Cardiovascular Diabetology

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A sex-disaggregated analysis of the prognostic value of lean type 2 diabetes mellitus in the adult population with acute myocardial infarction

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Abstract

Background Emerging evidence has demonstrated the unfavourable cardiovascular risk of individuals with lean type 2 diabetes mellitus (T2DM). Our study aims to investigate the prognostic value of lean T2DM in patients with acute myocardial infarction (AMI), stratified by sex.

Methods The study cohort examines the clinical characteristics and long-term outcomes of individuals with AMI, stratified by four phenotypes based on T2DM and lean body category—lean T2DM, non-lean T2DM, lean non-T2DM and non-lean non-T2DM. The primary outcome was long-term all-cause mortality. Cox regression model was constructed to investigate the associations of lean and non-lean T2DM phenotypes with mortality, adjusted for age, ethnicity, previous AMI, AMI type, chronic kidney disease, angiotensin converting enzyme inhibitor or angiotensin receptor blockers, beta-blockers, and smoking status.

Results A cohort of 9545 AMI patients was examined, with a mean follow-up duration of 3.4 ± 2.4 years. Majority had the non-lean T2DM phenotype (40.4%), followed by non-lean non-T2DM (29.8%), lean non-T2DM (15.9%), and lean T2DM (13.9%). In the T2DM group, one-quarter was lean ($N = 1324$), while the vast majority (74.5%) was non-lean. Individuals with lean T2DM tended to be female and older. Patients with lean T2DM had the highest rates of heart failure (23.3%, $p < 0.001$), cardiogenic shock (9.1%, $p = 0.036$), and long-term all-cause mortality (32.6%, $p < 0.001$). Cox regression demonstrated that lean T2DM was an independent predictor of mortality (adjusted hazard ratio [aHR] 1.171, 95% CI 1.040–1.319, $p = 0.009$) after adjustment. The presence of higher mortality risk following AMI was present in males (aHR 1.201, 95% CI 1.037–1.391, $p = 0.015$), but not in females (aHR 1.066, 95% CI 0.869–1.308, $p = 0.538$).

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Conclusions The lean T2DM phenotype was present in one-quarter of the AMI cohort with T2DM. The lean T2DM phenotype was an independent predictor of long-term mortality following AMI, although this association was stronger in males than in females.

Keywords Lean, Type 2 diabetes mellitus, Acute myocardial infarction, Cardiovascular outcomes, Sex differences

Research insights

What is currently known about this topic?
- Lean T2DM phenotype has a worse prognosis than non-lean T2DM in primary prevention cohorts.

What is the key research question?
- What is the prognosis of lean T2DM patients with acute myocardial infarction (AMI)?

What is new?
- Identifies prognostic outcomes of lean T2DM in patients presenting with AMI.
- Insights into sex differences across lean and non-lean phenotypes in T2DM.

How might this study influence clinical practice?
- To better risk-stratify the AMI cohort and enhance secondary prevention strategies.

Introduction

The global prevalence of type 2 diabetes mellitus (T2DM) has observed a 1.56% annual increase, with T2DM-related mortality rates also rising by 8% over the past 2 decades [1]. As the incidence of T2DM is anticipated to surge in the years ahead, studies have shown that the prevalence of lean T2DM is growing more rapidly than that of non-lean T2DM. Although non-lean T2DM is traditionally thought to be the predominant phenotype in the T2DM cohort [2], its prevalence has not risen significantly; while the prevalence of lean T2DM has instead surged by 17.8% from 2015 to 2020 in the United States [2]. Current literature suggests that individuals with lean T2DM within the community portended a greater risk of all-cause mortality compared to their non-lean counterparts [3]. In the heart failure population, individuals with lean T2DM had the highest risk of mortality or hospitalisation within one year of discharge, compared to four other distinct multi-morbidity groups [4].

While existing data shed light on the unfavourable prognosis of the lean T2DM phenotype, majority of the studies have been derived from primary preventative community cohorts [3, 4]. At present, little is known about the prognostic outcomes of lean T2DM in patients presenting with acute myocardial infarction (AMI). The incidence of AMI is anticipated to rise threefold in the next 25 years, and the burden of T2DM in the AMI population is projected to increase by 215% within the same timeframe [5–7]. More studies are warranted to further examine the relationship between lean body weight status and T2DM within the AMI cohort, with the concerted goal of improving risk stratification systems in patients presenting with acute coronary events [1, 7–9]. Thus this study seeks to examine the prognostic outcomes of lean and non-lean in AMI patients with and without T2DM, with sex-disaggregated analysis performed to uncover sex-specific disparities across these phenotypes. Identifying these high-risk profiles within the AMI cohort, can allow for implementation of tailored and effective secondary preventative strategies.

Materials and methods

Setting and design

In this retrospective cohort, we examined adult patients, aged 18 years and older, presenting with AMI at a tertiary hospital in Singapore between 1 January 2011 and 31 March 2021. Alongside two other spoke hospitals, the academic centre provides percutaneous coronary intervention (PCI) services to the western region of Singapore [10]. Patients included in this study either presented with ST-elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI), via the hub hospital's Emergency Department or interhospital transfers from the two spoke hospitals. Attending cardiologists made the diagnosis of AMI based on clinical evidence of acute myocardial ischaemia, detected by a rise and/or fall of troponin values with at least one value above the 99th percentile upper reference limit coupled with at least one of the following: (1) symptoms of myocardial ischaemia, (2) new ischaemic electrocardiographic changes, (3) development of pathological Q waves, (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology, or (5) identification of a coronary thrombus by angiography. These diagnoses met the current universal definition of type 1 AMI [11]. Patients' baseline demographic, clinical characteristics, past medical histories, angiographic and procedure characteristics and clinical outcomes were retrieved retrospectively from the electronic clinical records.

Patients were stratified by the presence of T2DM and lean phenotype into four groups– lean T2DM, non-lean T2DM, lean non-T2DM, and non-lean non-T2DM. Subgroup analysis was performed, stratified by sex. The adopted criteria of T2DM used in this study was fasting serum glucose ≥ 7 mmol/L, glycated haemoglobin (Hba1C) ≥ 6.5%, previously diagnosed T2DM, and/or on treatment for T2DM. Lean status was defined by a body mass index (BMI) threshold of < 23 kg/m^2 (< 25 kg/m^2 for Caucasians) and non-lean as ≥ 23 kg/m^2 (≥ 25 kg/m^2 for

Caucasians) [12], in accordance to current World Health Organization (WHO) recommendations. Outcomes for lean (BMI < 23 kg/m^2), overweight (BMI 23–27.49 kg/m^2) and obesity (BMI ≥ 27.5 kg/m^2) in the Asian subgroup were also compared.

