



Relationship of Risk Factors in NSTEMI Patients with Type 2 Diabetes Mellitus to the Incidence of Major Adverse Cardiac and Cerebrovascular Events (MACCE): A Cohort Study from Dr. Wahidin Sudirohusodo Hospital

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Volume 6, Issue 15, Oct 2024

Received: 15 Aug 2024

Accepted: 25 Sep 2024

Published: 21 Oct 2024

doi: [10.48047/AFJBS.6.15.2024.13014-13024](https://doi.org/10.48047/AFJBS.6.15.2024.13014-13024)

Abstract

Background: Patients with diabetes mellitus (DM) experiencing non-ST-elevation myocardial infarction (NSTEMI) have an increased risk for major adverse cardiac and cerebrovascular events (MACCE). This study aimed to explore the relationship among risk variables in NSTEMI patients with a history of Type 2 diabetes mellitus as well as those with newly diagnosed Type 2 diabetes mellitus concerning the incidence of MACCE.

Methods: This retrospective cohort study utilized data from the Acute Coronary Syndrome Registry at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, collected between January 2021 and December 2023. A total of 129 NSTEMI patients with diabetes were included and divided into two groups: those with a prior history of Type 2 DM (n=88) and those newly diagnosed with Type 2 DM at admission (n=41). The primary outcome was the occurrence of MACCE, which included all-cause mortality, recurrent myocardial infarction, stroke, and heart failure. Statistical analyses were conducted using logistic regression and Chi-square tests. **Results:** Patients with a prior diagnosis of diabetes had a significantly higher incidence of MACCE compared to those newly diagnosed (40.31% vs. 12.40%, OR 2.26, 95% CI: 1.06- 4.82, p=0.034). The most significant risk factors associated with MACCE were reduced left ventricular ejection fraction (LVEF), lack of revascularization, and elevated hs-Troponin I levels. Heart failure was the most prevalent MACCE component in patients with a history of diabetes (OR 8.17, p=0.002), while stroke occurred only in this group but was not statistically significant. Elevated hs-Troponin I levels were correlated with MACCE only in patients with a prior diagnosis of diabetes, indicating more severe underlying coronary artery disease.

Conclusion: NSTEMI patients with a prior history of Type 2 DM face a markedly higher risk of MACCE, particularly heart failure. Reduced LVEF, lack of revascularization, and elevated hs-Troponin I are significant predictors of adverse outcomes. These findings emphasize the need for rigorous risk factor control, timely revascularization, and vigilant cardiac function monitoring in diabetic NSTEMI patients. Further prospective research is warranted to refine risk stratification and management strategies for this high-risk population.

Keywords: NSTEMI, Type 2 Diabetes Mellitus, Risk Factors, MACCE

Introduction

Cardiovascular disease (CVD) continues to be the primary cause of morbidity and mortality globally, resulting in 17.9 million fatalities each year, which is 32% of all deaths (1). Acute coronary syndrome (ACS), especially Non-ST Elevation Myocardial Infarction (NSTEMI), substantially contributes to this burden (2). In Indonesia, coronary heart disease ranked as the second highest cause of mortality after stroke in 2012, resulting in around 128,400 fatalities (3).

The incidence of diabetes among NSTEMI patients has markedly risen in the last ten years, with recent estimates indicating that approximately 20% of NSTEMI patients also have diabetes (4). Diabetes is recognized to expedite atherosclerosis and correlates with more extensive and intricate coronary artery disease, resulting in poorer outcomes for individuals with acute coronary syndrome (ACS) (5).

Major adverse cardiac and cerebrovascular events (MACCE), encompassing mortality, recurrent myocardial infarction, stroke, and heart failure, frequently occur subsequent to NSTEMI (5). The correlation between diabetes and heightened cardiovascular risk is well-documented; nevertheless, the influence of diabetes duration and the significance of various risk factors in forecasting MACCE in NSTEMI patients with differing diabetes statuses is not well understood.

Comprehending the correlation between risk variables and the incidence of MACCE in NSTEMI patients with a history of Type 2 DM compared to those newly diagnosed is essential for several reasons. It assists in identifying high-risk patients who may require more intensive management techniques, facilitates the creation of customized risk assessment instruments for NSTEMI patients with diabetes, and guides therapeutic decision-making regarding the intensity of secondary prevention interventions and follow-up procedures.

