Original Article

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Biochemistry Section

Glycated Haemoglobin and TIMI Score as Risk Predictor in Patients with Acute Myocardial Infarction: A Cross-sectional Study

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ABSTRACT

Introduction: Cardiovascular Disease (CVD) is the leading cause of death and disability globally. The Thrombolysis in Myocardial Infarction (TIMI) score is calculated to assess the risk outcome among myocardial infarction patients. Researchers found that diabetic patients with myocardial infarction have relatively unfavourable outcomes when compared to myocardial infarction patients without diabetes.

Aim: To evaluate Glycated Haemoglobin (HbA1c) levels, the TIMI score in Acute Myocardial Infarction (AMI) patients and compare them between ST Elevation Myocardial Infarction (STEMI) and non STEMI (NSTEMI) patients.

Materials and Methods: This cross-sectional study was conducted at the Intensive Care Unit (ICU) of the Department of Cardiology at SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India, from July 2022 to June 2023. A total of 100 myocardial infarction patients were included and divided into two groups based on Electrocardiogram (ECG) findings and Creatine Phosphokinase-MB (CK-MB) values, with 50 STEMI and 50 NSTEMI. Patients blood samples were evaluated for HbA1c, total cholesterol, Triglycerides (TGL), High-density Lipoprotein Cholesterol (HDL-C), Low-density Lipoprotein Cholesterol (LDL-C), Very High-density Lipoprotein Cholesterol (VLDL-C), and CK-MB parameters. The TIMI score was calculated to evaluate the risk of developing complications among myocardial infarction patients. Pearson's correlation was used to correlate biochemical parameters with the TIMI score.

Results: A total of 100 myocardial infarction patients were analysed in the present study, with 50 being STEMI (mean HbA1c%: 8.0±0.2.8) and 50 being NSTEMI (mean HbA1c%: 7.2±2.0) with a p-value of <0.01*, a high TIMI score in STEMI patients (means 5.38±2.76) and 50 NSTEMI (mean 3.24±1.20) with a p-value of <0.0001*. Also, HbA1c was strongly positively correlated with the TIMI score in both the STEMI and NSTEMI groups, with r-value of 0.6 (p=0.0001*) and 0.7 (p=0.0001*), respectively. CK-MB was correlated with the TIMI score in both STEMI and NSTEMI, with r-value of 0.308 (0.03) and 0.375 (0.007). There was no correlation between the TIMI score and the lipid profile.

Conclusion: The study concluded that HbA1c, along with the TIMI score, is a significant predictor of risk outcome in AMI patients.

Keywords: Creatine Kinase-MB, Electrocardiogram, Lipid profile, Thrombolysis in myocardial infarction score

INTRODUCTION

The CVD is one of the leading causes of disease burden and deaths globally [1]. Coronary artery disease is a major cause of CVD and disability-adjusted life years, as well as one of the most typical causes of death in both industrialised and underdeveloped nations [2], with India recording the highest prevalence of CVD [3,4]. Developed countries like the United States of America (USA) and the United Kingdom (UK) recorded 151 in 100,000 and 122 in 100,000, respectively, according to the global burden of disease reports [5,6]. The global average for age-standardised CVD is 133 in 100,000, with India recording 282 in 100,000 in 2017, contributing to 24% of total deaths [6,7].

In India, Punjab, Tamil Nadu, and Kerala states record a high number of CVD and also have a high prevalence of blood pressure and cholesterol levels [8]. Early identification and management of risk factors are crucial [9,10]. Numerous specific factors have been discovered by studies as indicators of increased risk for death and heart ischaemic episodes [11-13]. Elements of the medical history, such as old age of 65 years and above, diabetes mellitus, and extra-cardiac atherosclerotic disease, are linked to increased chances of death or repeated ischaemic episodes [14].

