Cardiovascular Diabetology

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Combined risk estimates of diabetes and coronary angiography-derived index of microcirculatory resistance in patients with non-ST elevation myocardial infarction

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Abstract

Background Diabetes mellitus (DM) and coronary microvascular dysfunction (CMD) increase the risk of adverse cardiac events in patients with non-ST-segment elevation myocardial infarction (NSTEMI). This study aimed to evaluate the combined risk estimates of DM and CMD, assessed by the angiography-derived index of microcirculatory resistance (angio-IMR), in patients with NSTEMI.

Methods A total of 2212 patients with NSTEMI who underwent successful percutaneous coronary intervention (PCI) were retrospectively enrolled from three centers. The primary outcome was a composite of cardiac death or readmission for heart failure at a 2-year follow-up.

Results Post-PCI angio-IMR did not significantly differ between the DM group and the non-DM group (20.13 [17.91–22.70] vs. 20.19 [18.14–22.77], $P=0.530$). DM patients exhibited a notably higher risk of cardiac death or readmission for heart failure at 2 years compared to non-DM patients (9.5% vs. 5.4%, $P<0.001$). NSTEMI patients with both DM and CMD experienced the highest cumulative incidence of cardiac death or readmission for heart failure at 2 years (24.0%, $P<0.001$). The combination of DM and CMD in NSTEMI patients were identified as the most powerful independent predictor for cardiac death or readmission for heart failure at 2 years (adjusted HR: 7.894, [95% CI, 4.251–14.659], $p<0.001$).

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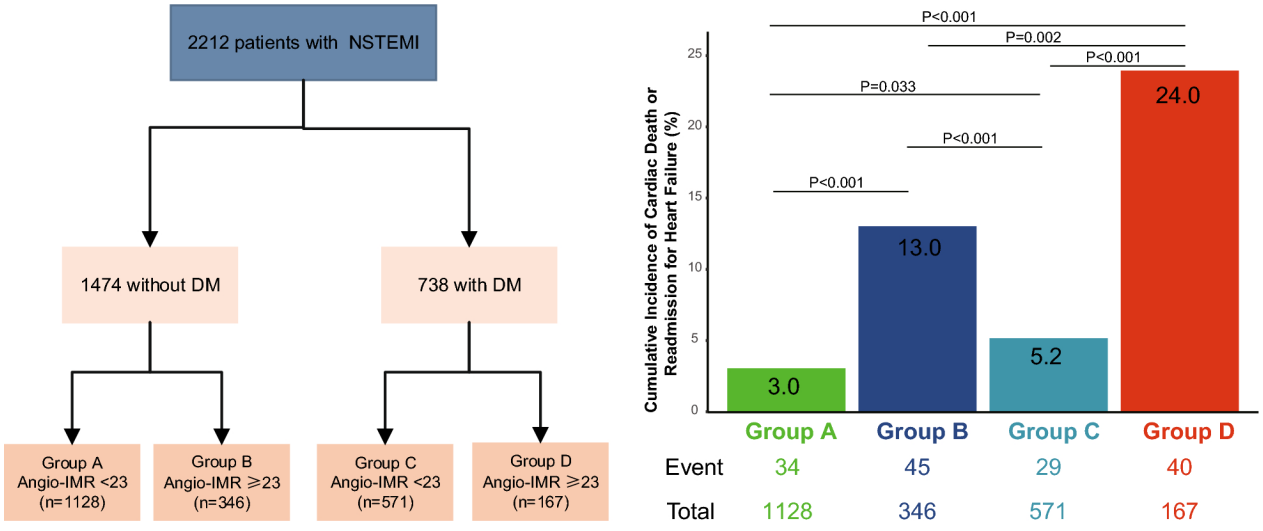
Conclusions In patients with NSTEMI, the combination of DM and CMD is an independent predictor of cardiac death or readmission for heart failure. Angio-IMR could be used as an additional evaluation tool for the management of NSTEMI patients with DM.

Trial registration URL: https://www.clinicaltrials.gov; Unique identifier: NCT05696379.

Keywords Diabetes mellitus, Coronary microvascular dysfunction, Non-ST-segment elevation myocardial infarction, Angiography-derived index of microcirculatory resistance

Graphical Abstract



Background

Diabetes mellitus (DM) is a well-recognized risk factor for cardiovascular disease (CVD), with its prevalence continues to increase globally [1, 2]. DM is a chronic condition that doubles the risk of death compared to individuals without DM, with CVD accounting for at least half of these fatalities [2]. There is clear evidence linking DM with additional cardiovascular risk and mortality in patients with acute coronary syndromes [3–5]. Although the increased use of prompt percutaneous coronary intervention (PCI) and the standardized application of drug therapy have significantly reduced the mortality rate associated with ST-segment elevation myocardial infarction (STEMI), the mortality rate for patients diagnosed with non-ST-segment elevation myocardial infarction (NSTEMI), who often present with a higher prevalence of comorbidities such as DM, obesity, and hypertension, appears to have reached a plateau [6].

Coronary microvascular dysfunction (CMD) is a clinical condition characterized by impaired blood flow through the coronary microcirculation and is increasingly recognized as a potential cause of myocardial ischemia, alongside epicardial atherosclerotic coronary artery disease [7]. CMD in DM is a multifactorial phenomenon, associated with alterations in perivascular and interstitial fibrosis [8], diminished capillary density and neovascularization [9], and autonomic neuropathy [10]. Observational research indicates that CMD carries an increased risk and can serve as a prognostic tool for predicting adverse cardiac events in DM patients, independent of traditional risk factors [11–14]. Therefore, timely recognition of CMD in DM patients, which can be achieved through various invasive and non-invasive methods, might have the potential to prevent adverse outcomes and improve their quality of life [15, 16].

