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Epidemiology

Association between diabetes and in-hospital outcomes in patients with metabolic dysfunction-associated steatotic liver disease hospitalized for cardiovascular disease: A nationwide database study

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Abstract

Aims: To evaluate the impact of diabetes on in-hospital outcomes among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who were hospitalized for cardiovascular disease (CVD).

Methods: We conducted a retrospective cross-sectional study using data from the nationwide Japanese Registry of All Cardiac and Vascular Diseases-Diagnosis Procedure Combination, from April 2012 to March 2023. A total of 10,614 patients with MASLD hospitalized for CVD were identified, of whom 4550 (42.9%) had diabetes. The primary outcome was in-hospital mortality, and secondary outcomes were major cardiac and non-cardiac complications.

Results: The median age was 66 years, and 66.9% were male. Compared with patients without diabetes, those with diabetes had higher rates of ischaemic heart disease (35.5% vs. 30.8%), acute coronary syndrome (18.8% vs. 16.9%) and heart failure (27.3% vs. 25.4%) (all $p < 0.05$). In-hospital mortality (5.6% vs. 3.3%; $p < 0.001$) and overall complication rates (23.6% vs. 19.7%; $p < 0.001$) were significantly greater in the diabetes group, driven mainly by cardiac events (16.8% vs. 10.5%; $p < 0.001$). Multivariable logistic regression confirmed diabetes as an independent predictor of in-hospital mortality (odds ratio, 1.99; 95% confidence interval, 1.60–2.47; $p < 0.001$).

Conclusions: Diabetes was associated with higher in-hospital mortality and complication rates among patients with MASLD hospitalized for CVD. Stratification of MASLD by metabolic phenotype, particularly in the presence of diabetes, may help improve risk assessment and inform more personalized clinical management in this population.

KEYWORDS

cardiovascular disease, diabetes, in-hospital mortality, metabolic dysfunction-associated steatotic liver disease

1 | INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide and represents an escalating public health concern.[1–3] Under the recently revised diagnostic framework, MASLD is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor such as obesity, hypertension, dyslipidaemia or diabetes.[4,5] Although the primary purpose of this updated nomenclature is to improve its clinical applicability and disease recognition, it remains unclear whether each component of the diagnostic criteria has an equivalent prognostic significance.

A growing body of epidemiological evidence supports the strong link between MASLD and cardiovascular disease (CVD), thus suggesting that cardiovascular risk assessment is an integral part of MASLD management.[6–8] Among the various metabolic risk factors, diabetes is particularly concerning because of its known association with liver-related complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma and systemic cardiometabolic dysfunction.[9–11] However, the non-hepatic effect of diabetes, particularly on CVD, remains inconclusive in MASLD populations.[12] Given the heterogeneity of metabolic profiles within the MASLD population, a subclassification based on diabetes status may help identify a higher-risk phenotype; therefore, this topic warrants intensive clinical attention. Large-scale studies are lacking on the prognostic implications of diabetes in patients with MASLD who were hospitalized for CVD.

To address this gap, we conducted a nationwide cross-sectional study using data from the Japanese Registry of All Cardiac and Vascular Diseases-Diagnosis Procedure Combination (JROAD-DPC), an administrative claims database encompassing cardiovascular hospitalization across Japan.[13] This study aimed to investigate the association between diabetes and in-hospital outcomes, including mortality and major complications, in patients with MASLD who were hospitalized for CVD.

What's new?

What is already known?

Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to an increased risk of cardiovascular disease (CVD). Diabetes is a key metabolic component within the diagnostic framework of MASLD and is known to predispose patients to liver-related complications.

What this study has found?

Among patients with MASLD hospitalized for CVD, diabetes was associated with higher in-hospital mortality and a greater incidence of cardiovascular complications. These associations remained significant after multivariable adjustment. Diabetes thus represents a high-risk metabolic phenotype within the MASLD spectrum.

What are the implications of the study?

Subclassifying MASLD according to metabolic phenotypes—particularly the presence of diabetes—may improve risk stratification and guide more personalized management strategies for patients hospitalized with CVD.

2 | METHODS

2.1 | Study population and diagnostic criteria

We analysed data from the JROAD-DPC database, which is a nationwide claims registry encompassing 992 Japanese hospitals, covering the period from April 2012 to March 2023. Among patients aged 18 years or older who were hospitalized for CVD, we identified 34,130 patients with hepatic steatosis at the time of admission, as defined by the relevant codes from the 10th revision of the International Classification of Diseases. Supplementary Methods S1 and S2 provide detailed descriptions of the methods and diagnostic criteria.