Study outcomes

The primary study outcome was long-term all-cause mortality. Secondary outcomes were cardiac arrest, heart failure, cardiogenic shock, stroke, 30-day all-cause and cardiac mortality. Outcomes were adjudicated according to prior AMI studies [10, 13–17]. All-cause mortality was defined as deaths from any cause, while cardiac mortality was any deaths due to cardiovascular causes. Cardiogenic shock was the diagnosis of persistent hypotension, characterized by a systolic blood pressure of < 90 mmHg or a mean arterial pressure 30 mmHg below the baseline value, cardiac index (< 1.8 L/min^2 or < 2.2 L/min/m^2 without and with hemodynamic support respectively), accompanied by adequate or elevated filling pressures (left ventricular end-diastolic pressure > 18 mmHg or right ventricular end-diastolic pressure > 10–15 mmHg). Heart failure was defined by clinical features and congestive symptoms, accompanied with structural and functional cardiac abnormalities [17]. Long-term mortality was retrieved from the mortality database accessible via the national integrated health information systems.

Statistical analysis

Statistical analysis was conducted on R 4.4.1 software in RStudio and STATA 18.0. Continuous variables were presented as mean (standard deviation), and categorical variables as number (percentage). Continuous variables were compared by Wilcoxon rank-sum (Mann-Whitney) test, while Pearson chi-squared test was used for categorical variables. To assess the association between clinical correlates and the likelihood for T2DM, a multivariable logistic regression analysis was performed with T2DM as the dependent variable, adjusted for age, sex, hypertension, hyperlipidemia, stroke, chronic kidney disease (CKD) and previous AMI. Lean status differences in the clinical correlates were tested for with an interaction term and adjusted for age.

Kaplan-Meier curves were constructed for long-term all-cause mortality with grouping by T2DM status and lean phenotype, and compared using the log-rank test. Subgroup analysis was performed based on sex. A multivariable Cox proportional hazard regression model was designed to investigate the independent predictors of long-term all-cause mortality for the overall population, within the non-T2DM and T2DM group, and stratified by sex. The model was adjusted for the lean and T2DM status, age, ethnicity, previous AMI, STEMI, CKD, angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARBs), beta-blockers, and smoking status. These variables were adjudicated based on their prognostic impact in AMI, as established in prior studies [17–19]. To assess whether sex influences the association between lean status in the T2DM group and long-term all-cause mortality outcome, the interaction between sex and T2DM adjusted for age, was analysed in the Cox regression model. To handle competing risks for 30-day cardiac mortality, Fine and Gray subdistribution hazard (sdH) model was used and adjusted with the mentioned confounders to obtain the adjusted subdistribution hazard ratio (sdHR). To analyse HbA1C and BMI association in the T2DM group, scatter plot was used with correlation coefficient R derived from Pearson correlation. A p-value of < 0.05 was considered statistically significant.

The study was approved by the local institutional review committee in accordance with the revised Declaration of Helsinki (NHG Research—DSRB: 2021/00089-AMD0001). The institutional review board waived the need for written patient consent as this study involved a retrospective analysis of clinically acquired data.

Results

Baseline characteristics

A total of 9545 AMI patients were included in the study, of whom 54.3% had T2DM (N = 5183). The mean age of the cohort was 64 ± 13 years, with the majority being male (76.7%), and presenting with NSTEMI (55.1%). The mean follow-up time for the study cohort was 3.4 ± 2.4 years. Amongst the cohort, 29.8% of patients were lean and 54.3% had T2DM. In AMI individuals with T2DM, 25.5% were lean (N = 1324). In the non-T2DM group, 34.8% were lean (N = 1520). The non-Chinese group comprised of patients of Malay (N = 2182), Indian (N = 1403) and Caucasian (N = 39) ethnicity. Table 1 and Fig. 1 demonstrates the baseline characteristics of the study group.

Patients who were lean tended to be older, female, and of Chinese ethnicity, compared to the non-lean counterparts, regardless of T2DM status (p < 0.001). Patients who were non-lean had higher prevalence of hypertension and hyperlipidemia, but lower stroke rates, compared to those who were lean regardless of T2DM status. There was higher prevalence of CKD amongst the lean individuals compared to non-lean counterparts in the non-T2DM group (10.1% versus 7.9% respectively, p = 0.017), but not in the T2DM group. Amongst both T2DM and non-T2DM groups, lean individuals had a lower mean HbA1c (T2DM: 7.6 ± 2.0% versus 7.9 ± 2.0%; non-T2DM: 5.6 ± 0.4% versus 5.7 ± 0.4%) compared to non-lean counterparts. The analysis of Hba1c and BMI association demonstrated that there was a significant, albeit weak, positive correlation observed between HbA1c and BMI (R = 0.0913, p < 0.001). Subgroup analysis revealed non-significant correlation between HbA1c and BMI,

Table 1 Baseline demographics and clinical characteristics of AMI cohort between T2DM status, stratified by lean status