The index of microcirculatory resistance (IMR) has been introduced as a surrogate indicator of CMD [17]. Previous studies have indicated that IMR can predict worse prognosis in patients with STEMI, NSTEMI, and chronic coronary syndromes (CCS) [13, 18–20]. However, the routine clinical application of IMR remains limited due to its invasive nature, extended procedural duration, and technical intricacy. To address these limitations, angiography-derived IMR (angio-IMR) has been developed. This novel technique allows for accurate evaluation of the microcirculation from coronary angiograms without invasive interventions [21]. Subsequent studies have confirmed the prognostic value of angio-IMR in patients with STEMI, myocardial infarction with non-obstructive coronary arteries (MINOCA), and CCS [14, 21–23]. Considering that CMD is an early feature of DM and the prognostic significance of angio-IMR in NSTEMI patients with DM comorbidity has not been clarified, we conducted this study to ascertain the combined risk

estimates of DM and CMD evaluated by angio-IMR in NSTEMI patients.

Methods

Study design

This study is a large-scale, multicenter observational investigation conducted across 3 medical centers (Second Affiliated Hospital of Zhejiang University Hangzhou, China; Shengjing Hospital of China Medical University, Shenyang, China; Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China). Eligible patients from these 3 cites were retrospectively enrolled between June 1, 2017, and May 31, 2020. The study was approved by the local institutional review board and adhered to the principles outlined in the Helsinki Declaration.

Patient population

Patients aged 18 years or older who had experienced NSTEMI and underwent successful PCI were considered for inclusion. NSTEMI was defined according to the Fourth Universal Definition of Myocardial Infarction [24]. Successful PCI was characterized by a visual post-PCI angiographic stenosis of less than 30% with improved reflow (thrombolysis in myocardial infarction flow grade 3) [25]. The diagnosis of diabetes was confirmed based on several criteria, including a previous medical diagnosis, use of oral hypoglycemic drugs or insulin, or a hemoglobin A1c (HbA1c) level exceeding 6.5% [26]. Exclusion criteria included prior coronary artery bypass graft, hemodynamic instability before PCI, ineligible coronary angiographic images (e.g., poor image quality, mismatch of data formats, image loss, only a single angiographic view of culprit vessels, severe vessel overlap or significant artifact, and single coronary angiography image after PCI). Invasive coronary angiography and PCI were performed using standard techniques and best local practices. Optimal medical treatments, including antiplatelet agents, statins, and antianginal medications, were administered at the discretion of the primary operator in accordance with current guidelines.

Baseline demographic and clinical data of all participants were extracted from medical records. The collected clinical data encompassed laboratory and angiographic characteristics, as well as drug regimens administered during hospitalization and at discharge.

Angio-IMR measurement

In this study, angio-IMR was measured in the culprit artery post-PCI. In cases where the electrocardiogram failed to identify the culprit vessel and multiple vessels exhibit comparable severe stenoses, angio-IMR was obtained for each suspected vessel, and a per-patient analysis was conducted using the highest value as the representative measurement. The computation of angio-IMR was performed in a blinded manner by an independent core laboratory using the AccuIMR software (version 1.0; ArteryFlow Technology, Hangzhou, China) [27, 28].

Outcomes and follow-up

The primary outcome was a composite of cardiac death or readmission for heart failure (HF) at 2 years post-successful PCI. Secondary outcomes comprised the individual components of the primary outcome, and patient-oriented cardiovascular outcome (POCO), including death, reinfarction and revascularization. All clinical outcomes were defined according to the Academic Research Consortium report [29]. Cardiac death was defined as any death caused by cardiac factors or either unknown or undeterminable factors [29]. Readmission for HF was defined as hospitalization due to new or worsening signs and symptoms of HF, combined with noninvasive imaging findings or increased B-type natriuretic peptide (BNP) and/or N-terminal pro-BNP concentration. All events were independently adjudicated by two expert cardiologists in a blinded fashion, with any discrepancies resolved by consensus.

Follow-up for clinical events was conducted through outpatient visits, medical record reviews, and telephone contacts.

Statistical analysis

Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, and comparisons were made using the Student's t-test or Mann–Whitney U test, depending on the distribution, which was verified by the Kolmogorov–Smirnov test and visual inspection of Q-Q plots. Categorical variables were expressed as numbers with percentages and compared using the chi-square test.

Because an established IMR cutoff value for CMD in NSTEMI patients with DM is lacking, we pre-defined high angio-IMR as the 75th percentile of the overall angio-IMR, setting it at angio-IMR ≥ 23 for our study [30, 31]. Additionally, a previous described cutoff of 25 was used in sensitivity analyses to evaluate the prognostic value of angio-IMR [13, 14, 19]. Kaplan–Meier analysis was employed to compute the cumulative incidence of outcomes, and differences between groups were evaluated by the log-rank test. The proportionality assumption was verified using the Schoenfeld residuals test. A multivariate Cox proportional hazard regression model was conducted to calculate hazard ratio (HR) and 95% confidence intervals (CI) to evaluate the relative risks as to the incidence of the primary outcome. Given the potential nonlinear association between post-PCI angio-IMR and outcomes, restricted cubic spline (RCS) curves

with five knots were utilized in the Cox regression models to generate HR curves [32]. Propensity score matching (PSM) analysis was conducted to control baseline characteristics.

