HCC) and liver-related complications, which included hepatic encephalopathy, ascites, and esophageal varices. The ICD-10 codes for HCC, hepatic encephalopathy, ascites, and esophageal varix were C22, K71–K79, R18, and I85, respectively. The secondary outcomes were cardiovascular disease (CVD) mortality and extrahepatic cancer mortality. CVD mortality was defined using the ICD-10 codes I20–I25 or I50. Extrahepatic cancer mortality was defined using ICD-10 codes C00–C21 or C23–C97. Participants were followed up from January 1, 2014, until their date of death, or until December 31, 2021. To minimize potential reverse causal relationships, we set 2013 as a lag period and excluded outcomes that occurred in 2013.

7. Measurements

Individuals with low income were defined as those receiving Medical Aid or in the lowest income quintile based on NHIS premiums. Smoking status was categorized as current smoker or nonsmoker. Daily alcohol intake (g/day) was calculated by multiplying the weekly drinking frequency by the alcohol quantity per session, with mild intake defined as <30 g/day for men and <20 g/day for women; moderate intake defined as 30–60 g/day for men and 20–50 g/day for women; excessive intake defined as >60 g/day for men and >50 g/day for women. Regular exercise was classified as vigorous activity ≥3 days/week or moderate activity ≥5 days/week. Body mass index was calculated from measured height and weight, with obesity defined as body mass index ≥25 kg/m^2. Waist circumference (cm) was measured at the midpoint between the upper margin of the iliac crest and the lower margin of the lowest rib. Systolic blood pressure and diastolic blood pressure were measured after a 5-minute rest. After at least 8 hours of fasting, fasting blood glucose, serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and creatinine levels were also measured. Type 2 diabetes mellitus (T2DM) was identified by fasting blood glucose ≥126 mg/dL or ICD-10 codes E11–E14 with ongoing anti-diabetic treatment. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or ICD-10 codes I10–I13 or I15. with ongoing anti-hypertensive treatment. Dyslipidemia was identified by total cholesterol ≥240 mg/dL or ICD-10 code E78 with ongoing lipid-lowering treatment.

8. Statistical analysis

Data are presented as numbers (percentages, %) for categorical variables and mean±standard deviation or median (25th, 75th percentile) for continuous variables after normality test. The chi-square test was used to compare differences of categorical variables among groups. Analysis of variance was used to compare differences among groups. The Kaplan-Meier survival curve was used to depict cumulative incidence rates of outcomes among groups, with the log-rank test for group comparisons. Cox proportional hazards models were used to calculate the hazard ratio (HR) with 95% confidence interval (CI) for liver-related mortality, CVD, and extrahepatic cancer mortality. In Model 1, we adjusted for age and sex as fundamental demographic confounders. In Model 2, we further adjusted for body mass index, low income, smoking, and physical activity, as these

lifestyle and socioeconomic factors are known to influence both the exposure and outcome. Finally, in Model 3, metabolic conditions (T2DM, hypertension, and dyslipidemia) were added to account for their potential mediating effects on the association. Sensitivity analyses were conducted on 859,952 participants by excluding patients with HCC and liver-related complications from 2009 to 2013, setting newly developed cases of HCC and liver-related complications from 2014 to 2021 as outcomes.

All statistical analyses were performed using R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SAS enterprise guide (version 7.1; SAS Institute Inc., Cary, NC, USA). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics

Table 1 presents the baseline characteristics of the study population across four groups. For the total 3,362,552 subjects, the mean age was 54.6 years (standard deviation: 13.6 years). Prevalence of MASLD and MetALD was 23.8% and 1.9%, respectively. Of those classified as MASLD and MetALD, 1.1% (8,481 individuals) and 4.7% (2,989 individuals) had a history of AUD in the index year (Fig. 1). Patients in the AUD misclassified as MASLD or MetALD group exhibited higher age, height, weight, waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood glucose, and triglycerides level than without AUD. The AUD group had a higher proportion of current smokers and lower rates of regular exercise. Notably, the prevalence of T2DM was nearly twice as high in the misclassified AUD as MASLD group compared to those without AUD.

