Received: 12 December 2023 | First decision: 1 January 2024 | Accepted: 12 April 2024

DOI: 10.1111/apt.18015

AP&T Alimentary Pharmacology & Therapeutics WILEY

Long-term clinical outcomes in steatotic liver disease and incidence of liver-related events, cardiovascular events and all-cause mortality

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Funding information
John C Martin Foundation, Grant/Award Number: RP124; National Institute on Alcohol Abuse and Alcoholism, Grant/Award Number: U01AA029019; National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: P30DK120515, R01DK106419, R01DK121378, R01DK124318, U01DK061734 and U01DK130190; National Heart, Lung, and Blood Institute, Grant/Award Number: P01HL147835; Ministry of Health, Labour and Welfare, Grant/Award Number: 23HC2001, 23HC2002 and 23HC2003; National Center for Advancing Translational Sciences, Grant/Award Number: 5UL1TR001442; Japan Agency for Medical Research and Development, Grant/Award Number: JP23fk0210104, JP23fk0210111, JP23fk0210123 and JP23fk0210125

Summary

Background: A multi-society consensus group proposed a new nomenclature for steatotic liver disease (SLD) including metabolic-dysfunction associated steatotic liver disease (MASLD), MASLD and increased alcohol intake (MetALD) and alcohol-associated liver disease (ALD). However, the risk of liver-related events, major adverse cardiovascular events (MACE) and all-cause mortality among various sub-groups is unknown.

Aims: To evaluate the risk of liver-related events, MACE and death among patients with SLD.

Methods: We conducted a nationwide, population-based study and enrolled 761,400 patients diagnosed with MASLD, MetALD or ALD. The primary endpoint was the occurrence of liver-related events, MACE and death in patients with MASLD, MetALD and ALD.

Results: The cumulative incidence of liver-related events and death were highest in ALD, followed by MetALD and MASLD ($p < 0.001$ for both liver-related events and death), while the incidence of MACE was highest in MASLD, followed by MetALD and ALD ($p < 0.001$). Using MASLD as the reference and adjusting for age, sex, smoking, diabetes mellitus, dyslipidaemia and hypertension, the adjusted hazard ratios (95% confidence intervals) for liver-related events, MACE and death in MetALD were 1.42 (1.1–1.8), 0.68 (0.63–0.73) and 1.13 (0.98–1.3), respectively. In ALD, they were 3.42 (2.6–4.6), 0.58 (0.49–0.67) and 1.60 (1.3–2.0), respectively, for liver-related events, MACE and death.

Conclusions: The new consensus nomenclature can be used to stratify the risk of complications and prognosis. The nomenclature is beneficial for risk stratification and identifying new mechanisms for disease-specific therapeutic implications.

Nobuharu Tamaki, Takefumi Kimura and Shun-Ichi Wakabayashi equally contributed to the study.

The Handling Editor for this article was Professor Cynthia Seow, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) affects over 25% of the global population.[1] Patients with NAFLD may develop liver-related events, including hepatocellular carcinoma (HCC) and liver decompensation, as well as major adverse cardiovascular events (MACE) and NAFLD is the leading cause of liver transplantation.[2–5] Since NAFLD is a significant health and economic burden, preventing the progression of NAFLD is a crucial clinical challenge.

The term NAFLD is based on exclusionary confounder terms and may be stigmatising. Therefore, the multi-society consensus group recently proposed a new nomenclature and diagnostic criteria for NAFLD, referring to it as steatotic liver disease (SLD) and its subgroups.[6] Within the subgroups of SLD, a classification into three groups has been proposed based on the level of alcohol consumption. These include metabolic-dysfunction associated SLD (MASLD), MASLD and increased alcohol intake (MetALD) and alcohol-associated liver disease (ALD). In the future, this new nomenclature and classification will be used in clinical practice. Although changes in the nomenclature and definition of disease may affect the natural history of pathologies, the impact of this classification on clinical outcomes has not been thoroughly examined.[7,8] In particular, SLD (MASLD, MetALD and ALD) may be a risk factor for liver-related events, MACE and death. However, it remains unclear whether MASLD, MetALD and ALD present different event risks and whether distinguishing between these three groups is clinically significant. To address the existing gap in knowledge, we utilised a nationwide, population-based cohort to examine the risk difference of liver-related events, MACE and prognosis in MASLD, MetALD and ALD.