This study aimed to examine the relationship between diverse risk variables and the incidence of MACCE in NSTEMI patients with a prior history of Type 2 DM versus those newly diagnosed with Type 2 DM at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. We hypothesized that the influence of specific risk variables on MACCE incidence would vary between these two cohorts, possibly indicating the cumulative consequences of chronic diabetes compared to the acute metabolic disturbances linked to newly diagnosed diabetes.

1. Materials and Methods

Study Design and Sample

This retrospective cohort analysis examined data from the Acute Coronary Syndrome Registry at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, collected between January 2021 and December 2023. A total of 129 patients meeting the inclusion and exclusion criteria were included. Patients were divided into two groups: individuals having a history of Type 2 Diabetes Mellitus (n=88) and those newly diagnosed with Type 2 Diabetes Mellitus at admission (n=41). The inclusion criteria comprised patients aged over 18 years, diagnosed with NSTEMI (Non-ST Elevation Myocardial Infarction), treated according to the medical guidelines at RSUP Dr. Wahidin Sudirohusodo, and diagnosed or newly diagnosed with diabetes. The exclusion criteria ruled out patients without diabetes, those with previous chronic heart failure or infarction, chronic kidney disease, sepsis, or previous stroke.

Data Collection

Information on demographics, medical history, clinical characteristics, test results, and details on in-hospital management were extracted from the register. The left ventricular ejection fraction (LVEF) was evaluated using echocardiography. Coronary angiography findings were documented when accessible. NSTEMI was characterized in accordance with the Fourth Universal Definition of Myocardial Infarction (6). A history of Type 2 Diabetes Mellitus was characterized by a prior diagnosis of diabetes or current utilization of anti-diabetic pharmacotherapy. Newly diagnosed Type 2 Diabetes Mellitus was characterized by admission glucose levels of ≥ 200 mg/dL, fasting glucose levels of ≥ 126 mg/dL, or HbA1c levels of $\geq 6.5\%$ in individuals without a previous diabetes diagnosis (7).

MACCE was defined as a composite of all-cause mortality, recurrent myocardial infarction, stroke, and heart failure occurring within six months of the initial NSTEMI.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD) and compared using Student's t-test for normally distributed data or Mann-Whitney U test for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages and compared using the Chi-square test or Fisher's exact test when appropriate. The primary outcome of Major Adverse Cardiac and Cerebrovascular Events (MACCE) was analyzed as a composite endpoint. The association

between diabetes status (previously known vs. newly diagnosed) and MACCE was evaluated using logistic regression analysis. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Individual components of MACCE (heart failure, recurrent infarction, stroke, and mortality) were analyzed separately using Chi-square tests or Fisher's exact tests. For significant associations, odds ratios were computed. Subgroup analyses were performed to assess the impact of various risk factors on MACCE in both previously known and newly diagnosed diabetic patients. Interaction terms were included in the logistic regression models to test for effect modification. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University (No. 282/UN4.6.4.5.31/PP36/2024) and Dr. Wahidin Sudirohusodo Hospital (No. DP.04.03/D.XIX.2/19168/2024).

2. Results

Baseline Characteristics and Risk Factor Profile

The baseline characteristics of 129 NSTEMI patients diagnosed with Type 2 diabetes mellitus as seen in Table 1. This table presents the baseline characteristics of 129 NSTEMI patients with Type 2 diabetes mellitus. The patients were divided into two groups: 88 with previously known DM and 41 newly diagnosed with DM. The mean age was similar in both groups ($\pm$ 61 years), and males predominated in both groups. Notably, newly diagnosed DM patients had a higher prevalence of smoking (58.54% vs 47.73%) and dyslipidaemia (82.93% vs 64.77%), while previously known DM patients had higher rates of hypertension (67.05% vs 60.98%) and obesity (40.91% vs 29.27%). Previously known DM patients had lower LVEF (38.72% vs 41.36%) and higher HbA1c levels (8.46% vs 7.66%), indicating worse cardiac function and glycaemic control.

Table 1. Baseline Characteristics of NSTEMI Patients with Type 2 Diabetes Mellitus

Characteristic	Previously Known DM (n=88)	Newly Diagnosed DM (n=41)	Total (n=129)
Age (years)	61.63 ± 9.95	61.61 ± 7.85	61.62 ± 9.3
Male	65 (73.8)	32 (78.05)	97 (75.19)
Smoker	42 (47.73)	24 (58.54)	66 (51.16)
Hypertension	59 (67.05)	25 (60.98)	84 (65.12)
Dyslipidaemia	57 (64.77)	34 (82.93)	91 (70.54)
Obesity	36 (40.91)	12 (29.27)	48 (37.21)
LVEF (%)	38.72 ± 11.59	41.36 ± 11.66	39.56 ± 11.63
HbA1c (%)	8.46 ± 2.08	7.66 ± 1.49	8.25 ± 1.97
Hs-Troponin I (ng/L)	6047.11 ± 10919.71	8453.38 ± 14068	6790.45 ± 11978.49