2. Liver-related mortality in AUD misclassified as MASLD and MetALD

Fig. 2A displays the cumulative incidence rates of liver-related mortality throughout the follow-up period. The AUD misclassified as MASLD and MetALD groups

Table 1. Baseline Characteristics of the Study Population

Variable	MASLD without AUD (n=792,407)	AUD misclassified as MASLD (n=8,481)	MetALD without AUD (n=60,394)	AUD misclassified as MetALD (n=2,989)	p-value
Male sex	127,768 (16.8)	1,288 (15.8)	8,036 (13.8)	446 (15.5)	<0.0001
Age, yr	55.0±13.6	56.2±11.8	49.1±12.7	54.3±10.8	<0.0001
Height, cm	158.6±9.0	163.6±8.7	166.5±8.3	166.6±7.3	<0.0001
Body weight, kg	65.9±12.1	70.8±13.0	74.3±13.0	72.7±12.8	<0.0001
BMI, kg/m^2	26.0±3.2	26.3±3.5	26.7±3.4	26.1±3.6	<0.0001
WC, cm	84.0±9.1	87.7±9.2	87.7±9.2	88.7±8.9	<0.0001
Low income	127,768 (16.8)	1,288 (15.8)	8,036 (13.8)	446 (15.5)	<0.0001
SBP, mm Hg	125.8±15.3	128.3±15.3	128.7±15.0	131.0±15.1	<0.0001
DBP, mm Hg	77.5±10.0	79.4±10.2	80.6±10.3	81.7±10.1	<0.0001
FBG, mg/dL	100.9±25.1	109.5±33.0	105.9±29.1	113.7±35.2	<0.0001
AST, U/L	25 (19–28)	28 (22–41)	25 (21–33)	35 (25–59)	<0.0001
ALT, U/L	16 (13–22)	20 (14–31)	19 (14–27)	24 (17–40)	<0.0001
r-GTP, U/L	19 (14–30)	42 (23–89)	40 (24–70)	87 (44–185)	<0.0001
Total cholesterol, mg/dL	198.7±38.3	194.1±41.8	198.7±37.8	194.4±42.7	<0.0001
HDL cholesterol, mg/dL	54.3±21.6	53.3±17.2	56.6±24.4	56.4±20.7	<0.0001
Triglyceride, mg/dL	135.4±96.9	171.4±150.5	173.3±146.9	215.4±217.6	<0.0001
eGFR, mL/min/1.73 m^2	81.5±31.2	82.4±31.8	84.8±33.9	86.1±29.3	<0.0001
Current smoker	81,793 (10.3)	2,379 (28.1)	23,008 (38.1)	1,295 (43.4)	<0.0001
Regular exerciser	199,969 (25.2)	2,454 (28.9)	20,521 (34.0)	876 (29.3)	<0.0001
HTN	305,766 (38.6)	3,995 (47.1)	24,412 (40.4)	1,594 (53.3)	<0.0001
T2DM	81,532 (10.3)	1,653 (19.5)	9,070 (15.0)	716 (24.0)	<0.0001
DLD	133,288 (16.8)	1,383 (16.3)	8,824 (14.6)	528 (17.7)	<0.0001
Mean follow-up, yr	9.8±1.1	9.4±1.8	9.8±1.1	9.4±1.8	0.0010
Death	47,331 (6.0)	1,279 (15.1)	3,160 (5.2)	463 (15.5)	<0.0001
Liver-related death	1,926 (0.2)	197 (2.3)	210 (0.3)	73 (2.4)	<0.0001
CVD death	5,032 (0.6)	72 (0.8)	221 (0.4)	15 (0.5)	<0.0001
Extrahepatic cancer death	13,981 (1.8)	273 (3.2)	1,143 (1.9)	108 (3.6)	<0.0001

Data are presented as number (%), mean±SD, or median (interquartile range).
MASLD, metabolic dysfunction-associated steatotic liver disease; AUD, alcohol use disorder; MetALD, metabolic dysfunction and alcohol-associated liver disease; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; r-GTP, gamma-glutamyltranspeptidase; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; HTN, hypertension; T2DM, type 2 diabetes mellitus; DLD, dyslipidemia, CVD, cardiovascular disease.

demonstrated markedly higher cumulative rates of liver-related mortality compared to the MASLD without AUD and MetALD without AUD groups (p-value for log-rank tests <0.0001). Table 2 presents the HR (95% CI) for liver-related mortality of AUD misclassified as MASLD, MetALD without AUD, and AUD misclassified as MetALD compared to the referent MASLD without AUD. The unadjusted HR (95% CI) for AUD misclassified as MASLD, MetALD without, and AUD misclassified as MetALD were significantly elevated at 10.04 (8.67 to 11.63), 1.42 (1.23 to 1.64), and 10.61 (8.39 to 13.40), respectively. These associations persisted in the multivariable models. In Model 3, the fully adjusted HRs (95% CIs) were 6.53 (5.60 to 7.61) for AUD misclassified as MASLD, 1.30 (1.11 to 1.51) for MetALD without AUD, and 6.98 (5.48 to 8.89) for AUD misclassified as MetALD.