2 | METHODS

2.1 | Data source

In this study, we examined a nationwide, population-based, extensive claims database developed by the Japan Medical Data Center (JMDC Co., Ltd. Tokyo, Japan).[9] The database comprises monthly claims from all medical facilities, including hospitals, tertiary centers, primary care facilities and pharmacies. Additionally, the outcomes of each patient's health checkup are also connected to this database. Medical and pharmacy claims encompass diagnosis, drug products, clinical procedures/treatments, materials and Japan's unique diagnosis procedure combination code for both inpatients and outpatients. The diagnoses were coded using the International Classification of Diseases, 10th revision (ICD-10). When a patient dies, the date of death and the corresponding ICD-code of the disease causing death are also documented in the database. Prescriptions were coded using the World Health Organization Anatomical Therapeutic Chemical classification system. This included details such as the prescription date, daily dosage per prescription, dose unit, number of administration days per prescription and dosage. The clinical practice data encompasses examination, treatment, surgery, anaesthesia and rehabilitation, all coded using Japan's unique procedure/treatment system. Since all claims were processed by the health insurance association, diagnosis and treatment could be tracked even when patients changed care providers. This allowed for an accurate long-term assessment of the disease course.[10,11]

The annual health checkup results included age, sex, physical examination findings, medical history, blood test results and questionnaire information on smoking and alcohol habits. The details of this database have been presented in the previous report.

2.2 | Study protocol

Currently, more than 10 million patients are included in the database. We investigated 3,382,660 patients who had undergone an annual health checkup more than twice between 2016 and 2021. The exclusion criteria were as follows: (1) other chronic liver diseases, such as viral hepatitis, autoimmune hepatitis and primary biliary cholangitis; (2) history of liver-related events and MACE; (3) Absence of SLD, defined by a fatty liver index greater than 60 and/or the diagnosis of fatty liver (as indicated by ICD-10 code K760). After excluding these patients, a total of 761,400 patients with SLD were included in the study. The patient selection process is depicted in Figure 1. The detailed definitions of the inclusion and exclusion criteria are provided in Table S1. The initial health checkup date was utilised as the reference point and the occurrence of liver-related events, MACE and prognosis were examined. Similarly, long-term follow-up data (the same dataset) from 2005 to 2023 were used to investigate the cumulative incidence of liver-related events and MACE up to 10 years.

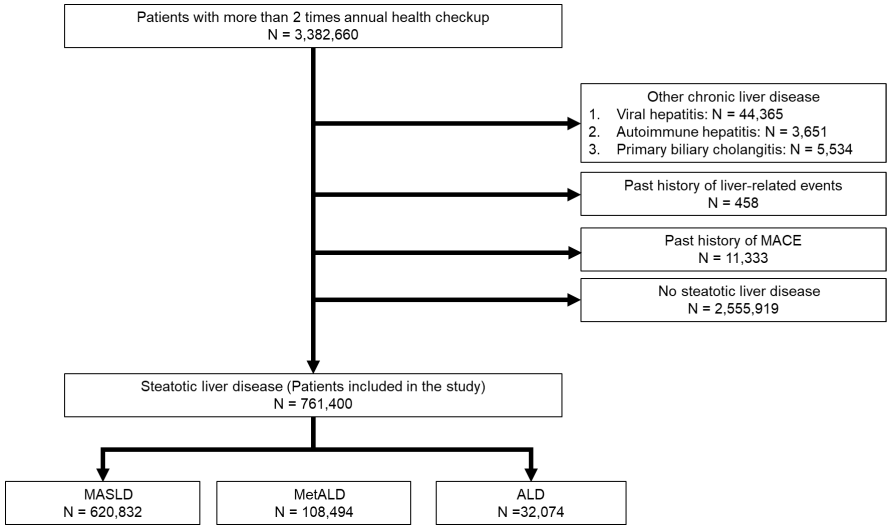
The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. Since all personal information was entirely removed from the database and no such data remained, ethics approval was not required.

2.3 | Definitions of HCC, hepatic decompensation, MACE, death and metabolic complications

Liver-related events were defined as HCC, ascites, variceal bleeding, hepatic encephalopathy, or death resulting from HCC. MACE was defined as myocardial infarction, stroke, or cardiovascular death. Liver-related events and MACE were identified using the diagnostic code (ICD-10) in conjunction with the corresponding procedure/treatment. For instance, HCC was identified by ICD-10 codes C220 and C227 and treated with methods such as radiofrequency ablation, liver resection, transcatheter arterial chemoembolization, or chemotherapy (sorafenib, lenvatinib, regorafenib, ramucirumab, cabozantinib, or atezolizumab plus bevacizumab). Combining diagnostic codes and procedure/treatment had 93% sensitivity and 100% specificity for diagnosing specific diseases and the diagnostic accuracy was higher than that of ICD-10 alone.[12] The comprehensive definitions for liver-related events and MACE are detailed in Table S2. The date of death is documented in the database and utilised for prognostic analysis.

Diabetes mellitus (DM) is defined as having an HbA1c level of ≥6.5%, a fasting blood glucose level of ≥126 mg/dL, or the use of

FIGURE 1 Patient selection.



antidiabetic medication. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or the use of lipid-lowering medication. Hypertension was defined as a systemic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication.