MASLD was defined as the presence of hepatic steatosis with at least one cardiometabolic risk factor: hypertension, dyslipidaemia, diabetes, use of corresponding medications or a body mass index (BMI) ≥23 kg/m^2 (the threshold for obesity in Asian populations).

The identification of MASLD was based on the International Classification of Diseases, 10th Revision (ICD-10) codes: hepatic steatosis was identified using K70.0, K75.8 and K76.0; hypertension was defined by codes I10–I13 and I15 or the use of antihypertensive agents; dyslipidaemia was defined by codes E78.0–E78.2, E78.4 and E78.5 or the use of lipid-lowering agents; and diabetes was defined by codes E10–E14 or the use of antidiabetic agents. We excluded patients with elective hospitalizations for diagnostic investigation purposes without therapeutic interventions (n = 20,552) and those with missing BMI data (n = 766). To minimize potential confounding, patients with coexisting diagnoses of alcoholic liver disease (F10.2, n = 161), viral hepatitis (B15–B19, n = 263), primary biliary cholangitis (K74.3, n = 42) or autoimmune hepatitis (K75.4, n = 37) were also excluded, as

these hepatic conditions are independently associated with adverse outcomes.[14–16] The final study cohort consisted of 10,614 patients with MASLD who were admitted for CVD treatment (Figure 1). To assess the effect of diabetes on in-hospital outcomes, the patients were stratified into two groups: those with and without diabetes.

2.2 | Data collection and definitions

The following data were extracted from the JROAD-DPC database: hospital identifiers, age, sex, height, weight, BMI, smoking status, in-hospital medication use and discharge status. The comorbidity burden (i.e. acute coronary syndrome [ACS], heart failure, cerebrovascular disease, chronic pulmonary disease and cancer) was calculated using the Charlson Comorbidity Index. Surgical procedures, percutaneous coronary intervention, blood transfusion and emergency (nonelective) admissions were determined using Diagnosis Procedure Combination codes. Supplementary Table S1 shows the full code lists. This study was approved by the University of Miyazaki Ethics Committee (authorization no. O-1536) and was conducted in accordance with the principles of the Declaration of Helsinki. Considering that all data were de-identified, the requirement for informed consent was waived.

2.3 | Clinical outcomes

The primary clinical outcome was in-hospital mortality. Secondary outcomes included the occurrence of new in-hospital complications during admission. These complications were categorized into two major groups: cardiac events and major non-cardiac events. Cardiac events were defined as composite outcomes comprising heart failure, ACS, venous thromboembolism, ventricular arrhythmia, or the need for advanced cardiopulmonary support, including intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO) or mechanical ventilation initiated after admission. Major non-cardiac events included pneumonia, sepsis, ischaemic stroke and major bleeding. Major bleeding was defined as intracranial haemorrhage, gastrointestinal bleeding or any bleeding event requiring red blood cell transfusion during hospitalization.[17]

2.4 | Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQRs), and categorical variables were expressed as numbers with percentages. Group comparisons for continuous and categorical variables were conducted using the Wilcoxon rank-sum test and chi-square test, respectively. Univariate and multivariable mixed-effects logistic regression models using institution as a random effect were performed, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for in-hospital mortality. Variables with a p-value <0.05 in the univariate analysis and clinically relevant variables were included in the multivariable model. All statistical analyses were performed using