Early risk assessment can help determine the prognosis of individuals with non ST elevation acute coronary syndrome. Several risk scores have been established to help predict outcomes in patients with acute coronary syndrome [15-17]. NSTEMI is often calculated using the TIMI risk score grading system, which employs a 7-point scale. The TIMI STEMI risk score ranges from 0 to 14 points. STEMI accounts for the smallest proportion of acute coronary syndromes, but it has the most severe consequences. The most beneficial medical results are obtained with the primary Percutaneous Coronary Intervention (PCI) approach [18,19]. Glycated haemoglobin is defined as a non enzymatic addition of glucose to the N-terminal of the valine of the beta chain of haemoglobin, and it is used for the diagnosis of diabetes and as an index for long-term control of blood glucose levels. Patients with diabetes have an increased chance of developing CVD and less favourable outcomes compared to people without diabetes [20].

Ambiguity in the optimum cut-off values for blood sugar in AMI individuals for predicting adverse events might vary within STEMI and NSTEMI patients, and the diabetic status of patients needs to be considered in order to prevent an erroneous assessment of the true incidence of stress-induced hyperglycaemia [21]. A number of studies have demonstrated that poor glycaemic control among those with Type 2 Diabetes Mellitus (T2DM) correlates with an increased risk of coronary heart disease [22-25]. The TIMI risk score is utilised in clinical research studies to identify a population

with greater event rates by excluding patients with low-risk scores [26,27]. Hence, the present study was conducted to evaluate HbA1c levels, TIMI score in AMI patients, and compare them between STEMI and NSTEMI patients.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted in the ICU Department of Cardiology at SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India, from July 2022 to June 2023. The study protocol was followed in accordance with the approval of the Institutional Ethics Committee (SRM IEC-ST0722-08), and informed written consent was obtained from all subjects.

Inclusion criteria: Patients aged between 31 to 80 years, with symptoms of Anaemia of Chronic Disease (ACD) such as chest pain, referred pain radiating to the epigastrium, arm, neck, and jaw with a confirmed diagnosis by definite (ECG) changes and elevated CK-MB (>24 IU/L) were included [28].

Exclusion criteria: Patients having chest pain with normal ECG and normal cardiac markers, chronic renal failure patients, a history of any other cardiac illness, pregnant patients, and chronic inflammatory conditions like rheumatoid arthritis were excluded.

Sample size calculation: Krishnan MN et al., calculated the prevalence (p) of ACS by age-adjusted prevalence of various parameters among Coronary Artery Disease (CAD) patients [4]. Using RAQ angina p (%) was 49.69 and was rounded to the nearest whole number, hence p=50. The formula used for sample size calculation was $n=4pq/d^2$, where q=100-p, and d=0.2*p, and the sample size calculated was n=100.

Study Procedure

All subjects were subjected to a detailed history as per the prepared proforma and relevant investigations. After obtaining informed and written consent, these include age, gender, TIMI score risk factors, and biochemical parameters. Blood samples were taken from the ward by specialised nurses in the Cardiology Department, and biochemical analysis was performed in the central laboratory's Department of Biochemistry at SRM Medical College Hospital and Research Centre. A 5 mL peripheral venous blood sample was collected from all the participants under strict aseptic precautions in appropriate vacutainers, and samples were centrifuged at 4500 rpm for seven minutes, and the serum/plasma was separated.

Biochemical parameters: The samples were subjected to biochemical investigations using the automated chemistry analyser Beckman Coulter AU480 for measurements of total cholesterol, TGL, HDL-C, LDL-C [12], CK-MB [29], and HbA1c [30]. VLDL Cholesterol cannot be measured directly; hence, it was computed using the Friedewald equation by TGL/5 cut-off value (<40 mg/dL) [Table/Fig-1] [12].

Risk stratification: The STEMI TIMI risk score is calculated by assessing the following parameters with the following points: ages ≥75 years are given 3 points, and ages ranging between 65 to 74 years are given 2 points, systolic blood pressure <100 mmHg is 3 points, heart rate >100 bpm and Killip's class II-IV 2 points each, anterior MI or LBB, weight <67, Time to treatment >4 hours are given 1 point each, and diabetes, history of hypertension, and prior angina all with 1 point each [18,19]. While the NSTEMI TIMI score has seven variables, one point each: age >65 years, ≥3 CAD risk factors known CAD (stenosis ≥50%), aspirin use in the past seven days, severe angina ≥2 episodes in 24 hours ECG ST changes ≥0.5 mm and positive cardiac marker [Table/Fig-2] [17,18].

