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Original Research Article

A Retrospective Cohort Study of the Short- and Long-Term Prognosis of Admission Hyperglycemia in Patients with and without Diabetes after an Acute Myocardial Infarction

Ahraz Ali Imam[1], Shubham Bhaskar[2], Vikram Aditya[3], Ajay Kumar Sinha[4]

[1]Senior Resident, Nalanda Medical College and Hospital, Patna, Bihar, India
[2]Senior Resident, Nalanda Medical College and Hospital, Patna, Bihar, India
[3]Senior Resident, Nalanda Medical College and Hospital, Patna, Bihar, India
[4]Associate Professor, Nalanda Medical College and Hospital, Patna, Bihar, India

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Corresponding author: Dr. Ajay Kumar Sinha
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Abstract

Objective: Acute myocardial infarction (AMI) patients with admission hyperglycemia had a worse prognosis; however, the effects of baseline diabetes status on this connection are yet unknown. The goal was to examine how admission hyperglycemia affected both short- and long-term outcomes in AMI patients with and without diabetes.

Method: 300 individuals who experienced their first AMI between March 2022 and February 2023 at Nalanda Medical College and Hospital, Patna were identified in this retrospective cohort analysis. 150 patients with diabetes and 150 patients without diabetes were separated into two groups among the participants. Following that, they were split into four groups based on a cut of fasting blood glucose (FBG) levels that was specific to a person's diabetes status and was identified via a limited cubic spline. Cardiac problems and in-hospital death were among the short-term results. All-cause mortality and serious adverse cardiovascular events were the long-term results (MACE). To account for baseline differences between the groups, inverse probability of treatment weighting (IPTW) was used. This was followed by a weighted Cox proportional hazards regression analysis to determine the hazard ratios and 95% confidence intervals for all-cause mortality associated with each FBG category. To assess the robustness of the findings, subgroup analysis, and sensitivity analysis were carried out.

Results: 113 patients passed away over a median follow-up of 1.2 years. During long-term follow-up, there was a significant ($p < 0.002$) interaction between diabetes status and FBG levels for all-cause mortality. Furthermore, among patients with diabetes, restricted cubic spline curves for the relationship between FBG and all-cause mortality had a J shape, while in patients without diabetes, they had a non-linear form. In both the diabetic and non-diabetic patient groups, the Kaplan-Meier analysis showed that non-hyperglycemic patients had a higher survival rate than hyperglycemic patients. Those with hyperglycemia who do not have diabetes have a higher survival rate than those who do. Admission hyperglycemia predicted increased short- and long-term mortality in the weighted Multivariable Cox analysis. The robustness of the findings was demonstrated by subgroup analysis and sensitivity analysis.

Conclusion: For patients without diabetes and those with diabetes, the infection points of FBG level indicating a bad prognosis were 5.50 mmol/L and 10.50 mmol/L, respectively. Hyperglycemia during admission was identified as an independent predictor.

Keywords: Hyperglycemia, Diabetes, Non-Diabetes, Myocardial infraction.

Introduction

Patients with AMI frequently experience hyperglycemia during hospitalisation, and this condition is independently linked to a worse prognosis [Figure 1; 1], though the relationship may not be linear [2] and there is conflicting evidence regarding whether it varies according to a patient's diabetes status [3]. Depending on how entry hyperglycemia is defined, 25–50% of patients experience this condition [4]. There is considerable disagreement over the blood glucose level that defines entrance into hyperglycemia. Diabetes is a well-known comorbidity among patients with cardiovascular disorders [5]. Compared to patients without diabetes, individuals with AMI have a risk of short- and long-term mortality that is more than twice as high [6].