All probability values were two-sided. A P-value of less than 0.05 was considered clinically significant for comparisons between two groups, while for comparisons involving more than two groups, a Bonferroni correction was applied to adjust for multiple comparisons. All statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 2212 consecutive NSTEMI patients who received successful PCI were enrolled in our study (Fig. 1). As listed in Table 1 and Table S1, 738 patients (33.4%) had DM, while 1474 patients (66.6%) did not. The DM group was characterized by older age, a higher proportion of females and smokers, and a greater burden of comorbidities such as hypertension, hyperlipidemia, and MI. Killip class, GRACE score, glycemic traits, and lipid profiles were higher in diabetic patients, whereas LVEF was lower. There were no significant differences in the use of cardiovascular medications between the two groups, except for beta-blockers.

During the PCI procedure, the DM group showed a lower proportion of culprit vessels in the left ascending artery, a higher frequency of multivessel disease, and more frequent use of smaller diameter implantation devices. The median post-PCI angio-FFR was slightly lower in the DM group compared to the non-DM group (0.92 [0.89–0.94] vs. 0.92 [0.89–0.95], p=0.048), while the post-PCI angio-IMR did not significantly differ between the two groups (20.13 [17.91–22.70] vs. 20.19 [18.14–22.77], p=0.530).

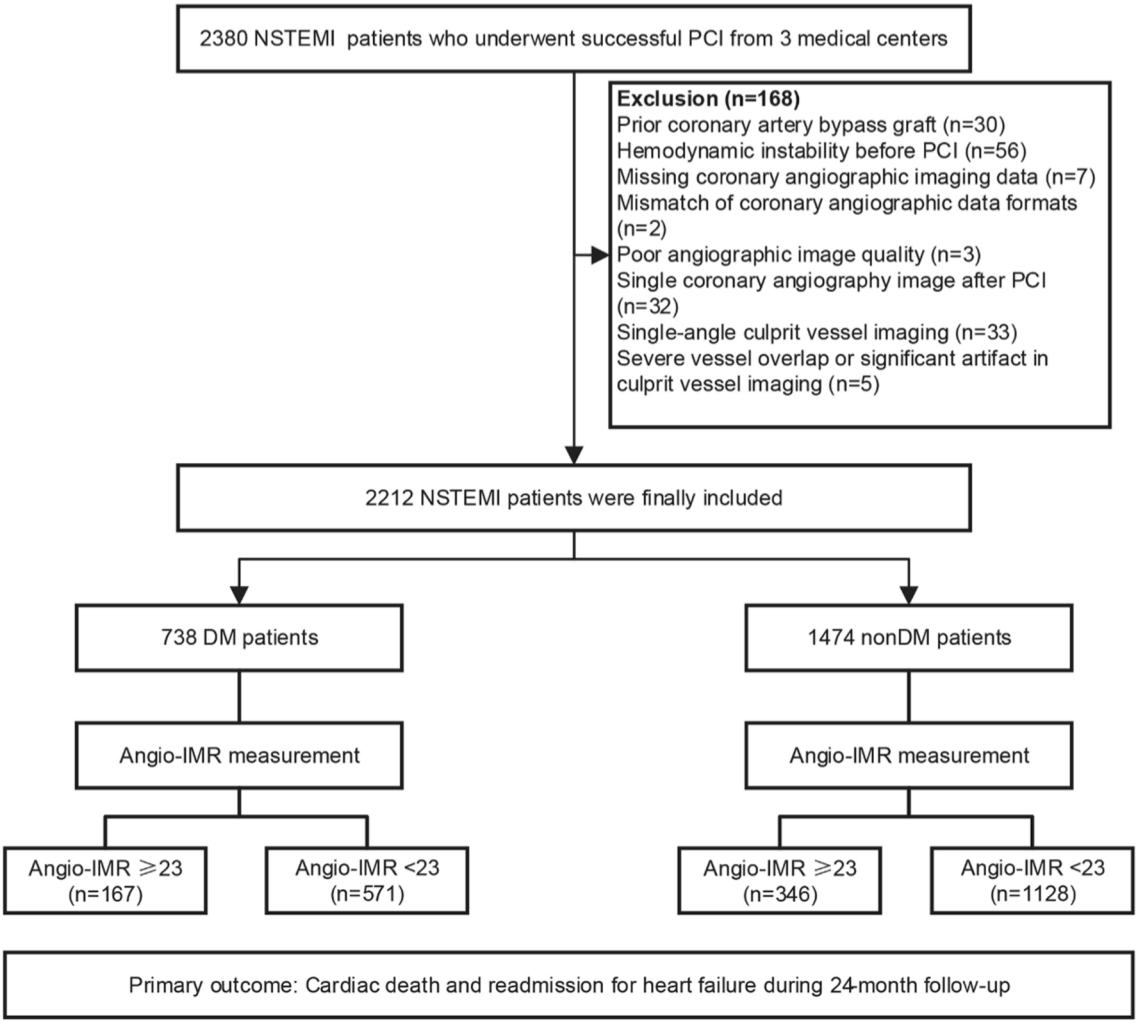


Fig. 1 Study flow. NSTEMI indicates non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; DM, diabetes mellitus; angio-IMR, angiography-derived index of microcirculatory resistance