MACCE Incidence

Table 2 presents the occurrence of Major Adverse Cardiac and Cerebrovascular Events (MACCE) within the study cohort. Of all, 52.71% of patients encountered major adverse cardiovascular and cerebrovascular events (MACCE). Patients with a prior diagnosis of diabetes mellitus had a markedly elevated incidence of major adverse cardiovascular and cerebrovascular events (MACCE) in comparison to those with newly diagnosed diabetes mellitus (40.31% vs 12.40%, OR 2.26, 95% CI: 1.06-4.82, p=0.034). This indicates that an extended duration of diabetes correlates with an increased risk of unfavourable cardiovascular outcomes in NSTEMI patients.

Table 2. Incidence of MACCE in NSTEMI Patients with Type 2 Diabetes Mellitus

DM Status*	MACCE		Total (n=129)	OR (95% CI)	p-value
	Yes (n=68)	No (n=61)			
ND	16 (12.40)	25 (19.38)	41 (31.78)	2.26 (1.06-4.82)	0.034
PK	52 (40.31)	36 (27.91)	88 (68.22)		

*ND (Newly Diagnosed)
PK (Previously Known)

Components of MACCE:

Table 3 delineates the constituents of MACCE in the two groupings. This table breaks down the components of MACCE in the two groups. Heart failure was significantly more common in previously known DM patients (92.86% vs 7.14%, OR 8.17, p=0.002). Recurrent infarction and mortality showed no significant difference between groups. Stroke occurred only in

previously known DM patients, but the difference was not statistically significant ($p=0.087$). These results suggest that long-standing diabetes particularly increases the risk of heart failure in NSTEMI patients.

Table 3. Components of MACCE in NSTEMI Patients with Type 2 Diabetes Mellitus

MACCE Component	Previously Known DM	Newly Diagnosed DM	OR (95% CI)	p-value
Heart Failure	26 (92.86)	2 (7.14)	8.17 (1.83-36.4)	0.002
Recurrent Infarction	8 (66.67)	4 (33.33)	0.92 (0.26-3.26)	0.904
Stroke	6 (100)	0 (0)	2.92 (0.34-25.13)	0.087
Mortality	30 (66.67)	15 (33.33)	0.89 (0.41-1.94)	0.782

Risk Factors Associated with MACCE

Table 4 illustrates the correlation between several risk factors and the incidence of MACCE. The left ventricular ejection fraction (LVEF) was markedly reduced in patients who suffered major adverse cardiovascular and cerebrovascular events (MACCE) (34.62% vs 45.06%, $p<0.001$). The absence of revascularization correlated with elevated MACCE rates ($p=0.047$). In previously diagnosed DM patients, elevated hs-Troponin I levels were strongly correlated with MACCE ($p=0.007$). These findings underscore the significance of cardiac function, revascularization, and myocardial injury in forecasting negative outcomes.

Table 4. Risk Factors Associated with MACCE in NSTEMI Patients with Type 2 Diabetes Mellitus