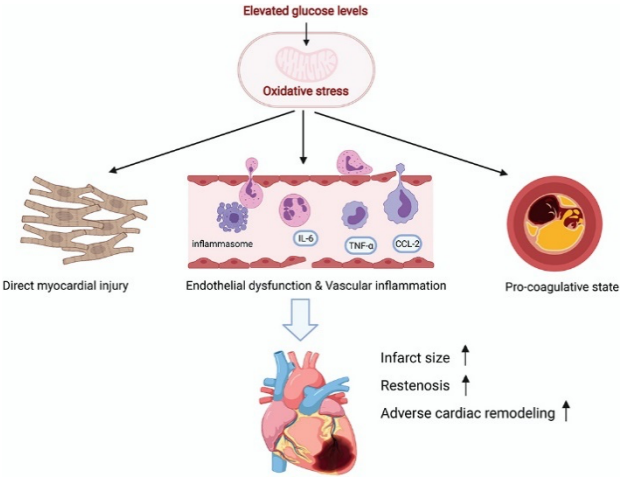

Figure 1: Association of Hyperglycemia with AMI

By utilizing the same predictive cutoff value for both diabetic and non-diabetic patients, prior investigations revealed a greater connection between a diagnosis of clinical diabetes and incident mortality in hyperglycemia patients than in non-hyperglycemia individuals without diabetes [1]. Although inequalities in the incidence of uncontrolled blood glucose and mortality are a possibility, the causes of such diabetes status-based differences are unclear. Also, there is a dearth of information regarding how diabetes status affects the prognostic significance of blood glucose levels for defining admission hyperglycemia.

Recent studies showed that admission hyperglycemia was an independent predictor of mortality in AMI patients without diabetes when used the same or different cutoff values for diabetic and non-diabetic patients, despite the fact that the relationship between admission hyperglycemia and mortality by diabetes status is less well understood [7]. There is a lack of information on how diabetes status affects the absolute mortality risk linked to admission hyperglycemia. Therefore, it is imperative to include the diabetes state of patients to prevent inaccurate calculation of the true prevalence of admission hyperglycemia.

The ideal cutoff values of FBG separately for diabetic and non-diabetic patients have not been used in studies evaluating diabetes status-based differences in mortality risk associated with admission hyperglycemia, nor have they shown whether differences in

mortality risk persist across different levels of FBG. To determine the value of FBG cutoff values in predicting the short- and long-term prognosis of patients with AMI, we examined the severity of hyperglycemia by diabetes status subgroups, differences in the risk of incident mortality across increasing levels of FBG between diabetes status subgroups, and FBG cutoff values in patients with and without diabetes.

Methods

Study Design: Patients who were referred to the chest pain center at Nalanda Medical College and Hospital, Patna for their first AMI between March 2022 and February 2023 were included in this retrospective, population-based cohort analysis.

Methodology: During the analysis of electrical medical records, baseline demographic and clinical data were gathered. Age, gender, body mass index (BMI), and ethnicity were included in the demographic information. Smoking and drinking patterns, as well as cardiovascular disease in the family. Diagnosis, medical history, laboratory test findings, medications taken upon discharge, and clinical therapy made up the clinical data. The FBG levels were evaluated 24 hours after admission. Pre-existing diabetes mellitus was defined as a history of diabetes that was known to have occurred at the time of admission and was managed either only by dietary and lifestyle changes or in conjunction with the use of oral glucose-lowering drugs and insulin. On the basis of the oral glucose tolerance test, the fasting glucose test, or the glycated hemoglobin level of 6.5% while hospitalized, newly diagnosed diabetes was determined. Individuals with HbA1c 6.5% mmol/mol and no prior history of diabetes were deemed to be free of the disease. For the first 23 hours, patients with pre-existing diabetes mellitus and admission glucose levels of more than 10 mmol/L received insulin-glucose infusions to lower blood glucose levels between 6 and 14 mmol/L, followed by subcutaneous insulin injections. Patients with newly discovered diabetes and those without the disease did not receive therapy to reduce blood sugar for the first 25 hours. For non-diabetic patients, hyperglycemia was defined as FBG levels of 5.5 mmol/L or 10.5 mmol/L.