Table 1 Baseline characteristics of the study population

	All (n = 2212)	DM (n = 738)	Non-DM (n = 1474)	*P* value
Age, years	62.94 ± 11.74	63.99 ± 10.83	62.42 ± 12.14	0.002
Female, n (%)	583 (26.4)	250 (33.9)	333 (22.6)	< 0.001
Current smoker	1233 (55.7)	359 (48.6)	874 (59.3)	< 0.001
Hypertension	1379 (62.3)	535 (72.5)	844 (57.3)	< 0.001
Hyperlipidemia	981 (44.3)	368 (49.9)	613 (41.6)	< 0.001
Previous MI	263 (11.9)	107 (14.5)	156 (10.6)	0.009
LVEF, %	58.49 ± 8.60	57.35 ± 8.73	59.06 ± 8.48	< 0.001
Killip class 3 or 4	161(7.3)	79 (10.7)	82 (5.6)	< 0.001
GRACE score	118.19 ± 35.46	123.14 ± 37.36	115.71 ± 34.21	< 0.001
GRACE score > 140	534 (24.1)	217 (29.4)	317 (21.5)	< 0.001
Creatinine, μmol/L	72.10 [62.00–86.00]	73.00 [60.50–92.00]	72.00 [62.95–84.00]	0.370
TG, μmol/L	1.99 ± 1.99	2.33 ± 2.55	1.82 ± 1.61	< 0.001
HDL-c, μmol/L	0.99 ± 0.27	0.94 ± 0.25	1.01 ± 0.27	< 0.001
LDL-c, μmol/L	2.71 ± 0.98	2.57 ± 1.01	2.78 ± 0.96	< 0.001
FBG, mg/dL	6.69 ± 2.77	8.88 ± 3.38	5.60 ± 1.51	< 0.001
HbA1c, %	6.69 ± 1.58	8.07 ± 1.64	5.92 ± 0.85	< 0.001
Post-PCI Angio-FFR	0.92 [0.89–0.94]	0.92 [0.89–0.94]	0.92 [0.89–0.95]	0.048
Post-PCI Angio-IMR	20.17 [18.06–22.75]	20.13 [17.91–22.70]	20.19 [18.14–22.77]	0.530

Values are expressed as mean ± SD, median [IQR], or n (%)

DM indicates diabetes mellitus, MI, myocardial infarction; LVEF, left ventricular ejection fraction; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, hmoglobin A1c; angio-FFR, angiography-derived fractional flow reserve; angio-IMR, angiography-derived index of microcirculatory resistance

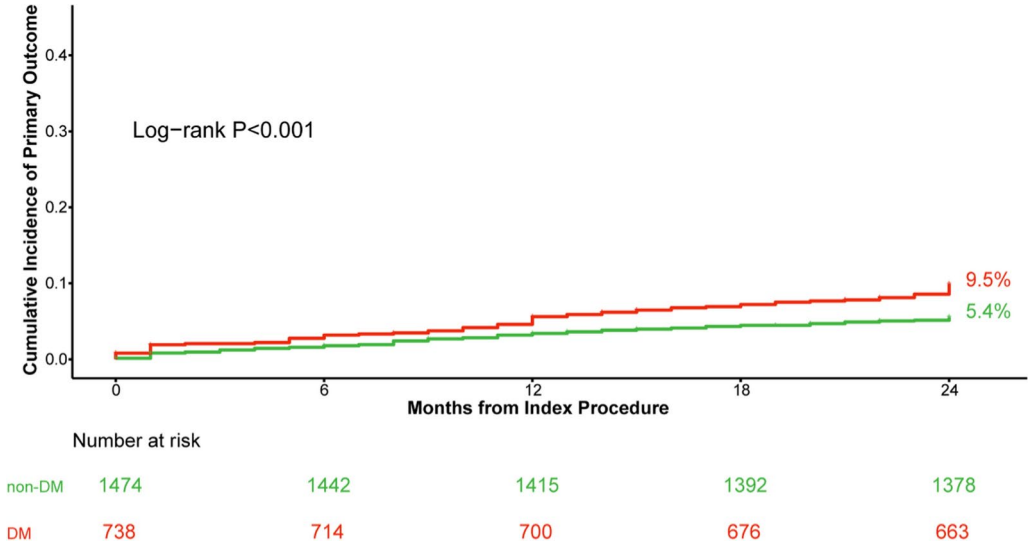


Fig. 2 Kaplan–Meier survival curves of primary outcomes in NSTEMI patients according to diabetes status

Patients grouping

Among the total population, the 75th percentile of angio-IMR values was 22.75. Therefore, we used an angio-IMR value of 23 as the cut-point, resulting in 513 (23.2%) patients with high angio-IMR (CMD) and 1699 (76.8%) patients with low angio-IMR (non-CMD). When combining angio-IMR levels with DM status, we identified four groups: 1128 non-DM patients with non-CMD (group A), 346 non-DM patients with CMD (group B), 571 DM patients with non-CMD (group C), and 167 DM patients with CMD (group D). The baseline characteristics among the four groups generally aligned with the presence of diabetes, except for stroke (Table S2).

Clinical outcomes of NSTEMI patients according to DM and CMD

A total of 2181 patients (98.60%) were available for a 2-year follow-up. DM patients had a notably higher risk of cardiac death or readmission for HF at 2 years compared to non-DM patients (9.5% vs. 5.4%, p < 0.001) (Fig. 2). Among all groups classified according to DM status and angio-IMR levels, the cumulative incidence of

cardiac death or readmission for HF at 2 years was 3.0%, 13.0%, 5.2%, and 24.0% for groups A, B, C, and D, respectively (p<0.001) (Fig. 3A). Group D exhibited the highest risk of cardiac death or readmission for HF compared to the other groups (p<0.001). For the individual components of the primary outcome, the incidence of cardiac death at 2 years was 1.9%, 8.1%, 3.6%, and 15.0% for groups A, B, C, and D, respectively (p<0.001) (Fig. 3B), whereas it was 1.3%, 5.6%, 2.4%, and 13.9% for readmission for HF at 2 years in groups A, B, C, and D, respectively (p<0.001) (Fig. 3C). Similarly, group D showed significantly increased risks of cardiac death, as well as readmission for HF than other groups (both p<0.001). The group D exhibited the highest risk of POCO compared to the other groups (p<0.001), mainly driven by death (Figure S1).