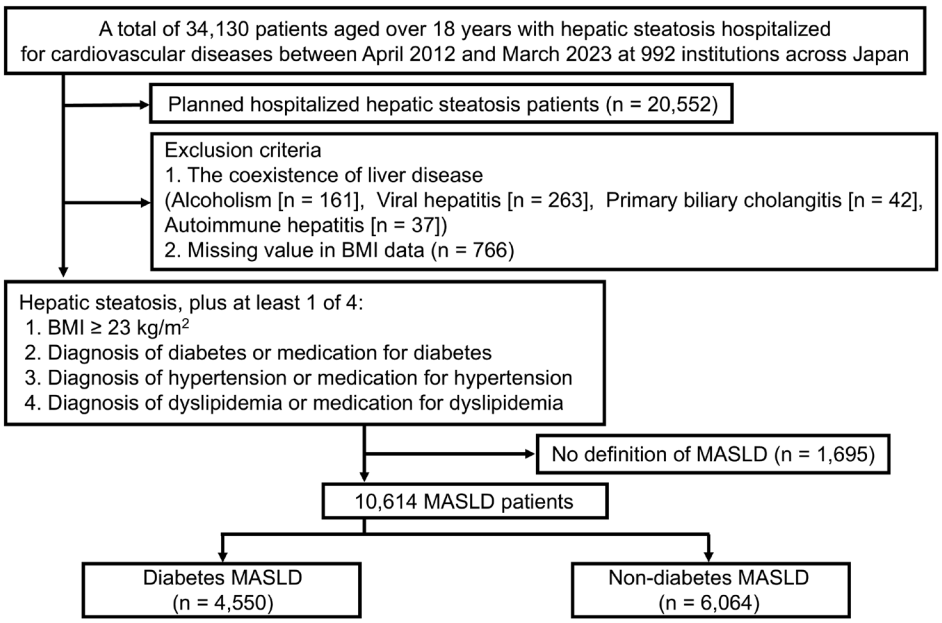

FIGURE 1 Flow chart of patient inclusion and exclusion. BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease.

STATA version 16 software (StataCorp, College Station, TX, USA). A two-sided *p*-value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics by diabetes status

Table 1 summarizes the patients' characteristics stratified by diabetes status. Among the 10,614 patients with MASLD who were admitted for CVD, 4550 (42.9%) had diabetes. The median age of the entire cohort was 66 years (IQR, 53–76 years). Patients with diabetes were older than those without diabetes (median 67 vs. 64 years; $p < 0.001$) and had a higher median BMI (26.0 kg/m^2 vs. 25.1 kg/m^2; $p < 0.001$). Obesity was highly prevalent in 71.7% of the whole cohort and was common in the diabetes group (75.6% vs. 68.7%; $p < 0.001$). Cardiometabolic comorbidities including hypertension (84.6% vs. 78.5%) and dyslipidaemia (57.8% vs. 45.8%) were significantly more common in patients with diabetes than in those without diabetes (all $p < 0.001$). No significant differences were observed in smoking status or sex distribution. For the CVD diagnosis for admission, patients with diabetes had higher rates of ischaemic heart disease (35.5% vs. 30.8%; $p < 0.001$), ACS (18.8% vs. 16.9%; $p = 0.016$) and heart failure (27.3% vs. 25.4%; $p = 0.031$), whereas atrial fibrillation was modestly more common in the non-diabetes group (14.9% vs. 13.3%; $p = 0.017$). With respect to non-cardiac comorbidities, diabetes was associated with a higher prevalence of chronic kidney disease (7.6% vs. 4.6%; $p < 0.001$), haemodialysis (1.4% vs. 0.8%; $p = 0.003$) and any cancer (15.5% vs. 13.5%; $p = 0.003$), including hepatic tumours (5.8% vs. 3.1%; $p < 0.001$). No significant differences were observed for cerebrovascular disease, pulmonary hypertension, chronic obstructive pulmonary disease, collagen disease or mental illness.

TABLE 1 Clinical characteristics of MASLD patients hospitalized for CVD: Comparisons between those with and without diabetes.

Variables	All ($n = 10,614$)	Diabetes ($n = 4550$)	Non-diabetes ($n = 6064$)	*p* value
Age, median (IQR)	66.0 (53.0–76.0)	**67.0 (56.0–76.0)**	**64.0 (51.0–75.0)**	**<0.001**
Male, *n*, (%)	7102 (66.9)	3047 (67.0)	4055 (66.8)	0.92
BMI (kg/m^2) (IQR)	25.5 (22.5–28.9)	**26.0 (23.1–29.6)**	**25.1 (22.1–28.4)**	**<0.001**
Smoking, *n*, (%)	4312 (40.6)	1842 (40.5)	2470 (40.7)	0.71
Charlson score, median (IQR)	2.0 (2.0–4.0)	**3.0 (3.0–4.0)**	**2.0 (1.0–3.0)**	**<0.001**
Full score BI at admission, *n*, (%)	4398 (41.4)	1824 (40.1)	2574 (42.4)	0.063
Obese, *n*, (%)	7608 (71.7)	**3438 (75.6)**	**4170 (68.7)**	**<0.001**
Hypertension, *n*, (%)	8616 (81.2)	**3851 (84.6)**	**4765 (78.5)**	**<0.001**
Dyslipidaemia, *n*, (%)	5408 (51.0)	**2632 (57.8)**	**2776 (45.8)**	**<0.001**
Hyperuricemia, *n*, (%)	1381 (13.0)	565 (12.4)	816 (13.4)	0.12
Atrial fibrillation, *n*, (%)	1513 (14.3)	**606 (13.3)**	**907 (14.9)**	**0.017**
Ischaemic heart disease, *n*, (%)	3489 (32.9)	**1616 (35.5)**	**1873 (30.8)**	**<0.001**
ACS, *n*, (%)	1885 (17.8)	**855 (18.8)**	**1030 (16.9)**	**0.016**
Heart failure, *n*, (%)	2789 (26.3)	**1244 (27.3)**	**1545 (25.4)**	**0.031**
Chronic kidney disease, *n*, (%)	630 (5.9)	**345 (7.6)**	**285 (4.6)**	**<0.001**
Haemodialysis, *n*, (%)	113 (1.1)	**64 (1.4)**	**49 (0.8)**	**0.003**
Cerebrovascular disease, *n*, (%)	3063 (28.9)	1297 (28.5)	1766 (29.1)	0.49
Pulmonary hypertension, *n*, (%)	69 (0.7)	30 (0.7)	39 (0.6)	0.92
Chronic lung disease, *n*, (%)	607 (5.7)	244 (5.4)	363 (5.9)	0.17
Cancer, *n*, (%)	1525 (14.4)	**706 (15.5)**	**819 (13.5)**	**0.003**
Hepatic tumour, *n*, (%)	453 (4.3)	**266 (5.8)**	**187 (3.1)**	**<0.001**
Collagen disease, *n*, (%)	229 (2.2)	108 (2.4)	121 (2.0)	0.18
Mental illness, *n*, (%)	1042 (9.8)	436 (9.6)	606 (10.0)	0.48