	Overall (*N* = 9545)	**T2DM (*N* = 5183)**			**Non-T2DM (*N* = 4362)**			**Lean (*N* = 2844)**	**Non-lean (*N* = 6701)**
		Lean (*N* = 1324)	**Non-lean (*N* = 3859)**	**P-value**	**Lean (*N* = 1520)**	**Non-lean (*N* = 2842)**	**P-value**	**T2DM vs. non-T2DM**	**T2DM vs. non-T2DM**
Demographics									
Age (years)	64 (13)	69 (12)	64 (12)	**< 0.001**	67 (14)	60 (12)	**< 0.001**	**< 0.001**	**< 0.001**
Female	2220 (23.3)	433 (32.7)	1048 (27.2)	**< 0.001**	376 (24.7)	363 (12.8)	**< 0.001**	**< 0.001**	**< 0.001**
BMI (kg/m^2)	25.3 (4.5)	21.0 (1.6)	27.7 (4.2)	**< 0.001**	20.7 (1.8)	26.7 (3.3)	**< 0.001**	**< 0.001**	**< 0.001**
Ethnicity				**< 0.001**			**< 0.001**	**< 0.001**	**< 0.001**
Chinese	5921 (62.0)	897 (67.7)	2037 (52.8)		1166 (76.7)	1821 (64.1)			
Non-Chinese	3624 (38.0)	427 (32.3)	1822 (47.2)		354 (23.3)	1021 (35.9)			
Current smoker	3037 (31.8)	309 (23.3)	987 (25.6)	0.113	564 (37.1)	1177 (41.4)	**0.006**	**< 0.001**	**< 0.001**
Past medical history									
Hypertension	6296 (66.0)	961 (72.6)	2971 (77.0)	**0.001**	772 (50.8)	1592 (56.0)	**0.001**	**< 0.001**	**< 0.001**
Hyperlipidaemia	6261 (65.6)	957 (72.3)	2913 (75.5)	**0.022**	765 (50.3)	1626 (57.2)	**< 0.001**	**< 0.001**	**< 0.001**
Stroke	792 (8.3)	164 (12.4)	376 (9.7)	**0.008**	101 (6.6)	151 (5.3)	**0.084**	**< 0.001**	**< 0.001**
Previous AMI	2712 (28.4)	455 (34.4)	1318 (34.2)	0.915	342 (22.5)	597 (21.0)	0.269	**< 0.001**	**< 0.001**
Previous PCI or CABG	3122 (32.7)	520 (39.3)	1549 (40.1)	0.602	380 (25.0)	673 (23.7)	0.351	**< 0.001**	**< 0.001**
Chronic kidney disease	1688 (17.7)	315 (23.8)	996 (25.8)	0.155	153 (10.1)	224 (7.9)	**0.017**	**< 0.001**	**< 0.001**
Laboratory and echocardiographic variables									
Platelets (x10^9/L)	223 (91.4)	218 (99.1)	223 (87.2)	**0.035**	221 (107.0)	227 (82.5)	**0.020**	0.576	0.010
Total bilirubin (μmol/L)	14.8 (10.6)	14.6 (10.1)	14.0 (9.8)	0.250	15.8 (11.8)	16.1 (11.9)	0.705	0.081	**< 0.001**
HDL cholesterol (mmol/L)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	**< 0.001**	1.3 (0.3)	1.1 (0.3)	**< 0.001**	**< 0.001**	**< 0.001**
LDL cholesterol (mmol/L)	2.9 (1.2)	2.7 (1.2)	2.8 (1.2)	0.447	3.0 (1.0)	3.1 (1.2)	**0.001**	**< 0.001**	**< 0.001**
Triglycerides (mmol/L)	1.8 (1.4)	1.6 (1.1)	2.0 (1.7)	**< 0.001**	1.4 (0.8)	1.7 (1.1)	**< 0.001**	**< 0.001**	**< 0.001**
Peak creatinine (μmol/L)	160 (188)	174 (189)	198 (228)	0.056	126 (137)	118 (123)	0.319	**< 0.001**	**< 0.001**
Troponin I (ng/L)	8440 (15200)	8450 (15800)	8690 (15700)	0.797	7890 (14900)	8340 (14300)	0.137	0.130	0.622
Left ventricular ejection fraction (%)	47 (13)	43 (14)	46 (13)	**< 0.001**	49 (13)	50 (12)	**0.029**	**< 0.001**	**< 0.001**
HbA1c (%)	6.9 (1.9)	7.6 (2.0)	7.9 (2.0)	**< 0.001**	5.6 (0.4)	5.7 (0.4)	**0.002**	**< 0.001**	**< 0.001**
In-hospital management									
Myocardial infarction type				0.850			0.061	**< 0.001**	**< 0.001**
STEMI	4285 (44.9)	546 (41.2)	1578 (40.9)		723 (47.6)	1438 (50.6)			
Culprit vessel				0.205			**0.005**	0.460	**0.023**
Left main	60 (0.6)	9 (0.7)	22 (0.6)		13 (0.9)	16 (0.6)			
Left anterior descending	1892 (19.8)	262 (19.8)	669 (17.3)		333 (21.9)	628 (22.1)			
Circumflex	321 (3.4)	35 (2.6)	135 (3.5)		52 (3.4)	99 (3.5)			
Right coronary artery	1421 (14.9)	159 (12.0)	513 (13.3)		224 (14.7)	525 (18.5)			
Symptom to door time (min)	310 (816)	416 (2030)	316 (447)	0.305	275 (348)	281 (465)	0.156	**0.022**	**< 0.001**
Door to balloon time (min)	88 (327)	108 (367)	83 (214)	0.182	105 (520)	78 (284)	0.172	0.296	0.144
Number of stents				0.488			0.128	**0.039**	**< 0.001**
1	3714 (38.9)	435 (32.9)	1350 (35.0)		614 (40.4)	1315 (46.3)			
2	1184 (12.4)	153 (11.6)	448 (11.6)		197 (13.0)	386 (13.6)			
≥3	376 (3.9)	47 (3.5)	153 (4.0)		44 (2.9)	132 (4.6)			
CABG	271 (2.8)	31 (2.3)	130 (3.4)	0.087	43 (2.8)	67 (2.4)	0.348	0.580	**0.014**
Discharge medications									
Beta blocker	7653 (85.8)	1028 (86.5)	3202 (89.7)	**0.006**	1109 (78.0)	2314 (84.3)	**< 0.001**	**< 0.001**	**< 0.001**
ACEi or ARB	6063 (68.0)	773 (65.0)	2506 (70.2)	**0.002**	878 (61.8)	1906 (69.5)	**< 0.001**	0.085	0.677
Anti-platelets	8705 (97.6)	1156 (97.2)	3484 (97.6)	0.481	1385 (97.5)	2680 (97.7)	0.768	0.794	1

Table 1 (continued)

	Overall (*N* = 9545)	T2DM (*N* = 5183)			Non-T2DM (*N* = 4362)			Lean (*N* = 2844)	Non-lean (*N* = 6701)
		Lean (*N* = 1324)	Non-lean (*N* = 3859)	P-value	Lean (*N* = 1520)	Non-lean (*N* = 2842)	P-value	T2DM vs. non-T2DM	T2DM vs. non-T2DM
Oral anticoagulants	253 (2.8)	30 (2.5)	119 (3.3)	0.165	40 (2.8)	64 (2.3)	0.579	0.530	0.117
Statin	8719 (97.7)	1152 (96.9)	3496 (98.0)	0.117	1375 (96.8)	2696 (98.3)	**0.003**	0.877	0.237

Categorical variables are presented as n (%) and continuous variables are presented as mean (standard deviation). p < 0.05 is taken as statistical significance (in bold). The non-Chinese group comprised of patients of Malay (N=2182), Indian (N= 1403) and Caucasian (N=39) ethnicity. Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; HbA1C, Hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; STEMI, ST elevatation myocardial infarction; T2DM, type 2 diabetes mellitus

amongst the lean group ($R = 0.0283$, $p = 0.429$), and a significant, albeit weak, positive correlation ($R = 0.0828$, $p < 0.001$) in the non-lean group (Supplementary Fig. 1, Additional File 1).

Adjusting for comorbidities, patients who were female in lean and non-lean groups had higher odds of having T2DM than males in their respective groups. Amongst females ($p_{interaction}$ <0.001) or patients with CKD ($p_{interaction}$ = 0.005), non-lean individuals had higher odds of having T2DM than their lean counterparts (Fig. 2). Following AMI, the lean groups had lower left ventricular ejection fraction (LVEF), lower triglycerides levels, and higher high-density lipoprotein (HDL) cholesterol levels compared to the non-lean individuals, regardless of T2DM status. AMI individuals who were lean had lower prescription rates of beta-blockers, and ACEi or ARBs compared to the non-lean counterparts, regardless of T2DM status (Table 1).

Unfavourable outcomes in lean individuals with T2DM

Patients with the lean phenotype had higher rates of heart failure (T2DM: 23.3% versus 18.7% respectively, $p < 0.001$; non-T2DM: 10.5% versus 6.9%, respectively, $p < 0.001$) and cardiogenic shock (T2DM: 9.1% versus 7.4% respectively, $p = 0.036$; non-T2DM: 6.3% versus 3.6% respectively, $p < 0.001$) compared to the non-lean counterparts.