3. CVD mortality according to presence of AUD in MASLD/MetALD

Fig. 2B illustrates the cumulative incidence rates of CVD mortality throughout the follow-up period. While the differences between the groups were not substantial, the highest rates were observed in the misclassified AUD as MASLD group, followed by MASLD without AUD, misclassified AUD as MetALD, and MetALD without AUD, indicating some level of increased risk associated with AUD (p-value for log-rank tests <0.0001). However, adjusted HRs for CVD mortality was not different according to presence of AUD in both MASLD/MetALD (Table 2).

4. Extrahepatic cancer mortality according to presence of AUD the MASLD/MetALD

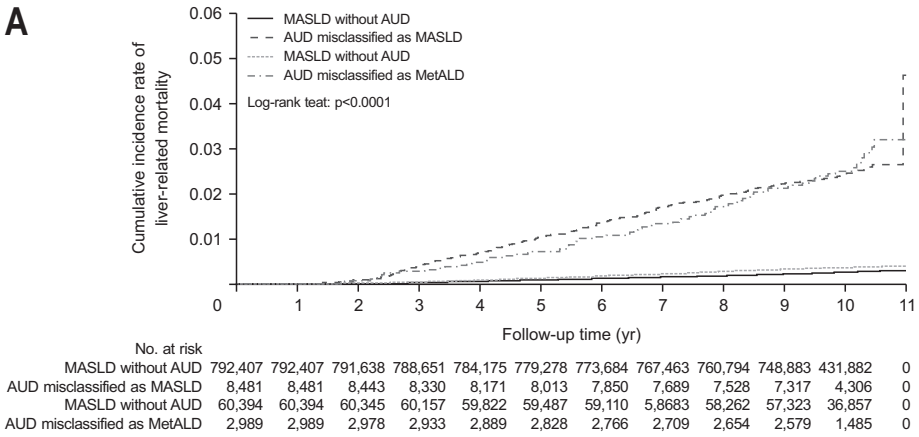
Fig. 2C illustrates the cumulative incidence rates of extrahepatic cancer mortality, demonstrating that both the misclassified AUD as MASLD and misclassified AUD as MetALD groups exhibited significantly higher rates compared to their counterparts without AUD (p-value for log-rank tests <0.0001). Misclassified AUD as MASLD was associated with a markedly elevated risk of extrahepatic cancer mortality across adjusted models as shown in Table 2. The adjusted HR for extrahepatic cancer-related mortality was 1.33 (95% CI, 1.18 to 1.50) in the fully adjusted model (Model 3). Similarly, MetALD without AUD displayed a modestly increased risk across adjusted models, with an HR of 1.07 (95% CI, 1.00 to 1.14) in Model 3. However, misclassified AUD as MetALD presented the highest risk, with an unadjusted HR of 2.17 (95% CI, 1.79 to 2.62) and an adjusted HR of 1.44 (95% CI, 1.18 to 1.76) in the fully adjusted Model 3.

5. Risk of all-cause mortality in AUD misclassified as MASLD and MetALD

During a total of 8,468,619.64 person-years with a mean follow-up of 9.8 years, 52,233 mortality cases were reported with 2,406 liver-related deaths, 5,340 CVD deaths, and 15,505 extrahepatic cancer deaths. Fig. 2D illustrates the cumulative incidence rates of all-cause mortality over the follow-up period. Both the AUD misclassified as MASLD and MetALD groups exhibited significantly higher cumulative all-cause mortality rates compared to the pure MASLD (MASLD without AUD) and pure MetALD (MetALD without AUD) groups (p-value for log-rank tests <0.0001). Table 2 presents HR (95% CI) for all-cause mortality of AUD misclassified as MASLD, MetALD without AUD, and AUD misclassified as MetALD was 2.66 (2.52 to 2.81), 0.87 (0.84 to 0.90), and 2.75 (2.51 to 3.01), respectively. The same trends were maintained in multivariable models in the AUD misclassified as MASLD and MetALD. In Model 3, the adjusted HR (95% CI) for all-cause mortality of AUD misclassified as MASLD and MetALD was 1.97 (1.86 to 2.08) and 2.12 (1.93 to 2.33), respectively.