Note: Data are presented as medians (interquartile ranges) or numbers (percentages). Bold values indicate statistical significance at the $p < 0.05$ level.
Obese = body mass index ≥23 kg/m^2.

Abbreviations: ACS, acute coronary syndrome; BI, Barthel index; BMI, body mass index; IQR, interquartile ranges; MASLD, metabolic dysfunction-associated steatotic liver disease.

3.2 | In-hospital mortality and complications by diabetes status

Table 2 shows the in-hospital mortality and complications according to diabetes status. Overall, in-hospital mortality was 4.3%. Patients with diabetes had a significantly higher mortality rate than those without diabetes (5.6% vs. 3.3%; $p < 0.001$), and this difference persisted within 30 days of admission (4.2% vs. 2.9%; $p < 0.001$). The median age at death did not significantly differ between the groups (71 years vs. 72.5 years; $p = 0.20$); however, among patients with diabetes, the length of hospital stay until death was significantly longer (median of 13 days [IQR, 4–29] vs. median of 7.5 days [IQR, 2–21.5]; $p = 0.001$). In-hospital complications were common and affected 21.4% of all patients, with diabetes having a higher incidence rate (23.6% vs. 19.7%; $p < 0.001$). The higher rate was primarily attributable to cardiac events (16.8% vs. 10.5%; $p < 0.001$), whereas rates of major non-cardiac events were similar (9.9% vs. 10.8%; $p = 0.17$). Within the cardiac category, diabetes was associated with a higher incidence of heart failure after admission (4.0% vs. 2.7%, $p < 0.001$), ACS (1.4% vs. 1.0%; $p = 0.049$) and greater use of advanced support (IABP [2.1% vs. 0.8%], ECMO [0.8% vs. 0.2%] and mechanical ventilation [10.2% vs. 5.2%]; all $p < 0.001$).

3.3 | Clinical determinants of in-hospital mortality and complications

As shown in Table 3, the univariate analysis of the overall MASLD cohort hospitalized for CVD demonstrated that older age, diabetes, sepsis, major bleeding and cancer were significantly associated with increased in-hospital mortality. In contrast, obesity, hypertension, dyslipidaemia and ischaemic heart disease were associated with reduced mortality. Multivariable analysis confirmed that age (OR, 1.03; 95% CI, 1.02–1.04; $p < 0.001$), diabetes (OR, 1.99; 95% CI, 1.60–2.47; $p < 0.001$), sepsis (OR, 6.97; 95% CI, 3.85–12.6; $p < 0.001$), major bleeding (OR, 2.18; 95% CI, 1.55–3.07; $p < 0.001$) and cancer (OR, 2.21; 95% CI, 1.73–2.81; $p < 0.001$) were independent determinants of in-hospital mortality. Notably, dyslipidaemia (OR, 0.35; 95% CI, 0.27–0.45; $p < 0.001$) and ischaemic heart disease (OR, 0.71; 95% CI, 0.54–0.95; $p = 0.021$) were independently associated with lower odds of mortality. Indeed, subgroup analysis of medication use revealed that antiplatelet therapy (OR, 0.37; 95% CI, 0.26–0.52; $p < 0.001$), statin use (OR, 0.53; 95% CI, 0.34–0.82; $p < 0.001$) and the use of ACE inhibitors or ARBs (OR, 0.32; 95% CI, 0.23–0.43; $p < 0.001$) were significantly associated with reduced in-hospital mortality risk (Supplementary Table S2). Furthermore, among patients with ischaemic heart disease, those undergoing percutaneous coronary intervention (PCI) had a significantly lower mortality rate than those who did not (1.5% vs. 2.8%, $p = 0.014$) (Supplementary Table S3).