Lean individuals had a higher 30-day all-cause mortality (T2DM: 10.2% versus 7.5%, $p = 0.003$; non-T2DM: 6.5% versus 3.4%, $p < 0.001$), 30-day cardiac mortality (T2DM: 8.4% versus 6.6%, $p = 0.029$; non-T2DM: 6.0% versus 3.0%, $p < 0.001$) and long-term all-cause mortality rates (T2DM: 32.6% versus 25.0%, $p < 0.001$; non-T2DM: 20.0% versus 11.3%, $p < 0.001$), compared to the non-lean counterparts (Table 2). Long-term all-cause mortality was higher in individuals with T2DM compared to the non-T2DM counterparts, for both lean ($p < 0.001$) and non-lean ($p < 0.001$) subgroups (Fig. 1). When comparing between sex, long-term all-cause mortality was consistently higher in females, regardless of lean phenotype or T2DM status (Supplementary Table 1, Additional File 1).

After adjusting for confounders, Cox regression demonstrated that non-lean T2DM (aHR 1.580, 95% CI 1.377–1.813, $p < 0.001$) and lean T2DM (aHR 1.791, 95% CI 1.541–2.081, $p < 0.001$) were associated with higher mortality, compared to non-lean non-T2DM phenotype in the AMI population (Table 3). Lean phenotype was associated with higher mortality in the T2DM group (aHR 1.171, 95% CI 1.040–1.319, $p = 0.009$). There were differences between all-cause mortality in the lean and non-lean groups by sex, regardless of T2DM status (T2DM: $p_{interaction} = 0.009$; non-T2DM: $p_{interaction} = 0.018$). Amongst males, the lean phenotype was associated with higher long-term all-cause mortality in the T2DM group (aHR 1.201, 95% CI 1.037–1.391, $p = 0.015$) compared to non-lean phenotype, but this increased mortality risk was not significant amongst females (Table 3, Fig. 1). Competing risk regression analysis demonstrated that non-lean T2DM (sdHR 1.605, 95% CI 1.241–2.075, $p < 0.001$) and lean T2DM (sdHR 1.566, 95% CI 1.180–2.080, $p = 0.002$) was associated with higher cardiac mortality. This trend was similarly noted in the male and female subgroups (Supplementary Table 2, Additional File 1).

In the overall AMI cohort, the Kaplan Meier curves demonstrated excess mortality in the lean T2DM group, followed by non-lean T2DM, lean non-T2DM, and non-lean non-T2DM ($p < 0.001$) (Fig. 3). Kaplan Meier curves with subgroup analysis based on sex demonstrated that the excess mortality between lean and non-lean patients with T2DM was more pronounced in males than in females (Fig. 4).

In the subgroup analysis across lean, overweight and obesity phenotypes, individuals with lean phenotype had the least favourable cardiovascular outcomes including heart failure, cardiogenic shock, 30-day and long-term all-cause mortality, compared to the overweight and obesity phenotypes in both T2DM and non-T2DM groups (Supplementary Table 3, Additional File 1). Importantly, favourable long-term mortality rates were observed in both overweight and obesity phenotypes in the T2DM (6.7% and 6.6%, respectively) and non-T2DM groups (1.0% and 1.8%, respectively). This extends the hypothesis

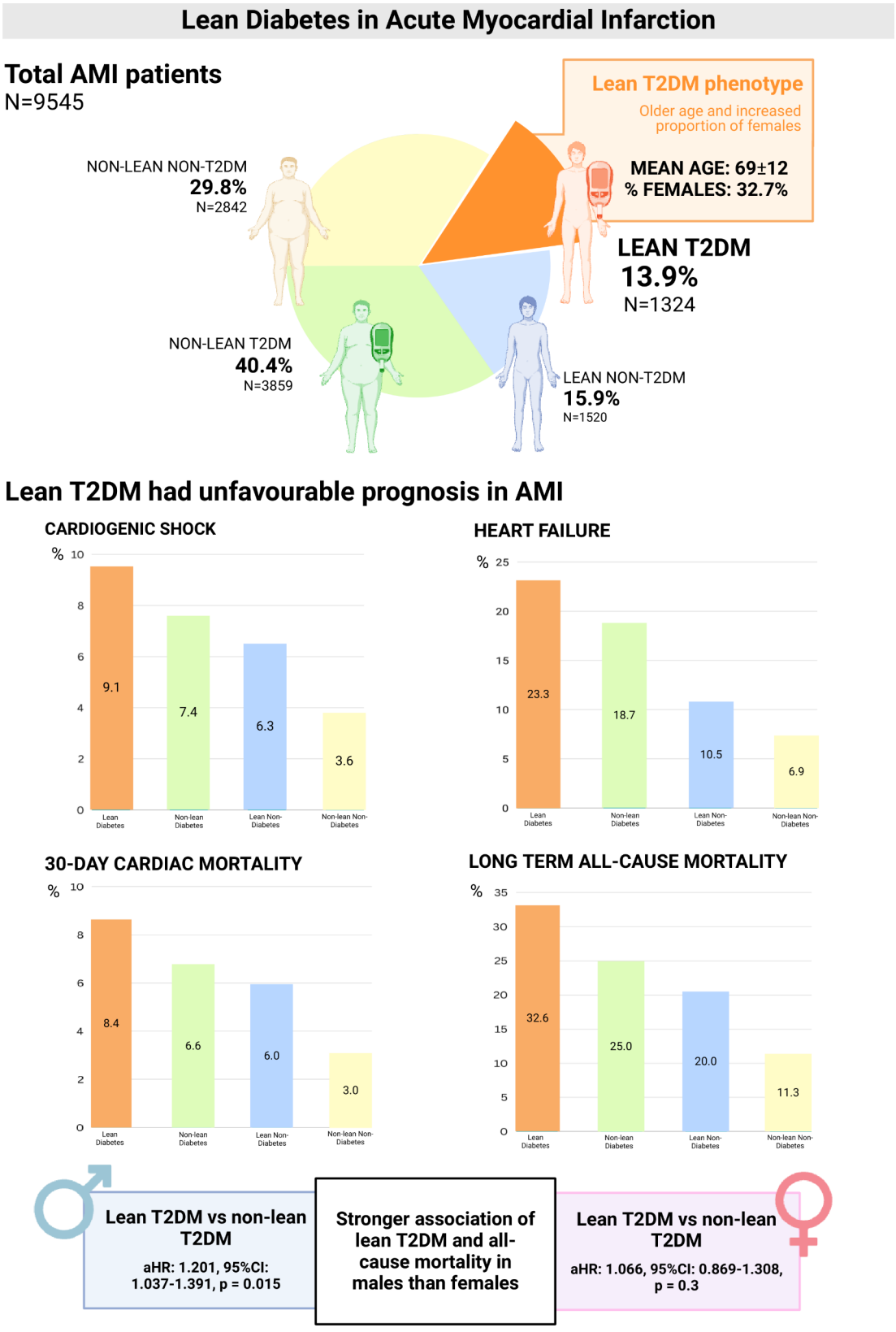

Fig. 1 The prognostic value of T2DM and lean body weight phenotypes in the cohort with AMI