2.4 | Definition of MASLD, MetALD and ALD

Patients with SLD were categorised into MASLD, MetALD and ALD based on their level of alcohol consumption.[6] Alcohol consumption was determined using questionnaire data on drinking habits. A comprehensive definition of alcohol consumption is provided in Table S3. Since questionnaires are commonly used in Japan for every 20 g of ethanol, the definition of alcohol intake in this study differs slightly from the original definition.

2.5 | Primary endpoint

The primary endpoint was the occurrence of liver-related events, MACE and death in patients with MASLD, MetALD and ALD. The risks of complications and death were compared among these three groups.

2.6 | Statistical analyses

The cumulative incidence of liver-related events, MACE and death was examined using the Kaplan–Meier method and the log-rank test. The multivariable analysis was performed using the Cox proportional hazard model to examine the hazard ratio (HR) with a 95% confidence interval (CI) for the risk of liver-related events, MACE and death. For the multivariable analysis, factors such as age, gender, current smoking status, DM, hypertension and dyslipidemia were selected in advance as co-variables. This data on co-variables was collected for all patients and there were no missing data. Statistical significance was defined as p-values of <0.05. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patient characteristics

This study included 620,832 patients with MASLD, 108,494 patients with MetALD and 32,074 patients with ALD. Patient characteristics are shown in Table 1. The median age (interquartile range [IQR]) in MASLD, MetALD and ALD were 51 (44–58), 52 (46–59) and 52 (46–58) years, respectively. Primarily, the study included males, with 83.3% in MASLD, 89.6% in MetALD and 86.5% in ALD. The prevalence of DM and dyslipidemia was highest in MASLD (9.9% and 71.8%), followed by MetALD (8.5% and 71.1%) and ALD (7.7% and 69.3%). The median ALT level was highest in MASLD (31 IU/L), followed by MetALD (30 IU/L) and ALD (29 IU/L). Meanwhile, the mean GGT level was highest in ALD (90 IU/L), followed by MetALD (72 IU/L) and MASLD (47 IU/L).

3.2 | Liver-related events in MASLD, MetALD and ALD

The median follow-up periods (IQR) were 4.3 (2.8–4.9) years. During the follow-up period, a total of 419 patients (0.1%) experienced liver-related events. The cumulative incidence of liver-related events among the three groups was examined (Figure 2A). The cumulative incidence of liver-related events in MASLD over 1-, 3- and 5-year periods were 0.01%, 0.04% and 0.06%, respectively. The cumulative incidence of liver-related events in MetALD over 1-, 3- and 5-year periods were 0.01%, 0.05% and 0.12%, respectively. Similarly, the incidences in ALD were 0.02%, 0.10% and 0.27% over the same periods. The incidence of liver-related events was highest in ALD, followed by MetALD and MASLD (ALD vs. MetALD, $p<0.001$; MetALD vs. MASLD, $p=0.01$).

TABLE 1 Patient characteristics.

	MASLD (*N* = 620,832)	MetALD (*N* = 108,494)	ALD (*N* = 32,074)
Males (%)	517,232 (83.3)	97,183 (89.6)	27,733 (86.5)
Age (years)	51 (44–58)	52 (46–59)	52 (46–58)
DM (%)	61,621 (9.9%)	9202 (8.5%)	2471 (7.7)
Hypertension (%)	280,671 (45.2)	55,784 (51.4)	17,058 (53.2)
Dyslipidemia (%)	445,761 (71.8)	77,119 (71.1)	22,223 (69.3)
BMI (kg/m^2)	26.8 (24.6–29.4)	25.8 (23.8–28.3)	25.2 (23.1–27.5)
Triglycerides (mg/dL)	140 (98–203)	155 (106–233)	158 (105–252)
HDL-cholesterol (mg/dL)	51 (44–59)	55 (47–66)	59 (50–71)
LDL-cholesterol (mg/dL)	130 (110–152)	123 (102–145)	118 (96–141)
AST (IU/L)	24 (20–31)	26 (21–34)	28 (22–37)
ALT (IU/L)	31 (21–47)	30 (21–43)	29 (21–43)
GGT (IU/L)	47 (30–76)	72 (44–120)	90 (54–154)
HbA1c (%)	5.6 (5.3–5.9)	5.5 (5.3–5.8)	5.4 (5.2–5.7)

Note: Continuous data are shown in median (interquartile range).

Abbreviations: ALD, alcoholic-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; GGT, γ-Glutamyl Transpeptidase, MASLD, metabolic dysfunction-associated steatotic liver disease; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetALD, MASLD and increased alcohol intake.