Table 4 presents the subgroup analysis for patients with diabetes. In this cohort, older age, sepsis, major bleeding and cancer were positively associated with in-hospital mortality, whereas obesity, hypertension, dyslipidaemia, ischaemic heart disease and cerebrovascular disease were associated with lower mortality. In the multivariable model, independent determinants of in-hospital mortality included age (OR, 1.02; 95% CI, 1.01–1.03; $p = 0.001$), sepsis (OR, 5.98; 95% CI, 2.81–12.7; $p < 0.001$), major bleeding (OR, 4.55; 95% CI, 2.50–8.28; $p < 0.001$) and cancer (OR, 1.52; 95% CI, 1.11–2.09; $p < 0.001$). By contrast, dyslipidaemia (OR, 0.34; 95% CI, 0.25–0.47; $p < 0.001$), hypertension (OR, 0.70; 95% CI, 0.50–0.97; $p = 0.032$), ischaemic heart disease (OR, 0.58; 95% CI, 0.41–0.83; $p = 0.003$) and cerebrovascular disease (OR, 0.38; 95% CI, 0.24–0.59; $p < 0.001$) were independently associated with reduced mortality. Supplementary Table S4 shows that among patients with non-diabetic MASLD, older age, sepsis, major bleeding and cancer were significantly associated with increased mortality, with age (OR, 1.03; 95% CI, 1.02–1.05; $p < 0.001$), sepsis (OR, 9.21; 95% CI, 3.87–21.9; $p < 0.001$), major bleeding (OR, 2.44; 95% CI, 1.54–3.86; $p < 0.001$) and cancer (OR, 2.78; 95% CI, 1.95–3.94; $p < 0.001$) emerging as independent determinants. Additionally, dyslipidaemia (OR, 0.34; 95% CI, 0.24–0.54; $p < 0.001$) remained protective in this group. The specific risk estimates for in-hospital mortality associated with diabetes are summarized in Supplementary Table S5. In multilevel mixed-effects logistic regression models, diabetes remained independently associated with increased in-hospital mortality across MASLD diagnostic categories and comorbid cardiovascular conditions, including ACS, heart failure and atrial fibrillation, with a significant interaction observed only between diabetes and ACS ($p = 0.048$).

With respect to in-hospital complications (e.g. infections, bleeding, stroke), Supplementary Table S6 indicates that male sex, hypertension, diabetes, heart failure, cerebrovascular disease and low Barthel Index score were all independently associated with an increased risk. Specifically, heart failure (OR, 3.38; 95% CI, 2.95–3.86; $p < 0.001$) and cerebrovascular disease (OR, 4.20; 95% CI, 3.67–4.80; $p < 0.001$) showed the strongest associations. By contrast, older age (OR, 0.98; 95% CI, 0.97–0.98; $p < 0.001$), obesity (OR, 0.82; 95% CI, 0.72–0.94; $p = 0.004$) and dyslipidaemia (OR, 0.81; 95% CI, 0.72–0.91; $p = 0.001$) were associated with a lower risk of complications.

TABLE 2 In-hospital outcomes of MASLD patients hospitalized for CVD: Comparisons between those with and without diabetes.