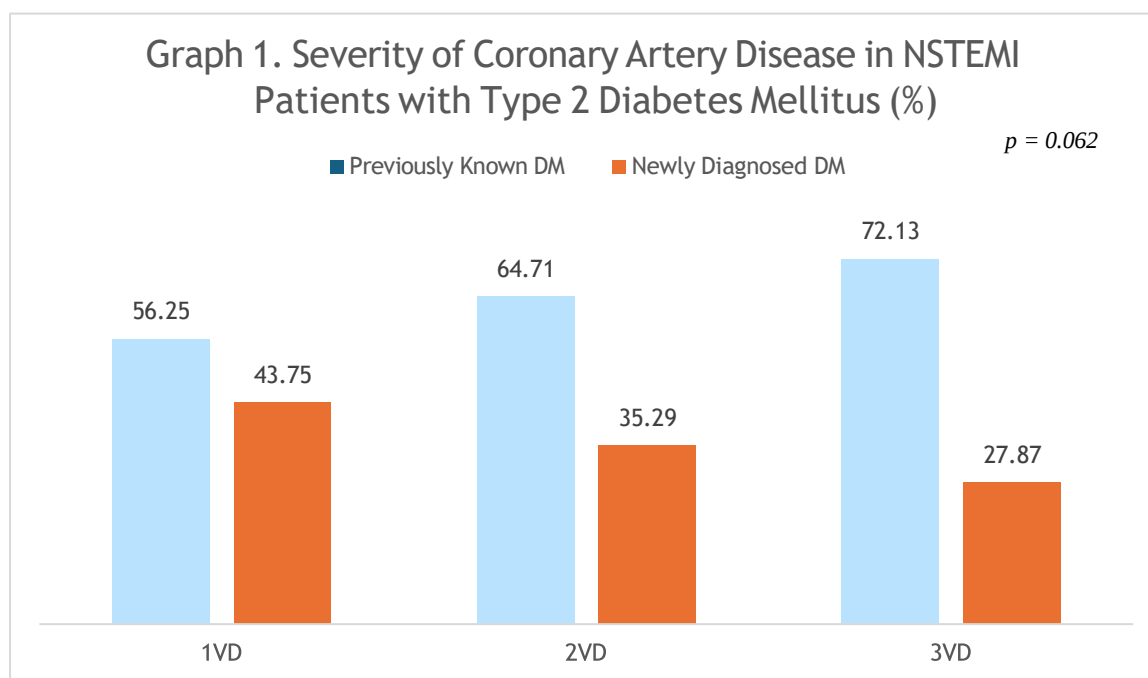
Risk Factors	MACCE		p-value
	Yes (n=68)	No (n=61)	
Age (years)	62.63 $\pm$ 8.79	60.49 $\pm$ 9.79	0.177
LVEF (%)	34.62 $\pm$ 10.31	45.06 $\pm$ 10.56	<0.001
Revascularization	56 (57.73)	41 (42.27)	0.047
hs-Troponin I (ng/L)*	8649.23 $\pm$ 13355.31	2288.48 $\pm$ 3450.16	0.007

*For previously known DM patients only

Severity of Coronary Artery Disease:

Table 5 illustrates the severity of coronary artery disease in both cohorts. Despite lacking statistical significance ($p=0.662$), a trend was seen indicating a higher prevalence of severe coronary artery disease (3VD) in patients with a prior diagnosis of diabetes mellitus (72.13%

vs 27.87%). This indicates that an extended duration of diabetes may correlate with more severe coronary atherosclerosis.



3. Discussion

Our analysis illustrates that the influence of diverse risk variables on MACCE incidence varies across NSTEMI patients with a prior history of Type 2 DM and those recently diagnosed with Type 2 DM. These findings hold significant implications for the risk categorization and management of NSTEMI patients with diabetes.

The elevated occurrence of MACCE in individuals with a history of Type 2 DM highlights the aggregated cardiovascular risk linked to prolonged diabetes. This aligns with prior research indicating that an extended duration of diabetes correlates with poorer cardiovascular outcomes (8,9). A meta-analysis conducted by Einarson et al. (2018) revealed that individuals with diabetes had a markedly elevated risk of severe adverse cardiovascular events subsequent to acute coronary syndrome (RR 1.41, 95% CI 1.26-1.57) in comparison to non-diabetic individuals (10). Our research expands upon previous findings by illustrating that, even among diabetic patients, individuals with a prolonged duration of the disease have an elevated risk. The mechanisms contributing to this heightened risk likely involve prolonged exposure to hyperglycaemia, resulting in advanced atherosclerosis, endothelial dysfunction, and diabetic cardiomyopathy (11).

The significantly elevated risk of heart failure in individuals with a prior diagnosis of diabetes (OR 8.17, $p=0.002$) is especially striking. This observation aligns with the idea of diabetic cardiomyopathy, wherein persistent hyperglycemia induces anatomical and functional alterations in the myocardial. A recent study by Seferović et al. (2020) underscored the bidirectional association between diabetes and heart failure, stressing the necessity for early cardiovascular risk evaluation in diabetic patients (12).

Reduced LVEF was identified as the most significant predictor of MACCE in both cohorts, underscoring the vital role of left ventricular function in assessing outcomes following NSTEMI. This conclusion aligns with prior studies that have recognized LVEF as a critical prognostic indicator in ACS patients (13). Left ventricular ejection fraction (LVEF) proved to be a significant predictor of major adverse cardiovascular and cerebrovascular events (MACCE) in our study. The significant correlation between low LVEF and MACCE in our study underscores the necessity for regular echocardiographic evaluation in NSTEMI patients with diabetes and indicates that those with diminished LVEF may require more rigorous monitoring and treatment. Our findings highlight the necessity of evaluating and monitoring cardiac function in diabetic NSTEMI patients.