STATISTICAL ANALYSIS

The data were analysed using the Statistical Package of Social Sciences (SPSS 22.0). Student's t-test was applied to analyse the difference between the mean levels of various parameters between the two groups. The correlation between the measured variables was assessed using the Spearman's correlation equation. The distribution of myocardial infarction based on biochemical risk factors and TIMI score was calculated. A p-value of <0.05 was considered statistically significant. Due to a wide range of CK-MB data, the median and interquartile range were calculated for the CK-MB values.

Biochemical Parameters	Method of estimation	Instruments	Cut-off range
Total Cholesterol	Cholesterol Oxidase Method	Beckman Coulter AU 480 autoanalyser	150-200 mg/dL desirable 200-239 mg/dl borderline ≥240mg/dL high risk
Triglyceride (TGL)	Enzymatic-glycerol Oxidase-peroxidase method	Beckman Coulter AU 480 autoanalyser	Upto150 mg/dL desirable 150-199 mg/dl borderline 200-499 mg/dL high >499 mg/dL very high
HDL-C	Direct antibody inhibition	Beckman Coulter AU 480 autoanalyser	40-60 mg/dL. >40 mg/dL for male >50 mg/dL for female <35 mg/dL high risk
LDL-C	Direct antibody inhibition	Beckman Coulter AU 480 autoanalyser	<130 mg/dL desirable 130-159 mg/dl borderline 160-189 mg/dL high ≥190 mg/dL very high
VLDL-C	Friedewald equation (TGL/5)		<40 mg/dL
CK-MB	High pressure liquid chromatography	Beckman Coulter AU 480 autoanalyser	0-24 IU/L
HbA1c	High pressure liquid chromatography	D-10 BIO-RAD	4.5-6.0% <5.7% normal 5.7-6.4% prediabetic ≥6.5% diabetic

[Table/Fig-1]: Instruments and methods for estimating biochemical parameters.

Parameters	TIMI score	
	STEMI	NSTEMI
Age >75 years	3	
Age 65-74 years	2	-
Systolic blood pressure <100 mmHg	3	-
Heart rate >100 bpm	2	-
Killip's class II-IV	2	-
Anterior MI or Left Bundle Branch (LBBB) block	1	-
Weight <67 kg	1	-
Time for treatment >4 hours	1	-
Diabetes, hypertension, prior angina	1	-
Age >65 years	-	1
≥3 risk factors for CAD	-	1
Use of ASA (last 7 days)	-	1
Known CAD (prior stenosis ≥50%)	-	1
>1 episode rest angina in <24 hours	-	1
ST-segment deviation	-	1
Elevated cardiac markers	-	1

[Table/Fig-2]: TIMI score risk stratification for STEMI and NSTEMI patients [17,18]. ASA:Acetylsalicylic Acid

RESULTS

The study was conducted on 100 myocardial infarction patients who were divided into two groups based on ECG findings: STEMI and NSTEMI. Each group included 50 participants aged between 30 and 80. It was found that the mean age of STEMI and NSTEMI patients was 58±11 and 60±12 years, respectively, and the p-value was not significant. Patients aged over 50 years had a higher chance of developing an AMI. Among the 50 STEMI patients, 31 (62%) were male and 19 (38%) were female, while among the 50 NSTEMI patients, 32 (64%) were male and 18 (36%) were female [Table/Fig-3].

Variables	STEMI n=50	NSTEMI n=50	p-value
Age (years) mean±SD	58±11	60±12	0.549
Age-wise distribution			
30-44	3	4	
45-64	33	29	
65-74	5	10	
≥75	9	7	0.0001*
Distribution of subject based on gender-wise			
Male	31 (62%)	32 (64%)	
Female	19 (38%)	18 (36%)	0.0001*

[Table/Fig-3]: Age and gender-wise distribution for STEMI and NSTEMI patients.
Comparison of variables by Students t-test.