Variables	All ($n=10,614$)	Diabetes ($n=4550$)	Non-diabetes ($n=6064$)	p value
In-hospital mortality, *n*, (%)	457 (4.3)	**253 (5.6)**	**204 (3.3)**	**<0.001**
30-day in-hospital mortality, *n*, (%)	368 (3.5)	**192 (4.2)**	**176 (2.9)**	**<0.001**
Age at in-hospital death, years, median (IQR)	72.0 (62.0–80.0)	71.0 (62.0–79.0)	72.5 (63.0–81.0)	0.20
Time from admission to in-hospital death, days, median (IQR)	13.0 (8.0–22.0)	**13.0 (4.0–29.0)**	**7.5 (2.0–21.5)**	**0.001**
Full score BI at discharge, *n*, (%)	7499 (70.7)	3104 (68.2)	4395 (72.5)	0.11
In-hospital complication, *n*, (%)	2267 (21.4)	**1075 (23.6)**	**1192 (19.7)**	**<0.001**
Cardiac events, *n*, (%)	1403 (13.2)	**766 (16.8)**	**637 (10.5)**	**<0.001**
Heart failure after admission, *n*, (%)	342 (3.2)	**181 (4.0)**	**161 (2.7)**	**<0.001**
ACS after admission, *n*, (%)	122 (1.1)	**63 (1.4)**	**59 (1.0)**	**0.049**
VTE after admission, *n*, (%)	170 (1.6)	81 (1.8)	89 (1.5)	0.20
Ventricular arrhythmia, *n*, (%)	88 (0.8)	46 (1.0)	42 (0.7)	0.073
IABP, *n*, (%)	142 (1.3)	**96 (2.1)**	**46 (0.8)**	**<0.001**
ECMO, *n*, (%)	45 (0.4)	**35 (0.8)**	**10 (0.2)**	**<0.001**
Mechanical ventilation, *n*, (%)	777 (7.3)	**463 (10.2)**	**314 (5.2)**	**<0.001**
Non-cardiac events, *n*, (%)	1104 (10.4)	452 (9.9)	652 (10.8)	0.17
Sepsis, *n*, (%)	88 (0.8)	**49 (1.1)**	**39 (0.6)**	**0.015**
Pneumonia, *n*, (%)	110 (1.0)	**58 (1.3)**	**52 (0.9)**	**0.036**
Major bleeding, *n*, (%)	791 (7.5)	**280 (6.2)**	**511 (8.4)**	**<0.001**
Ischaemic stroke, *n*, (%)	125 (1.2)	64 (1.4)	61 (1.0)	0.058
DIC, *n* (%)	64 (0.6)	**36 (0.8)**	**28 (0.5)**	**0.030**

Note: Data are presented as medians (interquartile ranges) or numbers (percentages). Bold values indicate statistical significance at the $p<0.05$ level. Obese = body mass index ≥23 kg/m^2.

Abbreviations: ACS, acute coronary syndrome; BI, Barthel index; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; IQR, interquartile ranges; MASLD, metabolic dysfunction-associated steatotic liver disease; VTE, venous thromboembolism.

4 | DISCUSSION

In this large nationwide cohort of over 10,000 patients with MASLD hospitalized for CVD, diabetes was present in approximately 43% of cases and was independently associated with a significantly higher risk of in-hospital mortality and complications. Even after adjusting for comorbidities and clinical demographics, diabetes remained a robust and independent predictor of adverse in-hospital outcomes, underscoring its clinical relevance as a high-risk metabolic phenotype in the MASLD spectrum.

The recent redefinition of MASLD places obesity, hypertension, dyslipidaemia, and diabetes on equal diagnostic footing. However, our findings indicate that

TABLE 3 Univariate and multivariable analysis on the clinical determinants for in-hospital mortality of MASLD patients hospitalized for CVD.

	Univariate analysis			Multivariable analysis		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age	**1.03**	**1.02–1.04**	**<0.001**	**1.03**	**1.02–1.04**	**<0.001**
Male	**0.79**	**0.65–0.96**	**0.018**	0.89	0.70–1.13	0.352
Smoking	**0.77**	**0.62–0.95**	**0.015**	1.03	0.80–1.32	0.814
Obese	**0.63**	**0.52–0.77**	**<0.001**	0.82	0.66–1.03	0.095
Hypertension	**0.66**	**0.53–0.83**	**<0.001**	0.79	0.61–1.02	0.076
Dyslipidaemia	**0.27**	**0.21–0.33**	**<0.001**	**0.35**	**0.27–0.45**	**<0.001**
Diabetes	**1.68**	**1.39–2.04**	**<0.001**	**1.99**	**1.60–2.47**	**<0.001**
Atrial fibrillation	0.99	0.76–1.31	0.969			
Ischaemic heart disease	**0.43**	**0.34–0.55**	**<0.001**	**0.71**	**0.54–0.95**	**0.021**
Heart failure	1.10	0.89–1.36	0.392			
Chronic kidney disease	1.34	0.93–1.92	0.116			
Cerebrovascular disease	0.80	0.64–1.00	0.052			
Sepsis	**8.36**	**4.94–14.1**	**<0.001**	**6.97**	**3.85–12.6**	**<0.001**
Major bleeding	**1.84**	**1.37–2.47**	**<0.001**	**2.18**	**1.55–3.07**	**<0.001**
Cancer	**2.91**	**2.35–3.60**	**<0.001**	**2.21**	**1.73–2.81**	**<0.001**
Barthel index score <100	1.42	0.15–13.6	0.761			

Note: Bold values indicate statistical significance at the $p < 0.05$ level. Age = 1-year increase. Obese = body mass index ≥23 kg/m^2.