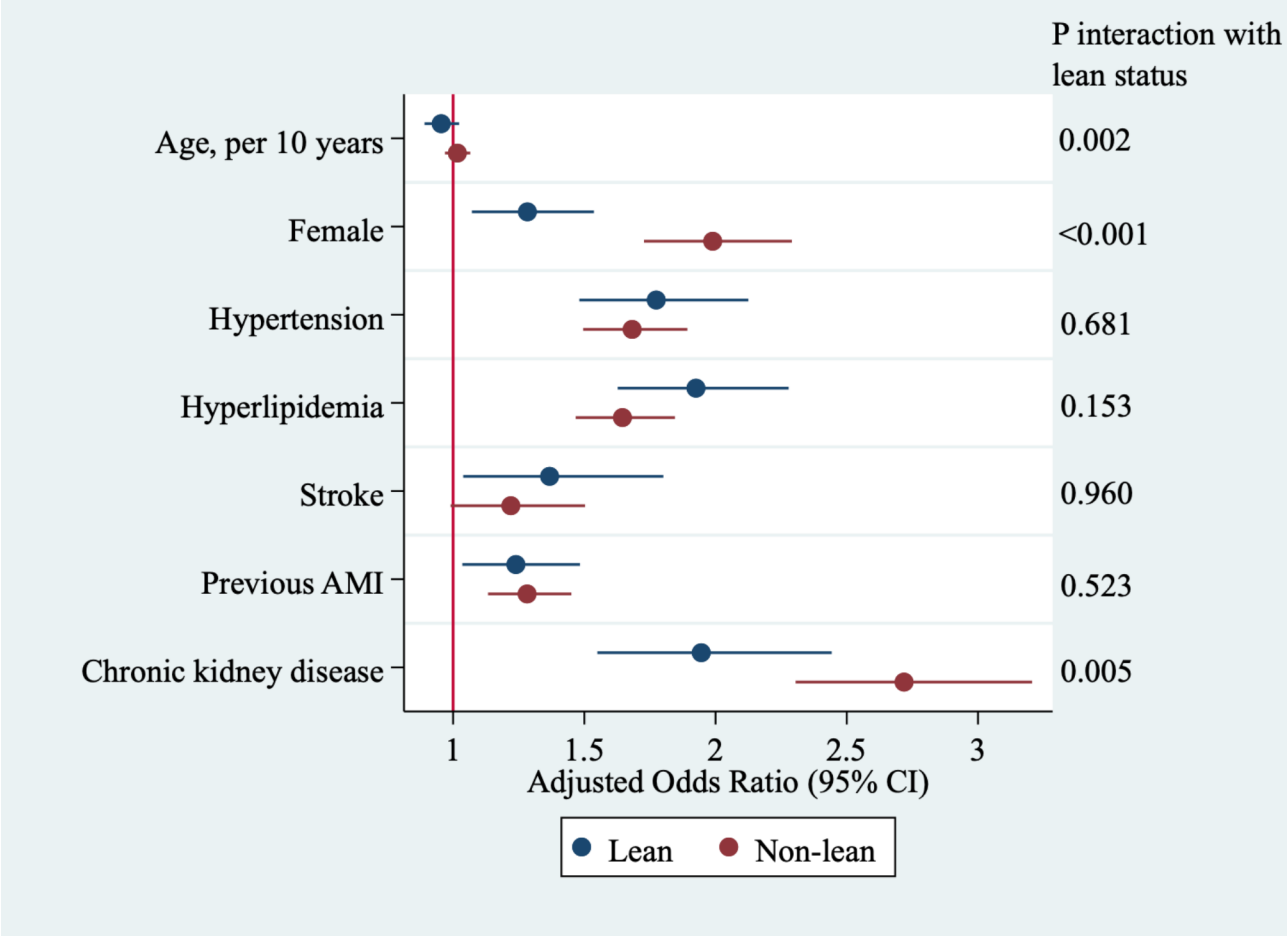

Fig. 2 Logistic regression of clinical correlates and T2DM. Odds ratios of T2DM adjusted for age, sex, hypertension, hyperlipidemia, stroke, previous AMI and chronic kidney disease

Table 2 In-hospital complications and outcomes of cohort with AMI between T2DM status, stratified by lean status

	Overall (*N* = 9545)	**T2DM (*N* = 5183)**			**Non-T2DM (*N* = 4362)**			**Lean (*N* = 2844)**	**Non-lean (*N* = 6701)**
		Lean (*N* = 1324)	**Non-lean (*N* = 3859)**	**P-value**	**Lean (*N* = 1520)**	**Non-lean (*N* = 2842)**	**P-value**	**T2DM vs. non- T2DM**	**T2DM vs. non-T2DM**
In-hospital complications									
Cardiac arrest	218 (2.3)	38 (2.9)	99 (2.6)	0.619	32 (2.1)	49 (1.7)	0.441	0.233	**0.026**
Heart failure	1388 (14.5)	309 (23.3)	723 (18.7)	**< 0.001**	159 (10.5)	197 (6.9)	**< 0.001**	**< 0.001**	**< 0.001**
Cardiogenic shock	606 (6.3)	121 (9.1)	287 (7.4)	**0.036**	96 (6.3)	102 (3.6)	**< 0.001**	**0.009**	**< 0.001**
Stroke	187 (2.0)	32 (2.4)	97 (2.5)	0.908	22 (1.4)	36 (1.3)	0.709	0.082	**< 0.001**
Outcomes									
30-day all-cause mortality	623 (6.5)	135 (10.2)	291 (7.5)	**0.003**	99 (6.5)	98 (3.4)	**< 0.001**	**< 0.001**	**< 0.001**
30-day cardiac mortality	540 (5.7)	111 (8.4)	253 (6.6)	**0.029**	91 (6.0)	85 (3.0)	**< 0.001**	**0.016**	**< 0.001**
Long-term all-cause mortality	2020 (21.2)	431 (32.6)	963 (25.0)	**< 0.001**	304 (20.0)	322 (11.3)	**< 0.001**	**< 0.001**	**< 0.001**

Categorical variables are presented as n (%). p < 0.05 is taken as statistical significance (in bold). Abbreviations: AMI, acute myocardial infarction; T2DM, type 2 diabetes mellitus

Table 3 Cox regression analysis for adjusted long-term all-cause mortality of cohort with AMI, stratified by sex