In the subgroup of patients with MASLD, patients were stratified by one or two and more MASLD criteria. The 5-year cumulative incidence of liver-related events in patients with one criterion and multiple criteria was 0.04% and 0.07%, respectively, and the incidence was significantly higher in patients with multiple criteria than in patients with one criterion ($p < 0.001$).

3.3 | MACE in MASLD, MetALD and ALD

During the follow-up period, a total of 5791 patients (0.8%) developed MACE. The cumulative incidence of MACE was also examined (Figure 2B). The cumulative incidence of MACE over 1-, 3- and 5-years were 0.2%, 0.6% and 1.1% in MASLD, 0.1%, 0.3% and 0.9% in MetALD and 0.1%, 0.4% and 0.7% in ALD, respectively. The incidence of MACE was highest in MASLD, followed by MetALD and then ALD (MASLD vs. MetALD, $p < 0.001$; MetALD vs. ALD, $p < 0.001$).

In the subgroup of patients with MASLD, the 5-year cumulative incidence of MACE in patients with one criterion and multiple criteria was 0.34% and 1.4%, respectively, and the incidence was significantly higher in patients with multiple criteria than in patients with one criterion ($p < 0.001$).

3.4 | Prognosis in MASLD, MetALD and ALD

During the follow-up period, a total of 1408 patients (0.2%) died. The cumulative incidence of death over 1-, 3- and 5- years were 0.02%, 0.03% and 0.26% in MASLD, 0.04%, 0.13% and 0.35% in MetALD and 0.06%, 0.15% and 0.52% in ALD, respectively (Figure 2C). The incidence of death was highest in ALD, followed by MetALD and MASLD (ALD vs. MetALD, $p < 0.001$; MetALD vs. MASLD, $p = 0.007$). In patients with MASLD, 4.0%, 14.9% and 81.1% of patients died from liver-related events, MACE and other causes, respectively. Similarly, 7.4%, 16.0% and 76.6% of patients with MetALD died from liver-related events, MACE and other causes and 18.8%, 14.6% and 66.7% of patients with ALD died from liver-related events, MACE and other causes. Liver-related mortality was significantly higher in patients with ALD than in those with MetALD and MASLD ($p < 0.001$).

3.5 | Risk difference between MASLD, MetALD and ALD

The risk differences for liver-related events, MACE and death between MASLD, MetALD and ALD were analysed. The analysis used MASLD as a reference and adjusted for factors such as age, gender, smoking, DM, dyslipidemia and hypertension (Figure 3). The multivariable analysis showed that the adjusted HRs (95% CI) for liver-related events were 1.42 (1.1–1.8) in MetALD ($p = 0.005$) and 3.42 (2.6–4.6) in ALD ($p < 0.001$). Similarly, adjusted HRs for MACE (MASLD as the reference) were 0.68 (0.63–0.73) in MetALD ($p < 0.001$) and 0.58 (0.49–0.67) in ALD ($p < 0.001$). The adjusted HRs for death (MASLD as the reference) were 1.13 (0.98–1.3) in MetALD ($p = 0.09$) and 1.60 (1.3–2.0) in ALD ($p < 0.001$).

3.6 | Incidence of liver-related events and MACE with long-term observation

Long-term follow-up data were used to examine the cumulative incidence of liver-related events and MACE up to 10 years. The