Among the 50 STEMI patients, 29 (58%) were diabetic, 15 (30%) were hypertensive, 10 (20%) had a heart rate >100, 7 (14%) were in Killip's class II-IV, 20 (40%) had a weight <67 kg, 10 (20%) had severe angina, and all patients were treated for >4 hours. Among the 50 NSTEMI patients, 10 (20%) had ≥3 risk factors for CAD, 22 (44%) had used aspirin in the past 7 days, 20 (40%) had prior stenosis ≥50, 38 (76%) had severe angina, 23 (46%) had segment deviation, and 33 (66%) had elevated cardiac markers. The number of patients aged ≥65 years was 18 (36%) and 14 (28%) in NSTEMI and STEMI, respectively [Table/Fig-4].

Variable characteristics	STEMI TIMI risk score (n=50)	Variable characteristics	NSTEMI TIMI risk score (n=50)
Age ≥75 years or	9 (18%)	Age ≥75 or	7 (14%)
Age 65-74 years	5 (10%)	65-74 years	11 (22%)
Systolic blood pressure <100 mmHg	17 (34%)	≥3 risk factors for CAD	10 (20%)
Heart rate >100 bpm	10 (20%)	Use of ASA (last 7 days).	22 (44%)
Killip's class II-IV	7 (14%)	Known CAD (prior stenosis ≥50%)	20 (40%)
Anterior MI or LBB	50 (100%)	>1episode rest angina in <24 hours	38 (78%)
Weight <67 kg	20 (40%)	ST-segment deviation	23 (46%)
Time for treatment >4 hours	50 (100%)	Elevated cardiac markers	33 (66%)
Diabetes,	29 (58%)		
Hypertension	15 (30%)		
Prior angina	10 (20%)		

[Table/Fig-4]: Distribution of subjects based on TIMI Score risk factors for STEMI and NSTEMI patients.

Biochemical parameters: The mean values of TIMI score, HbA1c, CK-MB, Total Cholesterol, TGL, HDL-C, LDL-C, and VLDL-C were compared between the STEMI and NSTEMI patients. It was found that the mean values of TIMI score, CK-MB, and HbA1c were significantly elevated in STEMI patients when compared to the NSTEMI patients. CK-MB values were widely ranged, hence the median and interquartile range were calculated for the CK-MB values. Lipid profile levels were also found to be elevated in STEMI patients when compared to the NSTEMI patients but were not statistically significant [Table/Fig-5].

Correlation of biochemical parameters: In STEMI and NSTEMI patients, HbA1c levels were strongly positively correlated with r values of 0.6 (p=0.0001*) and 0.7 (p=0.0001*), and CK-MB was significantly correlated with r values of 0.308 (p-value 0.03*) and 0.375 (p-value=0.007*), respectively. Lipid profiles were not significantly correlated and HDL-C was negatively correlated [Table/Fig-6-8].

DISCUSSION

The study involved 100 myocardial infarction patients who were grouped into two categories based on ECG findings: STEMI and NSTEMI. Both groups comprised 50 participants ranging in age from 31 to 80 years. The mean ages for the STEMI and NSTEMI groups were 58 and 60 years, respectively. The data indicated that patients aged over 50 years had a higher chance of developing MI.