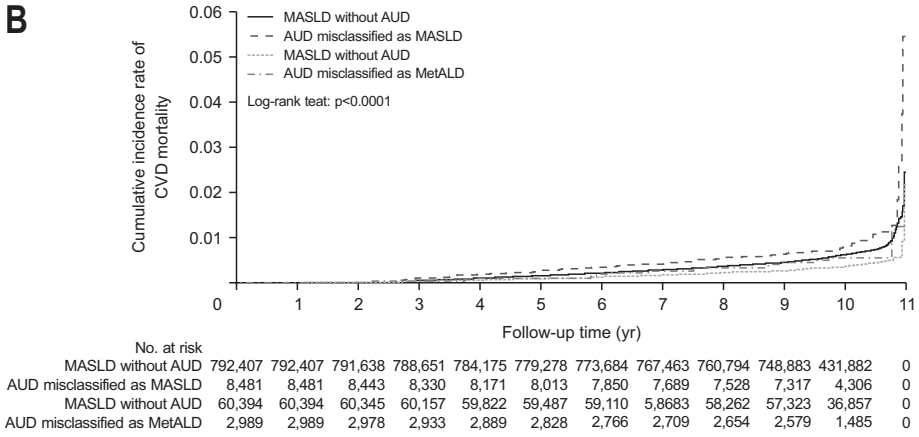
6. The incidence of HCC and liver-related events according to the presence of AUD in MASLD/MetALD

Fig. 3 illustrates the cumulative incidence rates of HCC and liver-related complications over the follow-up period. The misclassified AUD as MASLD and MetALD groups demonstrated significantly higher cumulative incidence rates for both HCC (Fig. 3A) and liver-related complications (Fig. 3B) compared to the pure MASLD and MetALD (MASLD without AUD and MetALD without AUD) groups (both p-values for log-rank tests <0.0001). Table 3 presents the HR (95% CI) for incident HCC and liver-related complications across MASLD and MetALD groups, with or without AUD. For incident HCC, the unadjusted HR (95% CI) for misclassified AUD as MASLD, MetALD without AUD, and misclassified AUD as MetALD was 10.77 (9.14 to 12.70), 2.22 (1.95 to 2.54), and 14.08 (11.11 to 17.84), respectively, compared to MASLD without AUD as the reference. In Model 3, the adjusted HR (95% CI) for incident HCC for misclassified AUD as MASLD and misclassified AUD as MetALD was 5.78 (4.88 to 6.86) and 7.00 (5.48 to 8.94), respectively. For incident liver-related complications, the unadjusted HR (95% CI) for misclassified AUD as MASLD, MetALD without AUD, and misclassified AUD as MetALD was 4.53 (4.02 to 5.11), 1.28 (1.17 to 1.38), and 6.10 (5.14 to 7.24), respectively, compared to MASLD without AUD as the reference. In Model 3, the adjusted HR (95% CI) for liver-related complications for misclassified AUD as MASLD and MetALD was 3.89 (3.43



No. at risk

MASLD without AUD	792,407	792,407	791,638	788,651	784,175	779,278	773,684	767,463	760,794	748,883	431,882	0
AUD misclassified as MASLD	8,481	8,481	8,443	8,330	8,171	8,013	7,850	7,689	7,528	7,317	4,306	0
MASLD without AUD	60,394	60,394	60,345	60,157	59,822	59,487	59,110	5,8683	58,262	57,323	36,857	0
AUD misclassified as MetALD	2,989	2,989	2,978	2,933	2,889	2,828	2,766	2,709	2,654	2,579	1,485	0



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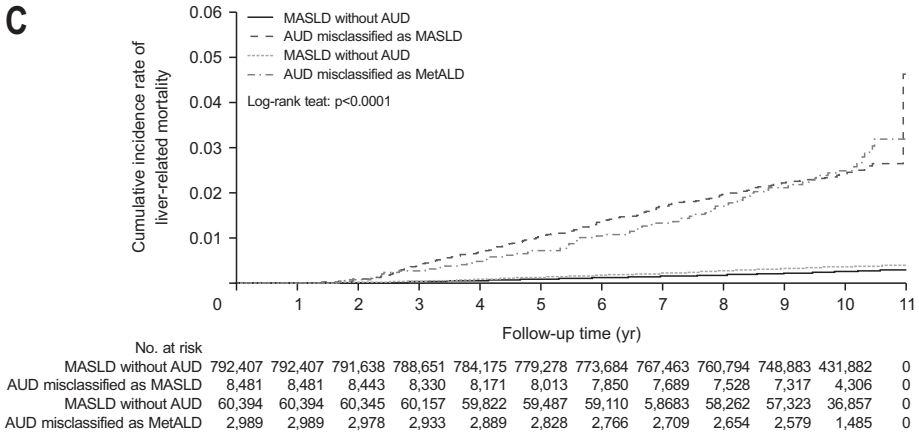
MASLD without AUD	60,394	60,394	60,345	60,157	59,822	59,487	59,110	5,8683	58,262	57,323	36,857	0
AUD misclassified as MetALD	2,989	2,989	2,978	2,933	2,889	2,828	2,766	2,709	2,654	2,579	1,485	0