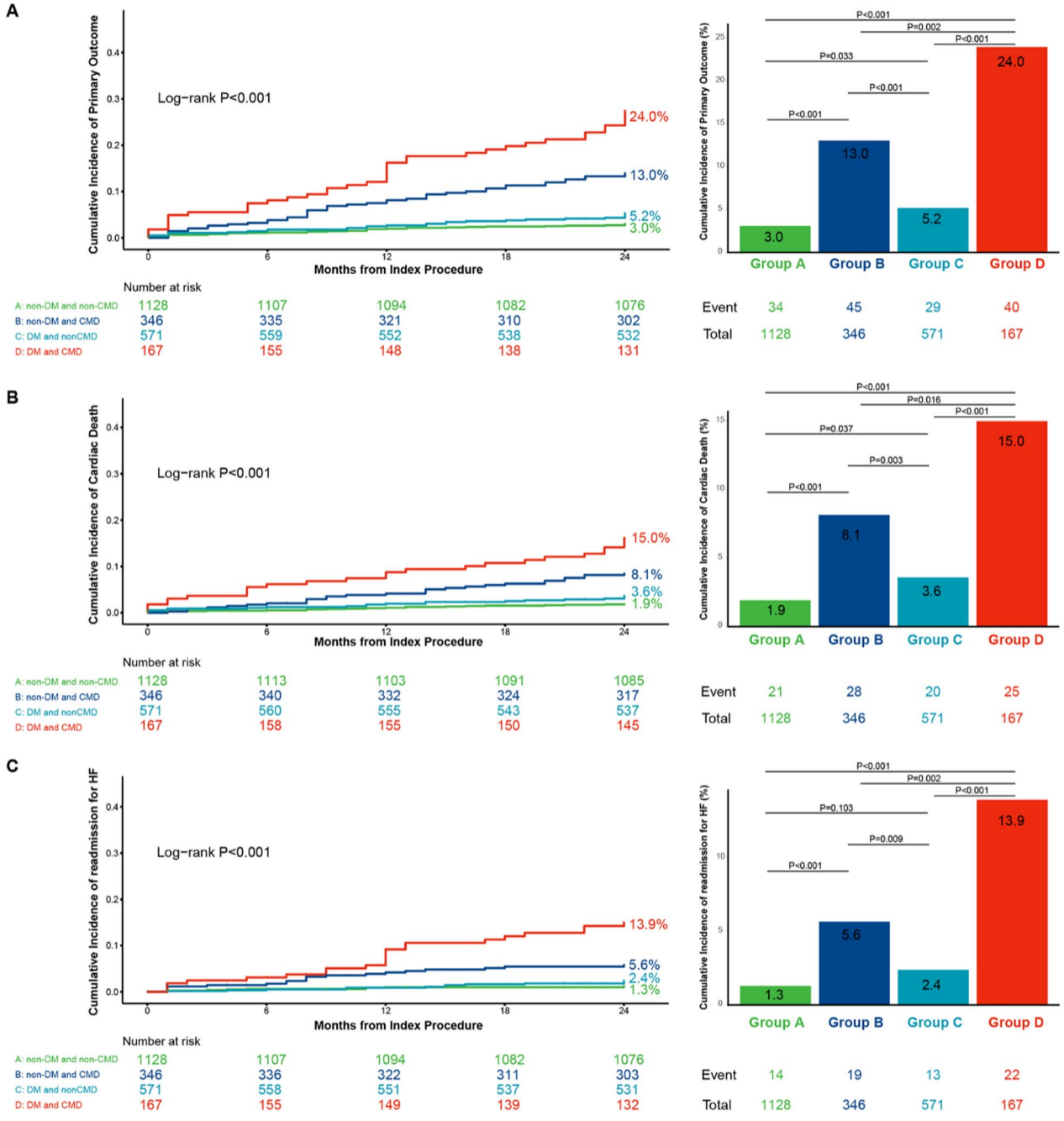


Fig. 3 Comparison of clinical outcomes at 2 years based on the presence of DM and CMD: **A** Cardiac death or readmission for heart failure, **B** Cardiac death, and **C** Readmission for heart failure. Results are estimated using the Kaplan–Meier method, so values may not calculate mathematically. Log-rank p-values are compared across the four groups and between any two groups, with a Bonferroni-corrected p-value of < 0.008 (0.05/6) indicating significance

Table 2 Comparison of primary outcome at 2 years according to the presence of DM and angio-IMR results

	Patient number	Cumulative incidence	Univariable		Multivariable*	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Group A: non-DM and non-CMD	1128	34 (3.0%)	Reference		Reference	
Group B: non-DM and CMD	346	45 (13.0%)	4.497 (2.881–7.021)	< 0.001	4.353 (2.512–7.545)	< 0.001
Group C: DM and non-CMD	571	29 (5.2%)	1.701 (1.037–2.792)	0.036	1.242 (0.608–2.537)	0.551
Group D: DM and CMD	167	40 (24.0%)	8.778 (5.556–13.867)	< 0.001	7.894 (4.251–14.659)	< 0.001