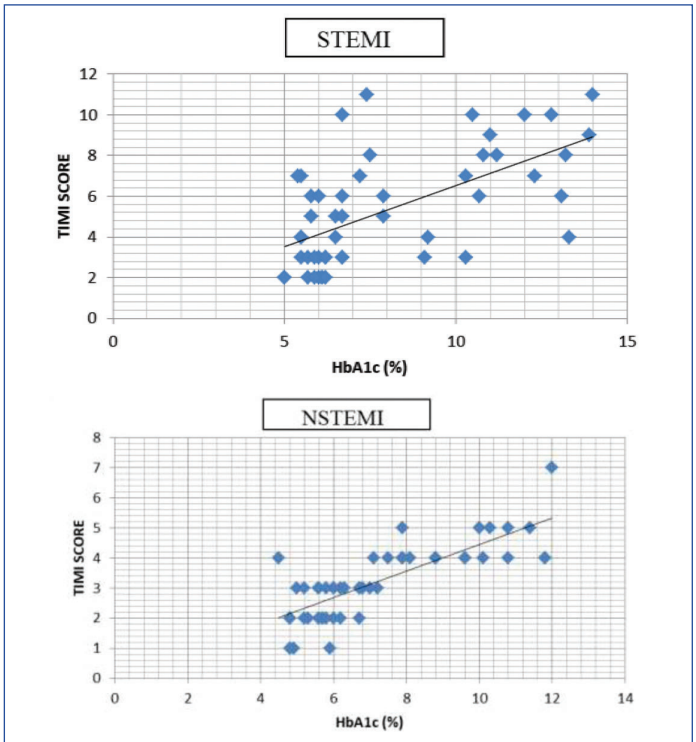
According to Raina K et al., the majority of AMI patients were in the 41 to 70-year-old age range [2]. Among 100 MI patients, 62% of STEMI and 64% of NSTEMI cases were male, while 38% of STEMI and 36% of NSTEMI cases were female. As demonstrated by Channamma G males are at a higher risk than females, as evidenced by the fact that there were 92.5% more men than women in the overall population [31]. The prevalence of various risk factors in the

Variables	STEMI n=50 Mean±SD	NSTEMI n=50 Mean±SD	p-value
HbA1c (%)	8.0±2.8	7.2±2.0	0.01*
TIMI score	5.38±2.76	3.24±1.20	0.0001*
CK-MB (IU/L)	Median (IQR=3rd-1st quartile) 68 (186-84=102)	Median (IQR=3rd-1st quartile) 33 (143-77=66)	0.001*
Total cholesterol (mg/dL)	180.22±42.93	167.76±57.92	0.249
Triglycerides (TGL) (mg/dL)	141±81.46	121±64.64	0.206
HDL-C (mg/dL)	44±10.69	42.52±10.60	0.440
LDL-C (mg/dL)	132.2±36.49	118±48.77	0.092
VLDL-C (mg/dL)	28±16.40	24.76±13.12	0.299

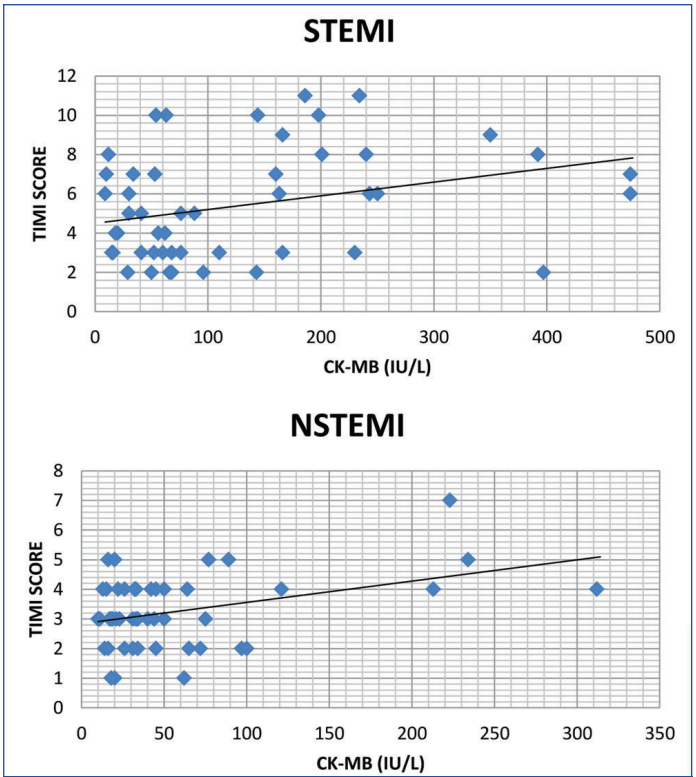
[Table/Fig-5]: Comparison of various biochemical parameters in STEMI and NSTEMI patients by Student's t-test.
Comparison of biochemical parameters by Student's t-test.