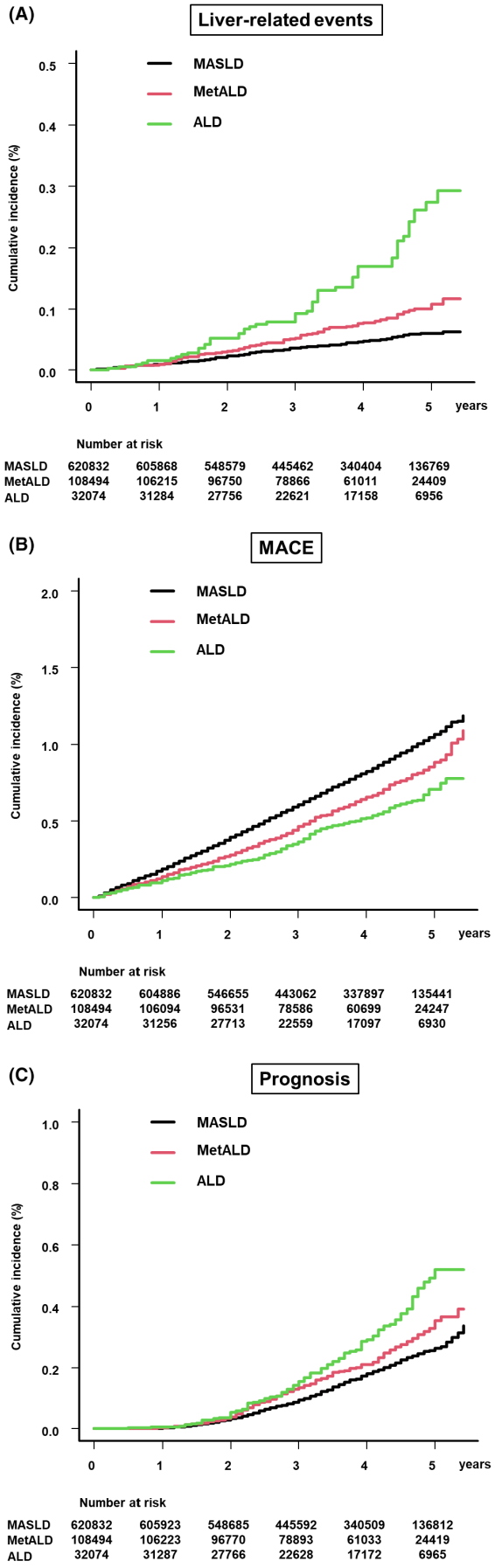


FIGURE 2 Cumulative incidence of liver-related events, MACE and prognosis. The cumulative incidence of (A) liver-related events, (B) MACE and (C) prognosis stratified by MASLD, MetALD and ALD was shown. ALD, alcohol-associated liver disease; MASLD, metabolic-dysfunction associated steatotic liver disease; MACE, major adverse cardiovascular events; MetALD, MASLD and increased alcohol intake.

cumulative incidence of liver-related events over 3-, 5- and 10-years were 0.03%, 0.06% and 0.12% in MASLD, 0.03%, 0.06% and 0.14% in MetALD and 0.05%, 0.14% and 0.33% in ALD, respectively (Figure 4A). The incidence of liver-related events was highest in ALD, followed by MetALD and then MASLD. Similarly, the cumulative incidence of MACE over 3-, 5- and 10- years were 0.5%, 0.9% and 2.0% in MASLD, 0.5%, 0.8% and 1.8% in MetALD and 0.4%, 0.7% and 1.7% in ALD, respectively (Figure 4B). The incidence of MACE was highest in MASLD, followed by MetALD and then ALD.

4 | DISCUSSION

4.1 | Main findings

In this nationwide, population-based cohort study that included 761,400 patients with MASLD, MetALD and ALD, we demonstrated that the risk of liver-related events significantly was highest in ALD, followed by MetALD and MASLD. Additionally, the risk of death was higher in ALD compared to MASLD. Conversely, the risk of MACE was highest in MASLD, followed by MetALD and ALD. The risk of complications and prognosis can be stratified using the new consensus nomenclature. The results underscore the usefulness of the new classification.

4.2 | In context with the published literature

The new consensus nomenclature recommends classification into MASLD, MetALD and ALD based on the amount of alcohol consumption. However, the clinical impact of these classifications remains unclear. In patients with NAFLD, several studies have explored the correlation between alcohol intake and the risk of liver-related complications. While it is widely recognised that heavy alcohol consumption is a significant risk factor for liver-related events, the impact of mild to moderate alcohol consumption on liver-related events in NAFLD remains a subject of debate.[13–15] Some studies have shown that mild to moderate alcohol consumption can reduce the risk of nonalcoholic steatohepatitis and advanced fibrosis.[16,17] On the contrary, other studies have demonstrated that the risk of advanced fibrosis or liver-related events increases with increased alcohol consumption.[18–21] The thresholds of alcohol consumption for liver-related events vary in these studies and notably, there are no available data recommending a safe level of alcohol consumption.[22] In this study, we demonstrated that the risk of liver-related events