Data are expressed as number of events (%). The cumulative incidences of primary outcome, cardiac death or readmission for heart failure, are presented as Kaplan–Meier estimates during the 2-year follow-up

DM indicates diabetes mellitus; angio-IMR, angiography-derived index of microcirculatory resistance; HR, hazard ratio; CI, confidence interval

*Adjusted for sex, hypertension, smoke, history of MI, hyperlipidemia, fasting blood glucose, HbA1c, LVEF, GRACE score, ACC/AHA class B2/C, post-PCI angio-FFR < 0.9

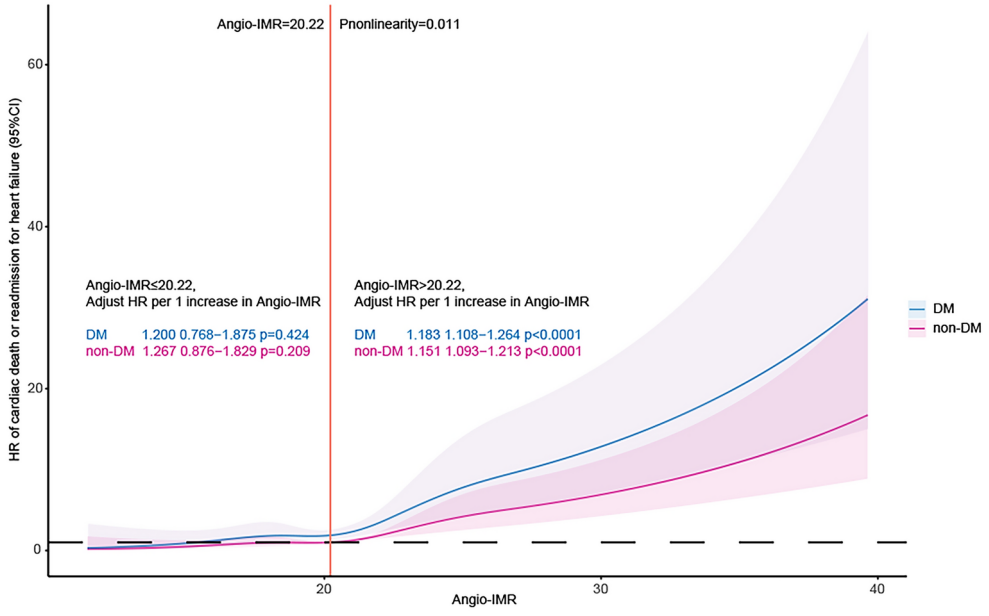


Fig. 4 Relationships between angio-IMR and the risk of cardiac death or readmission for heart failure in the DM and non-DM groups according to the restricted cubic spline analysis

Prognostic implications of DM and CMD in NSTEMI patients

In a multivariate regression model, we included covariates considered clinically relevant, such as sex, hypertension, smoking, history of MI, hyperlipidemia, fasting blood glucose, HbA1c, LVEF, GRACE score, ACC/AHA class B2/C, and post-PCI angio-FFR < 0.9. Patients with high post-PCI angio-IMR (groups B and D) showed a significantly higher risk of cardiac death or readmission for HF at 2 years regardless of the presence of DM (group B: adjusted HR: 4.353, [95% CI, 2.512–7.545], p < 0.001; group D: adjusted HR: 7.894, [95% CI, 4.251–14.659], p < 0.001) (Table 2). Notably, DM patients with high post-PCI angio-IMR (group D) were the most powerful independent predictor for cardiac death or readmission for HF.

Sensitivity analysis

Given the existing baseline differences in NSTEMI patients with and without DM, a 1:1 PSM analysis was applied using the nearest neighbor matching method with a caliper of 0.2. The PSM calculations included the following variables: age, sex, smoking status, all comorbidities present on admission, LVEF, GRACE score, culprit artery location, and ACC/AHA class B2/C. After PSM, baseline characteristics were comparable between the two groups (Table S3). NSTEMI patients with both DM and CMD remained suffered from the highest incidence of cardiac death or readmission for HF at 2 years (Figure S2).

A nonlinear relationship was observed between the log hazard of the primary outcome, cardiac death or readmission for HF, and angio-IMR value in both groups (Figure S3). As assessed by RCS analysis, the risk of cardiac death or readmission for HF was relatively flat until around 20.22 of post-PCI angio-IMR and then increased rapidly afterward (Pnonlinearity = 0.011) (Fig. 4). The cumulative incidences of cardiac death or readmission for HF at 2 years were consistent when grouping patients based on DM status and angio-IMR cutoff value of 20.22 (Figure S4).

We further performed a sensitivity analysis applying a cut-off value of 25 for post-PCI angio-IMR. As shown in Figure S5, in the comparison of primary outcomes across the four groups classified by DM and post-PCI angio-IMR, the cumulative incidences of cardiac death or readmission for HF at 2 years were 4.2%, 8.6%, 17.5%, and 17.4% in groups A to D, respectively. Consistently, multivariable Cox analysis showed that high post-PCI angio-IMR remained strongly correlated with the risk of cardiac death or readmission for HF in DM patients after adjusting for additional confounding risk factors (adjusted HR: 6.907, [95% CI, 3.105–15.366], $p<0.001$).