Variables	STEMI (TIMI score) r value (p-value)	NSTEMI (TIMI score) r value (p-value)
HbA1c (%)	0.6 (0.0001*)	0.7 (0.0001*)
CK-MB (IU/L)	0.308 (0.030*)	0.375 (0.007*)
Total cholesterol (mg/dL)	0.163 (0.260)	0.043 (0.767)
Triglyceride (TGL) (mg/dL)	0.130 (0.367)	0.129 (0.373)
HDL-C (mg/dL)	-0.067 (0.643)	-0.064 (0.659)
LDL-C (mg/dL)	0.102 (0.480)	0.004 (0.977)
VLDL-C (mg/dL)	0.162 (0.262)	0.119 (0.412)

[Table/Fig-6]: Correlation of HbA1c values with TIMI scores in both groups.



[Table/Fig-7]: Scattered plot correlating the HbA1c (%) levels with TIMI scores in STEMI and NSTEMI patients.



[Table/Fig-8]: Scattered plot correlating the CK-MB (IU/L) levels with TIMI scores in STEMI and NSTEMI patients.

present study was similar to the findings of a recent large-scale study from Kerala by Thankappan KR et al., [32].

The mean values of TIMI score, CK-MB, HbA1c, total cholesterol, TGL, HDL-C, LDL-C, and VLDL-C were compared between the STEMI and NSTEMI patients using a student's t-test. When STEMI patients were compared to NSTEMI patients, the mean values of these parameters were significantly higher in STEMI patients. As cited by Santos ES et al., early coronary intervention has consistently been shown to improve clinical outcomes in high-risk patients, making risk assessment crucial [33]. This may also provide clinicians with more diagnostic evidence, thereby reducing the fatality rate of AMI in the early stages [34]. The conventional atherogenic lipoprotein LDL-C and the inflammatory marker have been extensively studied in relation to the development and prediction of adverse cardiac events in T2DM patients [34].

Ali F et al., demonstrated significantly higher concentrations of cardiac markers in diabetic patients with AMI compared to non diabetic subjects with AMI [35]. Identifying individuals with cardiovascular risk factors and providing evidence-based care for them can minimise the morbidity and mortality [36]. In STEMI and NSTEMI patients, HbA1c levels were strongly positively correlated with the TIMI score, with r values of 0.6 (p=0.0001*) and 0.7 (p=0.0001*), respectively. Therefore, increases in HbA1c levels are associated with increased TIMI scores among STEMI and NSTEMI patients. Selvin E et al., conducted a 14-year monitoring study which revealed that, compared to fasting glucose in the non-diabetic population, HbA1c values are associated with the risk of diabetes and, to a greater extent, with the risks of CHD and mortality [37].

The impact of high blood glucose on the long-term outcome of AMI can be categorised into several processes and holds distinct relevance when contrasted with HbA1c. Numerous investigations have demonstrated that high glucose more strongly indicates the acute phase of diseases, whereas HbA1c depicts long-term metabolic issues. Timmer JR et al., as cited, indicated that the acute and short-term outcomes of AMI in non diabetic patients, such as the extent of the myocardial infarct and death within thirty days, are more closely related to admission levels of glucose than HbA1c [38]. As cited by Stratton IM et al., a one percent decrease in the revised mean HbA1c was linked to risk decreases of 21% for any endpoint associated with diabetic complications (95% CI: 17% to 24%, p<0.0001), 21% for diabetes-associated mortality (15 to 27%, p<0.0001), 14% for myocardial infarction (8% to 21%, p<0.0001), and 37% for complications of microvascular disease (33% to 41%, p<0.0001) [39]. Gillett M the International Expert Committee has proposed a threshold value of 6.5% for Glycated haemoglobin in the diagnosis of diabetes [40].

According to a study, there was a clear long-term connection between glycated haemoglobin and major adverse cardiac events [21]. According to the American Diabetes Association, individuals with HbA1c levels ranging from 5.7% to 6.4% could be classified as prediabetic, with a higher risk of diabetes and cardiovascular death [41]. Inoue K et al., highlighted that, in accordance with clinical recommendations, HbA1c is being measured more regularly. There is an urgent need to address the long-debated subject of the potential impact of comparatively low HbA1c levels on health, as there may be an increase in the likelihood that practitioners will recognise individuals with low HbA1c values [42-45]. Similar and contrasting scientific research studies are tabulated [Table/Fig-9] [15,17,20-22,25,35,37,39,42,45].