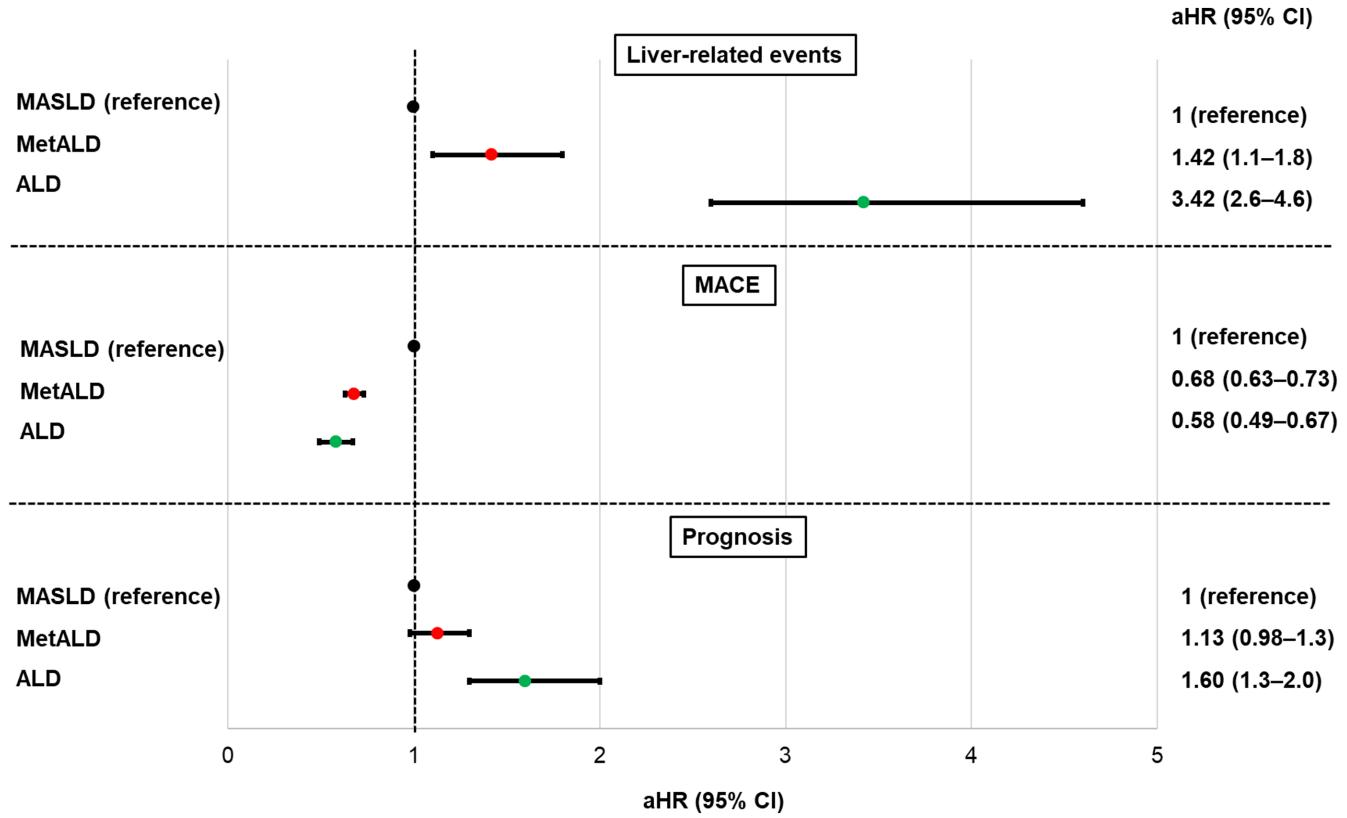


FIGURE 3 Adjusted HR for liver-related events, MACE and prognosis in MASLD, MetALD and ALD. In the multivariable analysis, MASLD was used as a reference and adjusted for factors such as age, gender, smoking, DM, dyslipidemia and hypertension. ALD, alcohol-associated liver disease; HR, hazard ratio; MACE, major adverse cardiovascular events; MASLD, metabolic-dysfunction associated steatotic liver disease; MetALD, MASLD and increased alcohol intake.

can be stratified among MASLD, MetALD and ALD. Therefore, the threshold for alcohol consumption in the new classification proves useful for risk stratification of liver-related events in patients with SLD. Further research is required to explore the impact of minimal alcohol intake (lower alcohol consumption threshold) in MASLD.

We showed a reduced MACE risk in MetALD and ALD compared to MASLD. The prevalence of DM and dyslipidemia in MASLD was higher than in MetALD and ALD. This increased prevalence of metabolic dysfunction could contribute to the elevated risk of MACE in MASLD. Furthermore, even after adjusting for these comorbidities, MetALD and ALD were independently associated with a favourable outcome in relation to MACE. In the general population, several studies have demonstrated that mild to moderate alcohol consumption is associated with a reduced risk of MACE.[23] Furthermore, a meta-analysis involving approximately 600,000 patients across 83 prospective studies demonstrated that the risk of myocardial infarction decreased in a dose-dependent manner with increased alcohol consumption.[24–26] In patients with NAFLD, some studies have shown that mild to moderate alcohol consumption is associated with a reduced risk of MACE.[27] Our findings align with those of previous studies, suggesting that the risk of MACE can be stratified in patients with SLD using the new classification.

The meta-analysis demonstrated that all-cause mortality increased with an increase in alcohol consumption in the general population.[24] Other research has also shown that the risk of mortality is higher in ALD compared to the general population.[28,29] However, the effects of alcohol consumption on SLD, particularly the implications of mild to moderate alcohol consumption on mortality, are less understood.[30,31] In this study, we demonstrated that while the prognosis in MASLD and MetALD are comparable, ALD has a poorer prognosis compared to MASLD.