Discussion

In this study, we evaluated the combined prognostic significance of DM and CMD, assessed by angio-IMR, in NSTEMI patients after PCI for the first time. The main findings are as follows: (1) Post-PCI angio-IMR was comparable between NSTEMI patients with or without DM. (2) Patients with both DM and CMD, indicated by a post-PCI angio-IMR≥23, were at an increased risk of cardiac death or readmission for HF; (3) Angio-IMR is an independent predictor of worsening clinical outcomes among NSTEMI patients with DM. These findings suggest that angio-IMR can facilitate early and rapid assessment of CMD and offer a new risk classification strategy for diabetic NSTEMI patients.

Relationship between DM and CMD

DM is a potent inducer of microvascular dysfunction and this relationship seems to be bidirectional as microvascular dysfunction in muscle and adipose tissue also contributes to the pathogenesis of DM [33]. CMD is increasingly recognized as a key component of DM-associated CVD. Levelt et al. revealed that CMD exacerbated derangement of cardiac energetics in response to increased oxygen demand in DM patients [34]. CMD driven by DM is characterized by decreased nitric oxide activity, increased reactive oxygen species production, elevated endothelin synthesis, reduced endothelial barrier function, and heightened inflammatory activity and oxidative stress [7]. Conversely, endothelial dysfunction and extracellular matrix remodeling caused by CMD can promote the progression from prediabetes to DM. Our findings revealed similar post-PCI angio-IMR values in both the DM group and the non-DM group. Additionally, a pooled analysis of STEMI patients from six cohorts demonstrated that the presence of DM did not vary significantly between the low and high IMR groups, while DM and IMR were the only independent risk factors of cardiac death [20]. This association may be partially attributed to acute microvascular changes during the ischemic and reperfusion phases of acute myocardial infarction [35]. Notably, DM and CMD exhibit a reciprocal interaction, and both can impact adverse cardiovascular outcomes [7, 36].

Prognostic roles of DM and CMD in NSTEMI patients

The incidence of both NSTEMI and DM has been increasing over the decades, with over a third of NSTEMI patients having DM [5]. Management of NSTEMI is relatively delayed and heterogeneous compared with the intended primary PCI approach to STEMI. The FAST-MI Program indicated that while the use of early PCI (≤72 h from admission) increased from 9% in 1995 to 60% in 2015, mortality gains for NSTEMI have been sustained since 2010 [6]. NSTEMI patients with DM are at a higher risk of mortality than those without DM, irrespective of therapeutic strategies [3]. DM has complex and far-reaching impacts on NSTEMI with respect to its long-term metabolic dysregulation, non-aggressive pharmacological treatment, and CMD [4, 33].

Clinical evidence indicates that CMD may contribute to persistent or recurrent angina following successful PCI after acute MI, and CMD in reperfused acute MI is associated with adverse remodeling, lower ventricular function, and worse prognosis [37]. CMD could be partly attributed to microembolization, microinfarcts, and the release of partial debris and soluble substances from the culprit lesion, which can sensitize the coronary microcirculation and contribute to angina in the absence of epicardial obstruction [38, 39]. Animal models suggested that suboptimal reperfusion after PCI was related to CMD secondary to endothelial injury and/or distal embolization [7]. Repetitive subclinical coronary microembolization could cause progressive loss of viable contractile cardiomyocytes and ultimately induce HF in the absence of overt MI [39]. Moreover, CMD limits coronary blood flow, leading to alterations in shear stress that affect endothelial function and enhance thrombus formation at the epicardial level. In line with most previous studies, we found that the existence of either DM or CMD in NSTEMI patients was strongly correlated with cardiac death or readmission for HF at 2 years, highlighting the importance of DM and CMD in the management of NSTEMI.

Optimal cutoff threshold of angio-IMR

IMR is a reliable and reproducible method for quantitatively assessing CMD. In patients with STEMI, a post-PCI IMR/angio-IMR>40 predicts adverse clinical outcomes and is used as a reliable cutoff to evaluate microcirculation status [20, 21, 40]. In patients with CCS, an established cutoff value of 25 for IMR/angio-IMR also predicts adverse events independently from FFR [13, 14, 19]. However, due to the lack of evidence from clinical trials, no unified cutoff value has been established for predicting prognosis in patients with NSTEMI or MINOCA.

Abdu et al. suggested an angio-IMR cutoff value of 43 as a strong predictor of clinical outcomes among MINOCA patients [22]. Similarly, Murai et al. found that a post-PCI IMR value of 15.4 could predict major adverse cardiovascular event in NSTEMI patients based on ROC analysis [18].

In our study, we classified CMD using a post-PCI angio-IMR cutoff of≥23, corresponding to the 75th percentile. Such a lower cutoff, indicating mild microvascular dysfunction, is in line with the aggressive management of NSTEMI, especially in those comorbid with DM, who might experience earlier impairment of myocardial microvasculature. Our results demonstrated that patients with both DM and CMD suffered from the highest risks of cardiac death or readmission for HF, while patients without CMD were at decreased risks of adverse outcomes, irrespective of diabetes status. Additionally, acknowledging the previous practice, we performed a sensitivity analysis using an angio-IMR value of 25 as a cutoff, which showed consistent results regarding the prognostic value for primary outcomes across different DM and IMR groups. However, using an angio-IMR>25 as a cutoff categorized only 206 patients as high risk, representing less than 10% of all enrolled patients in this study. Therefore, we believe that an angio-IMR cutoff of 23 allows for more accurate screening of high-risk NSTEMI patients.