	Age-adjusted $P_{interaction}$ with sex	Overall				Males				Females			
		No. at risk	No. of events (%)	Adjusted HR (95% CI)	P-value	No. at risk	No. of events (%)	Adjusted HR (95% CI)	P-value	No. at risk	No. of events (%)	Adjusted HR (95% CI)	P-value
Overall													
Non-T2DM, lean	**< 0.001**	1520	304 (20.0)	Reference		1144	203 (17.7)	Reference		376	101 (26.9)	Reference	
Non-T2DM, non-lean		2842	322 (11.3)	0.865 (0.737–1.015)	0.076	2479	241 (9.7)	0.801 (0.661–0.970)	**0.023**	363	81 (22.3)	1.108 (0.824–1.490)	0.496
T2DM, non-lean		3859	963 (25.0)	1.580 (1.377–1.813)	**< 0.001**	2811	615 (21.9)	1.524 (1.288–1.803)	**< 0.001**	1048	348 (33.2)	1.725 (1.356–2.194)	**< 0.001**
T2DM, lean		1324	431 (32.6)	1.791 (1.541–2.081)	**< 0.001**	891	278 (31.2)	1.788 (1.484–2.154)	**< 0.001**	433	153 (35.3)	1.776 (1.375–2.294)	**< 0.001**
Non-T2DM													
Non-lean	**0.018**	2842	322 (11.3)	Reference		2479	241 (9.7)	Reference		363	81 (22.3)	Reference	
Lean		1520	304 (20.0)	1.052 (0.891–1.243)	0.549	1144	203 (17.7)	1.169 (0.958–1.428)	0.124	376	101 (26.9)	0.815 (0.601–1.106)	0.190
T2DM													
Non-lean	**0.009**	3859	963 (25.0)	Reference		2811	615 (21.9)	Reference		1048	348 (33.2)	Reference	
Lean		1324	431 (32.6)	1.171 (1.040–1.319)	**0.009**	891	278 (31.2)	1.201 (1.037–1.391)	**0.015**	433	153 (35.3)	1.066 (0.869–1.308)	0.538

The Cox regression was adjusted for lean and T2DM status, age, ethnicity, previous AMI, STEMI, chronic kidney disease, ACEi or ARBs, beta-blockers, and smoking. $p < 0.050$ is taken as statistical significance (in bold).
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AMI, acute myocardial infarction; ARBs, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio; T2DM, type 2 diabetes mellitus

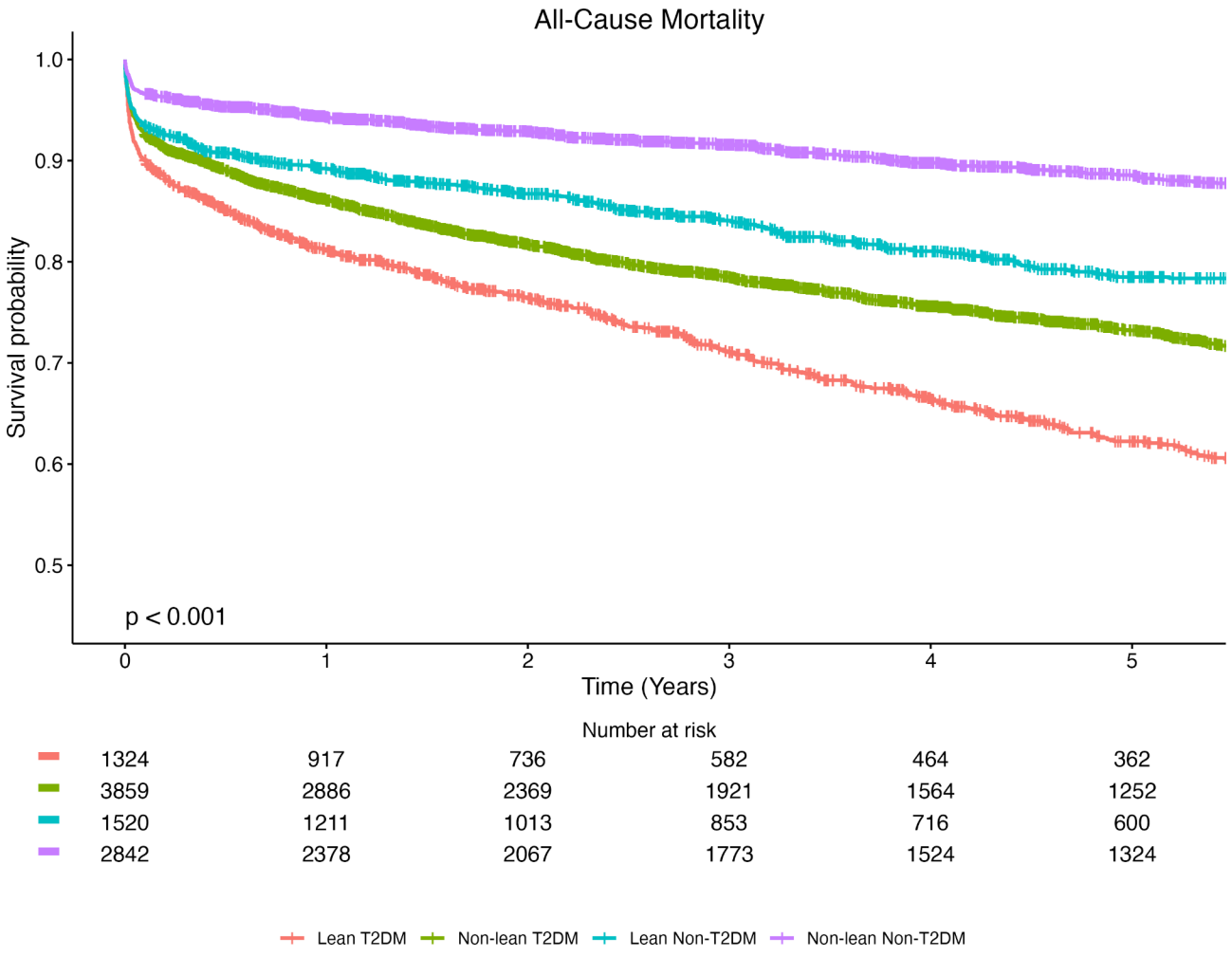

Fig. 3 Kaplan-Meier curve of all-cause mortality in the AMI population, stratified by T2DM and lean status