In a Japanese study of 6508 hospital-based patients with NAFLD with a mean age of 49 (23–86) years, the incidence of HCC was 0.43 per 1000 person-years.[32] Similarly, in a meta-analysis of 8,515,431 patients with NAFLD, the incidence of HCC was 0.44 per 1000 person-years (mainly hospital-based patients with a mean age of 50.4 years).[33] Considering that our study used a young population-based cohort, the number of events in the study is considered reasonable.

4.3 | Strengths and limitations

In this study, we investigated over 700,000 patients with SLD using the nationwide, population-based cohort. Liver-related events and MACE were identified using both ICD-code and procedure code, resulting in a more accurate diagnosis than using the ICD-code alone. Furthermore, since all diagnosis and treatment codes were integrated by health insurance, tracking of diagnosis and treatment was possible even when

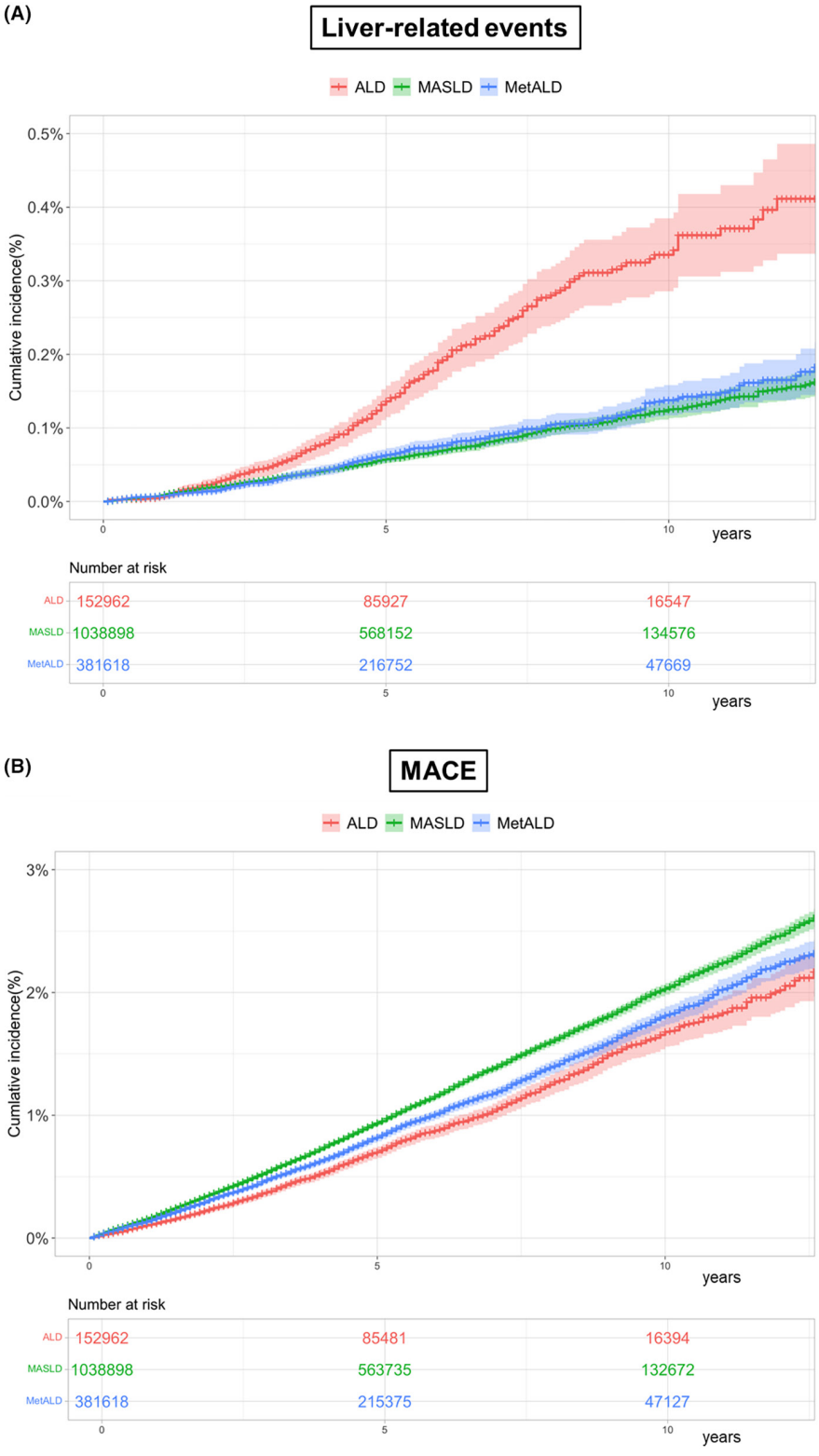


FIGURE 4 Incidence of liver-related events and MACE with long-term observation. The cumulative incidence of (A) liver-related events and (B) MACE stratified by MASLD, MetALD and ALD was shown. ALD, alcohol-associated liver disease; MACE, major adverse cardiovascular events; MASLD, metabolic-dysfunction associated steatotic liver disease; MetALD, MASLD and increased alcohol intake.