Clinical implications of combined risk estimates of CMD and DM

Our previous work has confirmed the independent predictive effects of angio-IMR on STEMI or NSTEMI [23, 41]. In the present study, we further investigated the combined risk estimates of CMD and DM in NSTEMI patients. In NSTEMI patients with CMD, DM significantly increased the rate of adverse clinical outcomes, with Kaplan–Meier estimates of the composite outcome of cardiac death or readmission for HF of 24.0% at 2 years. However, in NSTEMI patients without CMD, DM did not significantly impact adverse clinical outcomes. Therefore, the higher adverse event rate in DM patients was mostly driven by those with CMD, NSTEMI patients with both DM and CMD might benefit most from timely management with adjunctive therapeutic strategies aimed at improving microvascular function in addition to PCI. Recent studies have indicated that antiplatelet agents ticagrelor and anti-glycemic agent metformin could potentially improve coronary endothelial function [42, 43]. Therefore, in contemporary practice, our data revealed that angio-IMR may help physicians refine the early risk stratification of NSTEMI patients with DM and intensify in-hospital treatments and post-discharge management for those at higher risk.

Limitations

The present study acknowledges several limitations. First, the retrospective design inevitably introduces biases such as selection, follow-up, and information bias. However, our study is a large-scale, multicenter investigation with a relatively high rate of 2-year follow-up. All participants meeting the inclusion criteria were consecutively enrolled. Second, we excluded some patients without identifiable culprit lesions, which might limit the assessment of microvascular function in certain patients. Nevertheless, CMD in acute coronary syndrome was typically confined to the territory of the culprit vessel [35]. Third, several novel medications, including SGLT2 inhibitors and GLP-1 receptor agonists, which have demonstrated potential in reducing the risk of subsequent cardiovascular events, were not widely prescribed during our study period. Consequently, we were unable to collect data regarding their prescription, and their efficacy in NSTEMI patients with DM and CMD warrants further investigation. Fourth, we did not differentiate between type 1 and type 2 diabetes in our data collection. However, it is expected that only 1.1% of all MI patients and 2.7% of MI patients with DM have type 1 diabetes [44]. Regardless of the type of DM, these patients are classified as having a very high risk of adverse cardiovascular events. Fifth, considering the prevalence of multivessel disease among the majority of NSTEMI patients, our analysis did not include the impact of complete revascularization or the influence of non-target vessels on prognosis. Sixth, the correlation between changes in LVEF and CMD in HF patients during long-term follow-up requires further investigation. Moreover, the observational nature of the data limits definitive conclusions. Therefore, caution should be exercised when extrapolating the clinical implications of our findings.

Conclusions

In patients with NSTEMI, the combination of DM and CMD, as determined by an elevated noninvasive angio-IMR, is an independent predictor of cardiac death or readmission for heart failure. The integration of angio-IMR enhanced risk stratification in predicting the occurrence of adverse clinical outcomes in NSTEMI patients with DM.

Abbreviations

DM	Diabetes mellitus
CVD	Cardiovascular disease
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
CMD	Coronary microvascular dysfunction
IMR	Index of microcirculatory resistance
CCS	Chronic coronary syndromes
angio-IMR	Angiography-derived index of microcirculatory resistance
MINOCA	Myocardial infarction with non-obstructive coronary arteries
HbA1c	Hemoglobin A1c

HF	Heart failure
POCO	Patient-oriented cardiovascular outcome
BNP	B-type natriuretic peptide
RCS	Restricted cubic spline
PSM	Propensity score matching
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02400-1.

Additional file 1. Figure S1. Comparison of POCO at 2 years based on the presence of DM and CMD. A) POCO, a composite of death, myocardial infarction and revascularization, B) Death, C) Reinfarction and D) Revascularization. Results are estimated using the Kaplan–Meier method, so values may not calculate mathematically.

Additional file 2. Figure S2. The propensity score matching analysis. A) Distribution after matching. The propensity score matching calculations included the following variables: age, sex, smoking status, all comorbidities present on admission, LVEF, GRACE score, culprit artery location, and ACC/AHA class B2/C. B) Kaplan-Meier survival curves of cardiac death or readmission for heart failure for different subgroups after propensity score matching.

Additional file 3. Figure S3. Nonlinear relationship between the log hazard of cardiac death or readmission for heart failure and angio-IMR.

Additional file 4. Figure S4. Comparison of cardiac death or readmission for heart failure at 2 years based on the presence of DM and an Angio-IMR cutoff value of 20.22.

Additional file 5. Figure S5. Kaplan-Meier survival curves of cardiac death or readmission for heart failure for different subgroups. Comparison of cardiac death or readmission for heart failure at 2 years based on the presence of DM and an Angio-IMR cutoff value of 25. Adjusted covariates in multivariable model included sex, hypertension, smoking, history of MI, hyperlipidemia, fasting blood glucose, HbA1c, LVEF GRACE score, ACC/AHA class B2/C, and post-PCI angio-FFR <0.9.

Additional file 6. Table S1. Baseline Characteristics of the Study Population.

Additional file 7. Table S2. Baseline Characteristics According to the Diabetes and Angio-IMR Levels.

Additional file 8. Table S3. Baseline Characteristics of the Study Population after propensity score matching.

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Author contributions
D.C. and J.J. designed the study and drafted the article. D.C., Y.Z., A.Y., D.H., Y.Z., J.F., Q.G., J.H, Q.D. conducted data acquisition, D.C. and Y.Z. performed data analysis and interpretation. J.P, T.N., J.X., J.W., and J.J. revised the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Our study was conducted in accordance with the Helsinki Declaration and was approved by the ethical review board of Second Affiliated Hospital of Zhejiang University, Renji Hospital of Shanghai Jiao Tong University, and Shengjing Hospital of China Medical University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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