S. no.	Author's name	Place and year of the study	Sample size	Findings
1	Alexander T et al., [15]	Tamil Nadu, 2021	2420	Younger STEMI patients experienced shorter ischaemic times, lower fatality rates, and lower prevalence of conventional risk factors than older STEMI patients. Compared to young male STEMI patients, the mortality rate for female STEMI patients was greater.
2	Bashiruddin, A et al., [17]	Chattogram, 2019	200	Study showed the TIMI score is significantly correlated with the extent of CAD as assessed by the Gensini score. It is accurate for predicting severe CAD among Non ST elevation-acute coronary syndrome (NSTE-ACS) patients.
3	Chen CL et al., [20]	Taipei, 2017	341	HbA1c may be considered an effective indicator that facilitates the early detection of patients with potential adverse prognosis after non fatal MI
4	Sia CH et al., [21]	Singapore, 2021	9946	Shared Health Records (SHR) was the most consistent independent predictor of 1-year all-cause mortality in both diabetic and non-diabetic STEMI, whereas glucose was the best predictor in NSTEMI patients.
5	Celik M et al., [22]	Ankara, 2019	140	The present study showed that there is no relation between admission HbA1c levels and pre-Primary Percutaneous Coronary Intervention (PPCI) myocardial perfusion in patients with STEMI
6	Berry C et al., [25]	Boston 2010	426	Glycaemic status and measures of glycaemic control in a population of non-diabetic and diabetic participants are associated with the severity and progression of coronary atherosclerosis.
6	Ali F et al., [35]	Lahore, 2016	450	Study suggests elevated cardiac markers and reduced antioxidants in D-Acute Myocardial Infarction (AMI) patients compared to N-Acute Myocardial Infarction (AMI) patients.
7	Selvin E et al., [37]	USA, 2010	14,348	Glycated haemoglobin was similarly associated with a risk of diabetes and more strongly associated with risks of Cardiovascular Disease (CVD) and death from any cause as compared with fasting glucose.

8	Stratton IM et al., [39]	England, Scotland, and Northern Ireland. 2000	4585	Any reduction in HbA1c is likely to reduce the risk of complications, with the lowest risk being in those with HbA1c values in the normal range (<6.0%).
9	Inoue K et al., [42]	USA, 2021	39453	Using the US national database and adjusting for an extensive set of potential confounders with flexible modelling, authors found that adults with low HbA1c were at increased risk of all-cause mortality
10	Goto A et al., [45]	2013	3443	The present study findings suggest that severe hypoglycaemia is associated with a higher risk of CVD;
11.	Present study			HbA1c, along with the TIMI score, is a significant predictor of outcome in AMI patients. Evaluation of the TIMI score with HbA1c may strengthen clinical care.

[Table/Fig-9]: Review of the literature of both similar and contrasting articles [15,17,20-22,25,35,37,39,42,45].

Limitation(s)

The study was not prospective, but rather cross-sectional. The TIMI risk score for STEMI and NSTEMI is designed for early risk assessment after patient presentation and therefore doesn't include non invasive and invasive data. Consequently, the outcomes of the hospital patients' study were not tracked. The present study may not be sufficient to establish broader applicability.

CONCLUSION(S)

The study concludes that the TIMI score, along with HbA1c, should be considered as aids in the early prediction of MI patients at higher risk of developing complications. Among MI patients, risk factors such as hypertension, diabetes, and a family history of myocardial infarction were more common in STEMI compared to NSTEMI. Additionally, lipid profile values were higher in STEMI patients compared to NSTEMI patients. The level of the CK-MB biomarker was significantly higher among STEMI patients compared to NSTEMI patients. STEMI patients are at a higher risk of developing complications compared to NSTEMI patients. Therefore, HbA1c, along with the TIMI score, is a significant predictor of outcomes in AMI patients. Evaluation of the TIMI score with HbA1c may enhance clinical care.

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