patients switched care providers, enabling accurate long-term disease course assessment. In Japan, companies are required by law to provide annual health checkup for their employees and the dataset consists of annual health checkup and claims data. Therefore, the dataset includes data on individuals who have not been seen in any healthcare encounter, allowing for analyses from a cohort that is more population-based than hospital-based cohorts. However, since the cohort primarily consisted of relatively young male patients, further studies are needed in cohorts that include elderly patients or females. Liver fibrosis is a well-known risk factor for liver-related events, but the database lacks data for liver fibrosis assessment.[34,35] Therefore, additional research may be necessary to investigate the effects of the classification after

adjusting for liver fibrosis, especially in liver-related events. The definition of alcohol intake in this study differs slightly from the original definition and future analyses based on more accurate alcohol intake are needed. Notwithstanding this, we showed that the risk of complications and prognosis could be stratified using even a simple questionnaire, as shown in Table S3 and it is useful in daily clinical practice.

4.4 | Future implications

The new criteria of MASLD, MetALD and ALD can be used to stratify the risk of liver-related events, MACE and prognosis. Patients with moderate alcohol consumption, classified as MetALD in this nomenclature, have not been appropriately categorised previously. Since MetALD poses different risks compared to MASLD or ALD, its new clinical definition is significant. In clinical practice, follow-up and surveillance are necessary based on the risk of complications. The new definitions of MASLD, MetALD and ALD, which have significantly different complication risks, may be useful in developing appropriate surveillance strategies. Given the limited number of effective drugs for SLD, there is an urgent need for the development of novel therapies. Since the pathogenesis of MASLD, MetALD and ALD differs, identifying new mechanisms for disease-specific therapeutic implications is crucial for developing novel therapies. In this context, this novel nomenclature may have significant clinical implications.

In conclusion, the new consensus nomenclature can be used to stratify the risk of complications and prognosis. The nomenclature is beneficial for risk stratification and identifying new mechanisms for disease-specific therapeutic implications.

AUTHOR CONTRIBUTIONS

Nobuharu Tamaki: Conceptualization; methodology; formal analysis; funding acquisition; writing – original draft; writing – review and editing; data curation. **Takefumi Kimura:** Conceptualization; formal analysis; data curation; writing – original draft; writing – review and editing; methodology. **Shun-Ichi Wakabayashi:** Conceptualization; methodology; data curation; formal analysis; writing – original draft; writing – review and editing. **Takeji Umemura:** Supervision; funding acquisition; writing – review and editing; data curation. **Masayuki Kurosaki:** Conceptualization; methodology; data curation; supervision; project administration; writing – review and editing; funding acquisition. **Rohit Loomba:** Data curation; supervision; funding acquisition; writing – review and editing. **Namiki Izumi:** Conceptualization; methodology; data curation; supervision; funding acquisition; writing – review and editing; project administration.

ACKNOWLEDGEMENTS

Declaration of personal interests: Rohit Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Inc, Madrigal, Metacrine, Inc, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics, his employers received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals and is the co-founder of LipoNexus, Inc. The other authors have no conflicts of interest to declare.

FUNDING INFORMATION

Nobuharu Tamaki receives funding support from Japan Agency for Medical Research and Development (grant number: JP23fk0210111 and JP23fk0210104) and Japanese Ministry of Health, Welfare and Labor (grand number: 23HC2003 and 23HC2002). Masayuki Kurosaki receives funding support from Japan Agency for Medical Research and Development (grant number: JP23fk0210123). Namiki Izumi receives funding support from Japanese Ministry of Health, Welfare and Labor (grand number: 23HC2001). Takeji Umemura receives funding support from Japan Agency for Medical Research and Development (grant number: JP23fk0210125). Rohit Loomba receives funding support from NCATS (5UL1TR001442), NIDDK (U01DK061734, U01DK130190, R01DK106419, R01DK121378, R01DK124318, P30DK120515), NHLBI (P01HL147835), John C Martin Foundation (RP124) and NIAAA (U01AA029019).

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Tamaki N, Kimura T, Wakabayashi S-I, Umemura T, Kurosaki M, Loomba R, et al. Long-term clinical outcomes in steatotic liver disease and incidence of liver-related events, cardiovascular events and all-cause mortality. Aliment Pharmacol Ther. 2024;60:61–69. https://doi.org/10.1111/apt.18015