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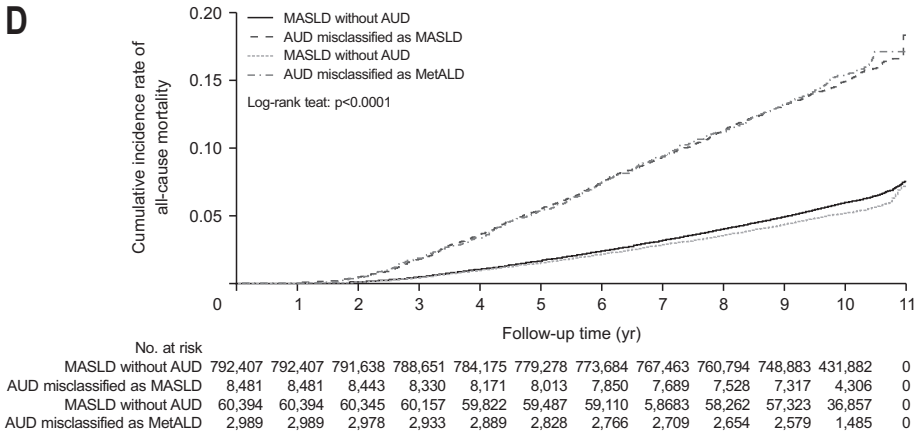

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AUD misclassified as MASLD	8,481	8,481	8,443	8,330	8,171	8,013	7,850	7,689	7,528	7,317	4,306	0
MASLD without AUD	60,394	60,394	60,345	60,157	59,822	59,487	59,110	5,8683	58,262	57,323	36,857	0
AUD misclassified as MetALD	2,989	2,989	2,978	2,933	2,889	2,828	2,766	2,709	2,654	2,579	1,485	0

Fig. 2. Kaplan-Meier survival curve showing cumulative incidence rates of liver-related mortality (A), CVD mortality (B), extrahepatic cancer mortality (C), and all-cause mortality (D) based on MASLD/MetALD with or without AUD status. CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; AUD, alcohol use disorder.

Table 2. Cox Proportional Hazard Regression for Cause-Specific Mortality

Variable	Model 1*		Model 2*		Model 3*		Model 4*	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause mortality								
MASLD without AUD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
AUD misclassified as MASLD	2.66 (2.52–2.81)	<0.0001	2.12 (2.00–2.24)	<0.0001	2.02 (1.91–2.14)	<0.0001	1.97 (1.86–2.08)	<0.0001
MetALD without AUD	0.87 (0.84–0.90)	<0.0001	1.11 (1.07–1.16)	<0.0001	1.03 (0.99–1.07)	0.1015	1.01 (0.97–1.05)	0.5503
AUD misclassified as MetALD	2.75 (2.51–3.01)	<0.0001	2.53 (2.31–2.78)	<0.0001	2.21 (2.01–2.43)	<0.0001	2.12 (1.93–2.33)	<0.0001
Liver-related mortality								
MASLD without AUD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
AUD misclassified as MASLD	10.04 (8.67–11.63)	<0.0001	6.84 (5.88–7.95)	<0.0001	6.74 (5.78–7.85)	<0.0001	6.53 (5.60–7.61)	<0.0001
MetALD without AUD	1.42 (1.23–1.64)	<0.0001	1.42 (1.22–1.64)	<0.0001	1.33 (1.13–1.54)	0.0003	1.30 (1.11–1.51)	0.0007
AUD misclassified as MetALD	10.61 (8.39–13.40)	<0.0001	7.54 (5.93–9.56)	<0.0001	7.19 (5.65–9.15)	<0.0001	6.98 (5.48–8.89)	<0.0001
CVD mortality								
MASLD without AUD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
AUD misclassified as MASLD	1.40 (1.10–1.76)	0.0047	1.26 (0.997–1.59)	0.0533	1.20 (0.94–1.52)	0.1371	1.16 (0.91–1.46)	0.2334
MetALD without AUD	0.58 (0.50–0.66)	<0.0001	0.88 (0.766–1.01)	0.0715	0.83 (0.71–0.95)	0.0077	0.80 (0.69–0.91)	0.0015
AUD misclassified as MetALD	0.84 (0.50–1.40)	0.5106	0.97 (0.58–1.61)	0.9099	0.89 (0.53–1.48)	0.6589	0.83 (0.50–1.38)	0.4754
Extrahepatic cancer mortality								
MASLD without AUD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
AUD misclassified as MASLD	1.92 (1.70–2.16)	<0.0001	1.40 (1.24–1.58)	<0.0001	1.34 (1.18–1.51)	<0.0001	1.33 (1.17–1.50)	<0.0001
MetALD without AUD	1.07 (1.00–1.13)	0.0320	1.16 (1.08–1.23)	<0.0001	1.08 (1.00–1.14)	0.0258	1.07 (1.04–1.14)	0.0385
AUD misclassified as MetALD	2.17 (1.79–2.61)	<0.0001	1.69 (1.39–2.04)	<0.0001	1.46 (1.19–1.77)	0.0002	1.44 (1.18–1.75)	0.0003

HR, hazard ratio; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; AUD, alcohol use disorder; MetALD, metabolic dysfunction and alcohol-associated liver disease; CVD, cardiovascular disease.

*Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, body mass index (BMI), low income, current smoker, and regular exerciser; Model 4: adjusted for age, sex, BMI, low income, current smoker, regular exerciser, hypertension, type 2 diabetes mellitus, and dyslipidemia.

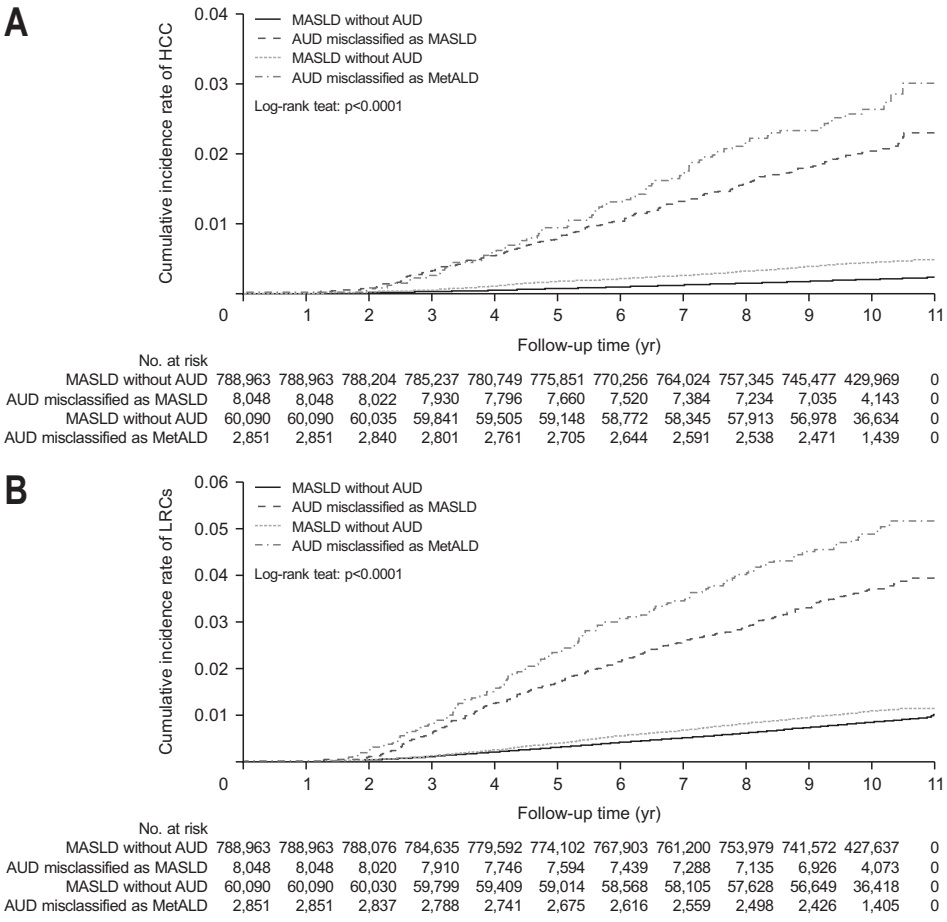

Fig. 3. Kaplan-Meier survival curve showing cumulative incidence rates of HCC (A) and LRCs (B) based on MASLD/MetALD with or without AUD status. HCC, hepatocellular carcinoma; LRCs, liver-related complications; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; AUD, alcohol use disorder.

to 4.40) and 5.10 (4.25 to 6.11), respectively.

DISCUSSION

In a large-scale study involving over 3.3 million individuals, 23.8% of participants were diagnosed with MASLD, and 1.9% with MetALD. Notably, among those diagnosed with MASLD and MetALD, 1.1% and 4.7%, respectively, had a history of AUD in the same index year. Considering that a significant portion of individuals with AUD or ALD may not seek clinical care, it is plausible that some cases of AUD might have been misclassified as MASLD or MetALD. Similarly, Nasr *et al.*[5] reported that 12% of individuals with MASLD had a prior diagnosis of ALD or AUD, with an additional 5% being diagnosed with ALD or AUD during follow-up.