Abbreviations: CI, confidence interval; CVD, Cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio.

their prognostic weights differ significantly, and diabetes demonstrated a stronger association with adverse in-hospital outcomes compared with other risk factors. These results suggest that even under the unified diagnostic label of MASLD, diabetes should be recognized as a high-risk phenotype associated with a poor prognosis, requiring specific vigilance.

Diabetes systematically induces metabolic stress and chronic pro-inflammatory and pro-thrombotic states, leading to both micro- and macrovascular injuries.[18] These pathophysiological alterations are associated with a heightened risk of acute cardiovascular events and long-term outcomes. Consistent with this finding, we observed a substantially higher burden of cardiovascular complications, including post-admission heart failure, ACS and use of advanced circulatory support in the diabetes group. By contrast, while diabetes was more commonly linked to specific non-cardiovascular complications—including sepsis, pneumonia and disseminated intravascular coagulation (DIC)—the overall incidence of non-cardiovascular complications did not differ significantly between the groups. These findings suggest that acute-phase vulnerability in patients with diabetes-MASLD is primarily cardiovascular in nature, thus warranting meticulous haemodynamic monitoring and timely intervention.

The unexpected inverse associations of hypertension, dyslipidaemia and ischaemic heart disease with in-hospital mortality are likely attributable to intensive clinical management—specifically, the use of cardioprotective pharmacotherapies (statins, antiplatelet agents, renin-angiotensin system inhibitors) and frequent monitoring—rather than inherent protective effects. Likewise, the favourable outcomes in patients who underwent PCI over conservative management in ischaemic heart disease may suggest an association with timely intervention combined with optimal pharmacotherapy, although causality cannot be inferred due to the observational design.

In contrast, diabetes remained independently associated with adverse outcomes across the MASLD cohorts, suggesting that current strategies may be insufficient to fully mitigate its systemic impact. Collectively, these findings highlight unmet clinical needs in the diabetes-MASLD population. Further research should assess whether optimizing treatment for diabetes and integrated cardio-hepatic care can improve CVD outcomes, beyond the currently available evidence.[19,20]

TABLE 4 Univariate and multivariable analyses of clinical determinants of in-hospital mortality in diabetes-MASLD patients hospitalized for CVD.

	Univariate analysis			Multivariable analysis		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age	**1.02**	**1.01–1.03**	**<0.001**	**1.02**	**1.01–1.03**	**0.001**
Male	0.98	0.74–1.29	0.881			
Smoking	0.86	0.65–1.14	0.288			
Obese	**0.6**	**0.45–0.79**	**<0.001**	0.81	0.60–1.09	0.164
Hypertension	**0.57**	**0.42–0.78**	**<0.001**	**0.70**	**0.50–0.97**	**0.032**
Dyslipidaemia	**0.24**	**0.18–0.32**	**<0.001**	**0.34**	**0.25–0.47**	**<0.001**
Atrial fibrillation	1.34	0.95–1.92	0.095			
Ischaemic heart disease	**0.4**	**0.28–0.55**	**<0.001**	**0.58**	**0.41–0.83**	**0.003**
Heart failure	1.09	0.82–1.46	0.541			
Chronic kidney disease	1.49	0.97–2.29	0.068			
Cerebrovascular disease	**0.61**	**0.44–0.84**	**0.003**	**0.38**	**0.24–0.59**	**<0.001**
Sepsis	**6.26**	**3.08–12.7**	**<0.001**	**5.98**	**2.81–12.7**	**<0.001**
Major bleeding	**1.95**	**1.26–3.00**	**0.003**	**4.55**	**2.50–8.28**	**<0.001**
Cancer	**2.46**	**1.84–3.29**	**<0.001**	**1.52**	**1.11–2.09**	**<0.001**

Note: Bold values indicate statistical significance at the $p < 0.05$ level. Age = 1-year increase. Obese = body mass index ≥23 kg/m^2.

Abbreviations: CI, confidence interval; CVD, Cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio.