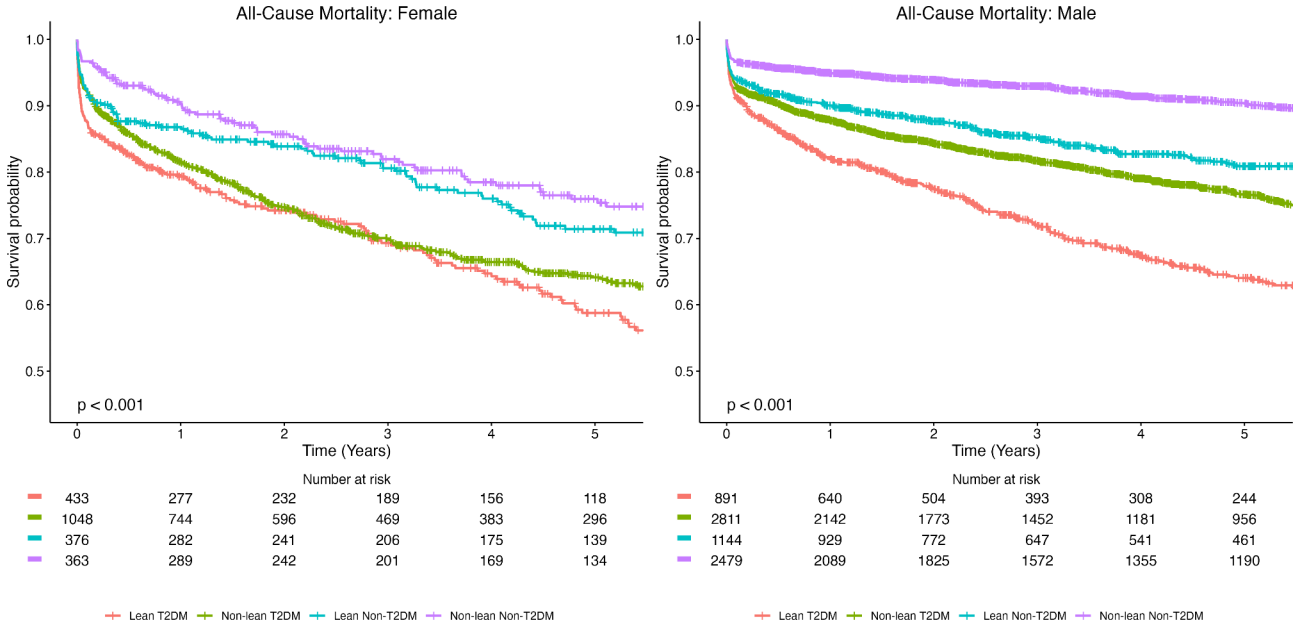

Fig. 4 Kaplan-Meier curve of all-cause mortality in the AMI population, stratified by T2DM-lean status and sex

that the obesity paradox may extend to those of overweight phenotype in the Asian cohort.

Discussion

While the presence of obesity is a well-established risk factor for T2DM [20–22], there is mounting evidence that T2DM is increasingly prevalent among lean individuals [23]. Primary preventative studies have also highlighted the "obesity paradox", where community-dwelling individuals with lean T2DM demonstrate a poorer prognosis compared to their counterparts with obesity [15, 19, 24]. To date, few studies have investigated how the lean phenotype influences the association between T2DM and AMI [25, 26]. This study provides insights into the association between the lean and T2DM phenotypes in the outcomes of the AMI population with sex-disaggregated analysis. The study had several key findings: (1) Lean T2DM phenotype was present in one-quarter of the AMI cohort with T2DM; (2) Lean individuals with T2DM tended to be older, female, smoker, and had a lower prevalence of hypertension and hyperlipidemia compared to the non-lean counterparts; (3) Following an AMI, the lean T2DM phenotype had the highest rates of cardiovascular complications, and was found to be an independent predictor of all-cause mortality; and (4) The association of lean T2DM and adverse prognostic outcomes following AMI was found to stronger in males than in females.

Our study reported a high prevalence of lean T2DM in the AMI cohort. This is supported by other studies reporting similar prevalence of lean T2DM within Africa and Asia, but higher than what has been reported in the United States [2, 27]. This has been postulated to be due to environmental and genetic factors, with individuals from Asia and Africa being at risk for T2DM at a lower BMI [28–30]. Lean T2DM individuals were also more likely to be female, as this might be driven by sex-specific differences in body composition, as supported by Mendelian randomization analysis [31–33]. Given that the prevalence of lean T2DM has been rising rapidly within the past decade particularly amongst females and those over 45 years of age, the significance of this phenotype will be increasingly important [2]. Moreover, the lean T2DM group was older and had higher smoking rates, which may suggest the possibility for reverse causation given that smoking is a well-established modifiable risk factor in T2DM [34], and advanced age and smoking have been associated with poorer cardiovascular outcomes in the AMI population [35, 36]. Notably, the lean T2DM phenotype remained an independent predictor of mortality after adjusting for these confounders. It is important to note, however, that cause-and-effect relationship cannot be determined with retrospective studies. Nevertheless, these findings are hypothesis-generating and provide a basis for designing future prospective studies to further elucidate this relationship.

Insights on the clinical characteristics of the lean T2DM phenotype can shed light on the challenges faced with managing this population in the setting of an AMI. AMI patients with lean T2DM phenotype tended to be older and female. Lower BMI in these subgroups may be attributed to behavioral and socio-economic factors, as well as the changes in body composition with age, with a lower bone mass and higher rates of sarcopenia [37–45]. Lean T2DM patients have been reported to be twice as likely to be sarcopenic, which result in reduced muscle capacity, limited physiological reserves and a higher risk of frailty [44, 46–48]. Our study also demonstrated higher rates of cardiac complications including mortality, heart failure and cardiogenic shock in the lean T2DM phenotype within the AMI cohort. This is consistent with findings from several studies highlighting the increased risk of AMI or stroke in lean individuals with T2DM compared to their non-lean counterparts [49–52]. This is likely due to the increased risk of sarcopenia and resultant frailty in lean T2DM individuals, (42) which may lead to lower metabolic reserves and increased vulnerability to the catabolic states of an acute coronary event [5, 18, 53]. Moreover, the presence of adipose tissue have been associated with a blunted response to renin-angiotensin-aldosterone system activation, which may provide the protective effects observed in the non-lean T2DM phenotype [5, 54–57]. Further studies are needed to examine the modifying effects of adiposity on outcomes after an AMI episode. It is also important to consider that poorly controlled T2DM can cause a catabolic state, leading to weight loss and potentially progressing to the lean T2DM phenotype. However, our findings suggest otherwise, as higher Hba1c levels were not associated with lower BMI. In addition, in the subgroup analysis across lean, overweight and obesity phenotypes, individuals with lean phenotype had the least favourable cardiovascular outcomes including heart failure, cardiogenic shock, 30-day and long-term all-cause mortality, compared to the overweight and obesity phenotypes in both T2DM and non-T2DM groups (Supplementary Table 3, Additional File 1). Importantly, long-term mortality rates between overweight and obesity phenotypes were similar in the T2DM (6.7% vs. 6.6%, respectively) and non-T2DM groups (1.0% vs. 1.8%, respectively). This suggest that the obesity paradox may extend to those of overweight phenotype in the Asian cohort.

There has been growing interest in unravelling the sex differences in the unfavourable outcomes of the lean T2DM phenotype. In our AMI cohort, we found that males with lean phenotype had worse survival outcomes than males with non-lean phenotype in both T2DM and non-T2DM groups. However, this trend was not observed

in females, which might be explained by the sex-related disparate survival in females following AMI, regardless of lean phenotype or T2DM status [58]. This finding was also observed in a previous study which found that males with T2DM had higher risk of cardiovascular mortality than females; [59] notably the 12-month mortality rates were higher in lean males compared to non-lean males, a trend that was not observed in females [60]. A meta-analysis also demonstrated that males with overweight status had the lowest mortality risk compared to those with normal weight or obesity, while mortality risk did not differ significantly across normal weight, overweight, or obese groups amongst females [61]. This phenomenon could be attributed to sex-specific physiological and pathophysiological differences [62], such as the influence of reproductive hormone variations. For instance, premenopausal females may have protective factors such as higher levels of estrogen and lower levels of androgen levels, which gradually reduces in its effect with menopause [63, 64]. Lean females have also been found to have a more favorable triglyceride and lipoprotein profile than lean males [65]. In addition, females may also present with atypical symptoms, resulting in delay in diagnoses and treatment [66], and receiving less optimal cardiovascular care [67].