An interesting observation is that clinical outcomes differ significantly between MASLD cases with and without a history of AUD. The presence of AUD significantly worsened health outcomes, leading to higher rates of T2DM, elevated blood pressure, and increased lipid levels. Moreover, the mortality rates for both all-cause and liver-related deaths were significantly higher in groups with AUD. These findings underscore the critical need for precise medical histories for alcohol abuse and highlight the importance of addressing history of alcohol use in these patients to better assess risk and improve outcomes.

MetALD is a newly defined disease category according to the new SLD nomenclature, and its prevalence is reported to be approximately 2% to 5% of the general population.[11,12] In the National Health and Nutrition Examination Survey in the United States, the prevalence of MASLD was 31.3% to 32.5%, with MetALD at 2% to 2.56%.[13,14] Similarly, in the Korean health examination cohort, MASLD was prevalent at 29.5%, while MetALD stood at 7.9%.[12] Likewise, in the health examination cohort in Taiwan, MASLD was observed at 31.6% and MetALD at 2.8%.[8] Overall, the prevalence of MetALD accounts for approximately 8% to 12% of MASLD cases in most cross-sectional studies. Considering the high-risk drinking rate defined by the World Health Organization to be around 20%[15] in the general population, the proportion of MetALD in SLD can be considered relatively small. This may be due to the fact that in most cross-sectional studies, alcohol consumption was dependent on self-reported questionnaires at the index year.[16] In this study, about 1%

Table 3. Sensitivity Analysis: Cox Proportional Hazard Regression for Incident HCC and Liver-Related Complications According to the Presence of MASLD/MetALD with or without AUD

Variable	Unadjusted		Model 1*		Model 2*		Model 3*	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Incident HCC								
MASLD without AUD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
MASLD with AUD	10.77 (9.14–12.70)	<0.0001	6.07 (5.13–7.18)	<0.0001	6.01 (5.08–7.13)	<0.0001	5.78 (4.88–6.86)	<0.0001
MetALD without AUD	2.22 (1.95–2.54)	<0.0001	1.64 (1.43–1.89)	<0.0001	1.56 (1.35–1.79)	<0.0001	1.51 (1.31–1.75)	<0.0001
MetALD with AUD	14.08 (11.11–17.84)	<0.0001	7.48 (5.88–9.51)	<0.0001	7.31 (5.72–9.33)	<0.0001	7.00 (5.48–8.94)	<0.0001
Incident liver-related complications								
MASLD without AUD	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
MASLD with AUD	4.53 (4.02–5.11)	<0.0001	4.08 (4.02–5.11)	<0.0001	3.94 (3.48–4.46)	<0.0001	3.89 (3.43–4.40)	<0.0001
MetALD without AUD	1.28 (1.17–1.38)	<0.0001	1.35 (1.24–1.48)	<0.0001	1.32 (1.21–1.44)	<0.0001	1.31 (1.20–1.43)	<0.0001
MetALD with AUD	6.10 (5.14–7.24)	<0.0001	5.57 (4.68–6.63)	<0.0001	5.21 (4.35–6.24)	<0.0001	5.10 (4.25–6.11)	<0.0001

HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; AUD, alcohol use disorder; HR, hazard ratio; CI, confidence interval.
*Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, body mass index (BMI), low income, current smoker, and regular exerciser; Model 3: Adjusted for age, sex, BMI, low income, current smoker, regular exerciser, hypertension, type 2 diabetes mellitus, and dyslipidemia.

of MASLD and 5% of MetALD patients had medical records of being treated for AUD within the same survey year. In this study, SLD with AUD could be classified into various scenarios. First, patients with ALD might have temporarily reduced their alcohol consumption. Second, despite continued significant alcohol consumption, these individuals might still be patients with true ALD who underreported their alcohol intake, leading to their misclassification as MetALD or MASLD. Our data showed that prevalence of MetALD based on a self-reported alcohol consumption questionnaire was found to be 1.9%. However, among those categorized as MASLD, who reported consuming significant alcohol at levels below 210 g per week for men and 140 g per week for women, approximately 1.1% had a history of AUD in the same index year. Considering these misclassified AUD as MASLD cases, it suggests that the actual prevalence of MetALD could increase by up to 2.1%. These figures are based on the medical history and self-reported alcohol consumption during the same index year. Additionally, including medical history and self-reported alcohol consumption up to 2 years prior among 850,712 individuals who also participated in the 2009 to 2010 National Health Screening Program, 37,626 (4.8%) with MASLD without AUD and 1,835 (22.0%) with AUD misclassified as MASLD reported moderate alcohol intake (Supplementary Fig. 1). Reflecting this, the prevalence of individuals who had at least one occurrence of MetALD could increase to as much as 3.1%. However, this prevalence heavily relies on self-reported alcohol consumption, and the real-world prevalence of MetALD is likely higher, which is medically significant as hidden MetALD may exhibit worse metabolic indicators and outcomes compared to overt MetALD. This study clearly demonstrates the importance of conducting a comprehensive investigation into alcohol intake when defining MASLD.