Furthermore, we observed a higher prevalence of chronic kidney disease in patients with diabetes-MASLD than in those without diabetes (7.6% vs. 4.6%; $p < 0.001$); this finding aligns with the conceptual framework of the cardiovascular-kidney-metabolic (CKM) syndrome.[21,22] This construct underscores the pathophysiological interdependence among metabolic, renal and cardiovascular dysfunction in driving adverse clinical outcomes. As a central component of the CKM syndrome, diabetes promotes widespread vascular and organ dysfunction.[23–26] Although the precise mechanisms underlying this organ crosstalk are not fully elucidated, our findings suggest that poor CKM health may directly or indirectly contribute to short-term adverse outcomes.[27,28] However, in our multivariable analysis, CKD was not significantly associated with either in-hospital mortality or in-hospital complications. One potential explanation for this apparent discrepancy is the absence of quantitative renal data—such as estimated glomerular filtration rate (eGFR), albuminuria, or CKD staging—which may have limited our ability to capture the full clinical spectrum and severity of renal dysfunction. As a result, the prognostic impact of CKD in diabetes-MASLD patients may have been underestimated. Future studies incorporating detailed renal metrics are warranted to more accurately define the pathophysiological role of CKD within the CKM continuum.

Our multivariable analysis identified sepsis, major bleeding and malignancy as the strongest predictors of in-hospital mortality, surpassing traditional cardiovascular risk factors in terms of prognostic weight. These complications likely reflect the systemic vulnerability arising from hepatic dysfunction, impaired immunity, or therapeutic fragility in the MASLD population.[29,30] Notably, the high prevalence of hepatic tumours in patients with diabetes-MASLD may further increase their susceptibility to cancer-related complications. Collectively, these findings underscore the need for infection control, bleeding risk assessment and oncological vigilance in the acute care of patients with MASLD.

In addition, impaired functional status, as indicated by low Barthel Index scores and a history of heart failure, was strongly associated with in-hospital complications. These findings emphasize the importance of physical frailty and reduced functional reserve in shaping acute care outcomes. Therefore, functional assessments should be incorporated into routine risk stratification, and comprehensive supportive strategies, including early rehabilitation and structured discharge planning, should be prioritized, particularly for elderly patients or those with multiple comorbidities.

This study has several strengths, including the use of a large nationally representative registry, contemporary application of updated MASLD criteria and robust multivariable modelling. However, this study also has

a few limitations. First, while BMI was available as a measured variable within the database, the diagnoses of MASLD and diabetes relied exclusively on administrative codes because laboratory confirmation was not feasible in the JROAD-DPC system. Consequently, a potential misclassification bias cannot be entirely ruled out. Nevertheless, the DPC-based diagnostic coding system in Japan has been validated and is widely utilized in large-scale national cardiovascular studies. Second, the JROAD-DPC dataset does not include detailed information on liver-specific parameters (e.g. fibrosis stage), laboratory parameters (e.g. haemoglobin A1c, lipid profiles) or the dosage and duration of prescribed medications. Therefore, our findings should be interpreted with caution. Further studies incorporating comprehensive treatment data and laboratory parameter information are warranted to validate these results. Third, residual confounding remains possible despite multivariable adjustments. Fourth, causal inferences are limited by the observational nature of the study. Finally, the absence of a non-MASLD control group prevents the direct attribution of outcome differences to MASLD itself.

5 | CONCLUSIONS

Diabetes was significantly associated with higher in-hospital mortality and cardiovascular complications among patients with MASLD hospitalized for CVD. While offering a unified framework and enhancing disease understanding, the redefinition of MASLD may inadvertently obscure prognostic heterogeneity. Given the substantial prognostic burden of diabetes relative to other components, a stratified approach to cardiovascular risk remains imperative. However, elucidating specific diabetes management strategies to improve cardiovascular outcomes within the MASLD population warrants further investigation.

AUTHOR CONTRIBUTIONS

S.K., Y.K., Y.M., and K.K. substantially contributed to the study conceptualization. M.N. significantly contributed to data analysis and interpretation. S.K. led the drafting of the manuscript. K.Y., H.T., M.Y., K.M., T.I., H.K., and T.T. contributed substantially to manuscript preparation. Y.M. provided overall supervision and contributed to writing—review and editing. All authors critically reviewed the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Derived data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy reasons.

ETHICS STATEMENT

The study was reviewed and approved by the Institutional Review Board and the Ethics Committee of the University of Miyazaki (Reference Number: O-1536). The requirement for informed consent was waived because all data were de-identified.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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