One of the key limitations of the study was the use of BMI as a proxy to evaluate the lean status of patients. While BMI is one of the most widely used anthropometric tools for stratifying body weight categories, it is unable to account for sex differences in body fat composition and central adiposity. Sex-specific differences in body fat composition can influence cardiovascular outcomes [68]. Males have increased muscle and lean mass compared to females. Females tend to have more subcutaneous adipose tissue in the femoral and neck regions compares to males, with higher amounts of brown adipose tissue, and this has been correlated with improved cardiometabolic outcomes [68]. However, ectopic fat accumulation in regions such as the abdomen, muscle, pericardium has been shown to strongly correlate with deleterious cardiometabolic effects in females compared to males [69, 70]. Visceral adiposity has been associated with higher incidence of cardiovascular risk factors, which is more prevalent in females [71, 72]. While the present study used BMI as a proxy to determine the lean status of the study cohort, alternative metrics such as waist-hip ratio and waist circumference would have provided more accurate assessments of visceral adiposity. Given the challenges of a retrospective 'all-comers' AMI registry, future studies are warranted to prospectively examine the sex-specific differences in fat distribution in a large, well-represented AMI cohort [71–73].

Clinical implications

The study highlights that the unique lean T2DM phenotype portends poor cardiovascular outcomes in individuals presenting with AMI, especially in males. The performance of contemporary risk stratification tools within the AMI cohort may be further enhanced with the incorporation of prognostically important clinical variables such as BMI category, T2DM status and sex. Moving forward, a large size cohort, that reflects a secondary prevention population with diverse geographic and ethnic groups, is necessary to evaluate the improvements in discrimination value and net reclassification with the incorporation of these variables in modified risk scoring tools. This is likely feasible given that anthropometric indices and clinical characteristics (such as T2DM and sex) are readily available in the acute care setting, allowing for easy implementation in clinical care. In terms of secondary prevention, therapeutic approaches for lean T2DM patients post-AMI may differ significantly from those for non-lean individuals. Despite the poor outcomes associated with lean T2DM, specific recommendations for the management of such patients remain limited. Existing guidelines focus on treatment options for T2DM and the overall metabolic milieu especially obesity, but recommendations of low-calorie diet and weight loss may not be applicable or effective in the lean T2DM phenotype with AMI [74, 75]. Additional weight loss in lean T2DM may conversely exacerbate bone loss and contribute to sarcopenic obesity [76, 77]. Lean individuals may have a higher propensity towards more pronounced beta-cell failure and an inability to cope with mild insulin resistance, often requiring earlier initiation of insulin therapy compared to their non-lean counterparts [76]. As such, the management of patients with lean T2DM should be shifted away from the traditional recommendations for weight loss, and incorporate the optimization of nutritional status and glycemic control. Our study also highlighted the lower prescription rates of guideline-directed medical therapy in individuals with lean T2DM phenotype. Therefore, clinicians should remain vigilant in optimizing secondary prevention therapy, such as betablockers and ACEi/ARB, especially in this high-risk group. Future research is necessary to determine individualized management strategies to improve outcomes in individuals with lean T2DM.

Limitations

First, the study was unable to account for the duration and level of control of T2DM prior to the onset of AMI [78]. Second, due to the differences in the clinical characteristics of T2DM between Asian and Western populations, caution should be exercised when generalizing and interpreting the findings of this study across other demographic groups. Third, data on the use of anti-diabetic

agents with weight-lowering properties, such as glucagon-like peptide 1 receptor agonists (GLP1RA) and/or sodium glucose co-transporter 2 inhibitors (SGLT2i) were scarce in the present study. This is partly due to low prescription rates of these antidiabetic agents for weight reduction prior to the recent emergence of the landmark SGLT2i [79] and GLP1RA trials [80, 81]. Fourth, due to the long timespan of the study, the presence of comorbidities, degree of T2DM control, and BMI phenotypes will likely evolve across time, driven by patient characteristics, healthcare practices, and medical advancements. However, the study lacked the granularity of temporal trends of BMI and comorbidity phenotypes. Future studies are warranted to examine the cardiovascular effects of body weight categories and T2DM phenotype transitions across time. Last, the retrospective study did not have data on beta cell-function, such as c-peptide or Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). As the study only included T2DM, the effect of lean body phenotype in the different forms of diabetes (such as autoimmune diabetes) could not be evaluated.

Conclusions

The lean T2DM phenotype was prevalent in the AMI cohort with T2DM, predominantly affecting individuals of older age and females. These individuals had the highest risk of heart failure, cardiogenic shock, and long-term mortality. The higher mortality risk was evident amongst the lean T2DM males. Identifying high-risk patients with lean T2DM is important to ensure clinicians tailor individualized secondary preventative strategies, best suited to this unique phenotype.

Abbreviations

T2DM	Type 2 diabetes mellitus
AMI	Acute myocardial infarction
PCI	Percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
Hba1C	Glycated hemoglobin
WHO	World Health Organization
BMI	Body mass index
CKD	Chronic kidney disease
LVEF	Left ventricular ejection fraction
HDL	High-density lipoprotein
ACEi	Angiotensin converting enzyme inhibitor
ARBs	Angiotensin receptor blockers
aHR	Adjusted hazard ratio
sdH	Subdistribution hazard
sdHR	Subdistribution hazard ratio
CI	Confidence interval
HOMA	IR-homeostatic model assessment for insulin resistance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02552-0.

Supplementary Material 1.

Acknowledgements

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables has not been previously published and that the manuscript is not under consideration elsewhere.

Author contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. All authors approve the final version of the manuscript, including the authorship list and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

This was supported by the NUHS Seed Fund (NUHSRO/2022/058/RO5 + 6/Seed-Mar/03), National University of Singapore Yong Loo Lin School of Medicine's Academic Fellowship Scheme, and NUHS Clinician Scientist Program (NCSP2.0/2024/NUHS/NCWS).

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

The study was approved by the local institutional review committee in accordance with the revised Declaration of Helsinki (NHG Research—DSRB: 2021/00089-AMD0001). The institutional review board waived the need for written patient consent as this study involved a retrospective analysis of clinically acquired data.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form.

Competing interests

M.Y.C. receives speaker's fees and research grants from Astra Zeneca, Abbott Technologies and Boston Scientific. N.W.S.C has received research grant support from NUHS Seed Fund (NUHSRO/2022/RO5+6/Seed-Mar/03), National Medical Research Council Research Training Fellowship (MH 095:003/008-303), National University of Singapore Yong Loo Lin School of Medicine's Academic Fellowship Scheme, and the NUHS Clinician Scientist Program (NCSP2.0/2024/NUHS/NCWS).

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Received: 22 October 2024 / Accepted: 19 December 2024
Published online: 07 February 2025

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