In addition to the underestimated prevalence of MetALD, the long-term outcomes of MetALD are also underestimated. To date, many studies have reported on the long-term outcomes of SLD, MASLD, and MetALD. Almost all of these studies have indicated that MASLD and MetALD are markedly associated with higher risks of overall mortality, liver-related mortality, HCC, and other liver-related events compared to non-SLD.[7,8,17,18] However, there was no statistically significant difference in the long-term outcomes between MASLD and MetALD across all studies.[7,8,17,18] Moreover, some data suggest that MetALD's long-term mortality is even better than that of MASLD. Two large-scale cohorts in Korea[7] and a U.S. Veteran cohort[19] indicate a potential reversal in mortality and liver cirrhosis rates in MASLD and MetALD. One of possible reason for the various long-term outcomes of MetALD may be that previous studies included a significant number

of MetALD or ALD in the MASLD group. To our knowledge, our results demonstrated that MetALD without AUD is associated with higher liver-related mortality than MASLD without AUD from a large cohort (Fig. 2). These results re-emphasize the harmful effects of moderate alcohol consumption in SLD as it exacerbates hepatic inflammation and oxidative stress, upregulates pro-inflammatory cytokines, which accelerates the progression of fibrosis and increases the risk of HCC.[20-23] And at the same time, it demonstrates once again that MASLD, MetALD, and ALD are not separate diseases but are spectrum diseases caused by alcohol intake in SLD.

This study had several limitations. First, we defined SLD using the HSI in the current study. Although the HSI is a well-validated, noninvasive test for steatosis, it has the disadvantage of overestimating CVD mortality and CVD events in SLD patients. However, HSI has demonstrated strong predictive performance for nonalcoholic fatty liver disease, with an area under the curve of up to 0.88 in females and 0.82 in males, and a sensitivity of 80% and specificity of 67% in men, making it a useful screening tool.[24] Future research using magnetic resonance imaging-derived proton density fat fraction,[25] the gold standard for SLD, will be necessary. Second, defining AUD solely based on ICD-10 codes has certain limitations. This approach cannot account for undiagnosed cases of AUD or assess its severity. Additionally, the definition of AUD in this study includes liver-related conditions and complications, such as K70.0-K70.4 and K70.9, which may lead to an overestimation of liver-related outcomes. Moreover, it is important to consider that some liver-related outcomes may include deaths caused by liver failure secondary to multiorgan failure. Third, we could not establish a causal relationship between MASLD/MetALD and CVD, liver diseases, and mortality risks. Further research involving large-scale clinical trials or Mendelian randomization studies may be required to establish firm causal relationships. Despite these limitations, this research emphasizes the necessity for more precise evaluation tools concerning alcohol intake, which could lead to improved management and understanding of the SLD spectrum.

In conclusion, our findings suggest that a substantial number of AUD cases may be included as MetALD or MASLD in cross-sectional assessments of alcohol consumption. A history of AUD has a negative impact on the clinical outcomes of SLD. When MASLD or MetALD is classified based solely on self-reported alcohol consumption, there is a substantial risk of misclassification for SLD subclassification. This highlights the need for the development of more quantitative biomarkers and a systematic, comprehensive investigation into alcohol consumption, including detailed medical histories, to improve the classification of SLD subtypes. The long-term outcomes associated with MetALD are also likely underestimated or overestimated due to reliance on unstructured questionnaires. This underestimation calls for a cautious approach, underscoring the importance of incorporating prior alcohol consumption history and a thorough medical review of AUD when classifying MASLD and MetALD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.H.L., S.H.A., D.W.J. Data acquisition: J.H.L., S.H.A., S.Y.J. Data analysis and interpretation: J.H.L., S.H.A., E.L.Y., H.S.L., D.W.J. Drafting of the manuscript: J.H.L., S.H.A., S.Y.J., E.L.Y., J.P. Critical revision of the manuscript for important intellectual content: H.S.L., D.W.J. Statistical analysis: J.H.L., H.S.L., J.P. Obtained funding: D.W.J. Administrative, technical, or material support; study supervision: H.S.L., D.W.J. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl250072.

DATA AVAILABILITY STATEMENT

The data used in this study are owned by the Korean National Health Insurance Service (NHIS) and cannot be shared by the authors. Researchers can apply for access via the NHIS website (https://nhiss.nhis.or.kr).

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