Our study reveals a significant protective benefit of revascularization, especially in patients with recently diagnosed diabetes mellitus. This indicates that early invasive intervention may be particularly advantageous for this population, potentially by alleviating the immediate impacts of hyperglycemia on the ischemic myocardium. The ideal revascularization technique for diabetic patients with NSTEMI continues to be an area of active investigation (14). The correlation between insufficient revascularization and elevated MACCE rates in our study corroborates existing guidelines advocating for an early invasive approach for high-risk NSTEMI patients. A recent network meta-analysis conducted by Jobs et al. (2021) shown that an early invasive technique diminished the incidence of myocardial infarction and recurrent ischemia in NSTEMI patients. Our findings indicate that this advantage may be especially significant for diabetic people (15).

The correlation between increased hs-Troponin I levels and MACCE in individuals with a history of diabetes mellitus, but not in those with newly diagnosed diabetes, is noteworthy. Elevated levels of hs-Troponin I correlated with MACCE in individuals with a prior diagnosis of diabetes, underscoring the predictive significance of this biomarker. Our findings indicate that hs-Troponin I may be especially beneficial for risk stratification in diabetic NSTEMI patients. This may indicate more extensive underlying coronary artery disease or increased

myocardial susceptibility in persons with chronic diabetes. It also indicates that hs-Troponin I may possess varying prognostic consequences contingent upon diabetes status and duration.

Despite elevated glycemic indices (HbA1c, fasting, and random plasma glucose) in individuals with a history of diabetes mellitus, their lack of substantial correlation with major adverse cardiovascular and cerebrovascular events in our study is unexpectedly noteworthy. This may be attributable to the limited follow-up duration or the significant influence of other risk variables such as LVEF. Nonetheless, it highlights the intricate link between glycemic regulation and cardiovascular results in the context of acute coronary incidents.

Our study has several limitations that should be considered when interpreting the results. Being a single-center study conducted at a tertiary care hospital limits the generalizability of our findings to other populations or healthcare settings. Additionally, the retrospective design of this study introduces potential biases, particularly in data collection and patient selection. The relatively small sample size of 129 patients may have limited the detection of significant differences in subgroup analyses, while the short-term follow-up period of six months may not provide insights into the long-term impact of diabetes on NSTEMI outcomes. Furthermore, we did not have detailed information on the type and quality of diabetes management prior to the NSTEMI event, which could influence patient outcomes. The lack of standardization in revascularization approaches introduces variability in the results, and limited data on other comorbidities, despite adjusting for several risk factors, could also affect our findings.

Prospective, multicenter studies across multiple centers are necessary to provide more robust evidence and improve generalizability. Longer-term follow-up periods, extending to five to ten years, would offer more comprehensive insights into the long-term impact of diabetes on cardiovascular outcomes after NSTEMI. Research focusing on different diabetes management strategies, such as intensive versus standard glycemic control, could inform clinical practice, while randomized controlled trials comparing different revascularization strategies specifically in diabetic NSTEMI patients could help optimize management approaches. The investigation of novel biomarkers or combinations of existing ones for risk stratification in diabetic NSTEMI patients could improve prognostication. Additionally, basic and translational research to elucidate the pathophysiological mechanisms underlying the increased cardiovascular risk in long-standing diabetes could identify new therapeutic targets. Future studies exploring genetic or metabolomic profiles to predict MACCE risk in diabetic NSTEMI patients may pave the way for individualized treatment strategies. Lastly, cost-

effectiveness analyses of different management strategies for diabetic NSTEMI patients would be valuable for informing healthcare policy and resource allocation.

4. Conclusion

NSTEMI patients with Type 2 diabetes who have a prior diagnosis of diabetes face a markedly elevated risk of MACCE, especially heart failure. Reduced LVEF, absence of revascularization, and increased hs-Troponin I are significant risk factors for negative outcomes. The findings underscore significant implications for NSTEMI care in diabetic patients, highlighting the necessity for rigorous risk factor control, timely revascularization where indicated, and vigilant monitoring of cardiac function. Future prospective studies with bigger sample numbers and extended follow-up durations are necessary to clarify the intricate relationship between diabetes status, diverse risk variables, and cardiovascular outcomes in NSTEMI patients. This research may facilitate the creation of enhanced risk classification instruments and individualized management strategies for this high-risk demographic.

5. Acknowledgements

We extend our gratitude to the personnel of the Cardiology Department of Dr. Wahidin Sudirohusodo Hospital for their support in data collecting and management.

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