Sample Size: 300 patients who met the inclusion criteria were eligible for this study.

Exclusion criteria: Myocardial infarction in the past, malignancies, severe valvular heart disease, severe renal failure, or missing vital laboratory data (FBG on admission or glycated hemoglobin [HbA1c]).

Statistical analysis: Descriptive statistics were used to summarize the baseline characteristics of the patients by categorical FBG level (where appropriate, frequencies with proportions or means with SDs). The Kruskal-Wallis test for continuous variables and the chi-square test for categorical data were used to compare demographic and clinical characteristics. The Multivariate Imputation by Chained Equations (MICE) library in Python was used to impute missing data at baseline using random forest imputations. The reverse Kaplan-Meier method was used to estimate the median follow-up time. Using FBG as a categorical variable (to account for the glycemic threshold) and then as a restricted cubic spline, to investigate a potential nonlinear relationship between FBG and mortality, Cox proportional hazard models were used to evaluate the correlation between FBG and mortality.

Ethical Consideration: The study was approved by the ethical committee of Nalanda Medical College and Hospital, Patna after written consent was obtained from the subjects.

Results

The study enrolled 300 individuals with AMI for the first time in total. The participants' average age was 56.2 years (SD 12.2), 77% of them were men, and 32% of them had diabetes. Of the patients, 32% were classified as having neither non-hyperglycemia nor hyperglycemia without diabetes, 34% as having neither, 18% as having neither non-hyperglycemia nor hyperglycemia with diabetes, and 12%) as having both.

Across groups, the patient features were contrasted according to FBG level (**Table 1**). Patients with hyperglycemia tended to have higher heart rates, Killip classes, procalcitonin, c-reactive protein, triglycerides, HDL cholesterol, LDL cholesterol, apolipoprotein A, and peak hs Troponin I, whether they had diabetes or not. Total cholesterol was lower in hyperglycemia patients among non-diabetic patients while it was greater in diabetic patients. More uric acid and a higher incidence of STEMI were seen in non-diabetic patients with hyperglycemia, although no statistically significant differences were seen in diabetic patients.

Table 1: Baseline Characteristics of Patients

Characteristics	Patients without Diabetes			Patients with Diabetes			P-Value
	Non-hyperglycemia	Hyperglycemia	P-Value	Non-hyperglycemia	Hyperglycemia	P-Value	
Age							
< 54	54	53	0.735	42	41	0.735	0.735
>54	46	46	0.735	58	56	0.735	0.735
BMI	25.94	20.05	0.581	26.15	26.05	0.263	0.546
Smoking status							
Never smoked	515	50%	0.497	61%	65%	0.497	0.497
Former Smoker	42%	40%	0.497	31%	25%	0.497	0.497
Current Smoker	6%	7%	0.497	7%	7%	0.497	0.497
Drinking	12%	12%	2.000	11%	11%	2.000	0.057
Killip Class							
<II	51%	37%	<0.002	34%	25%	<0.002	<0.002
>II	51%	61%	<0.002	64%	75%	<0.002	<0.002
LVEF %							
<30	9%	11%	0.192	13%	17%	0.192	0.192
>30	93	91%	0.192	86%	83%	0.192	0.192
STEMI	66%	74%	<0.002	62%	64%	0.472	<0.002
Heartrate	81	84	<0.002	83	91	<0.002	<0.002
Laboratory Values							
Procalcitoni	0.04	0.05	<0.002	0.05	0.06	0.002	<0.002
CRP	5.47	11.34	<0.002	9.93	17.83	<0.002	0.001
Total Cholesterol	3.80	4.15	0.001	3.82	4.15	0.002	<0.002
HDL cholesterol	2.45	2.75	<0.0002	2.46	2.66	0.036	<0.0002
LDL Cholesterol	0.87	0.96	<0.0002	0.85	0.88	0.001	0.356
Apolipoprotein	1.01	1.04	0.001	0.97	1.00	0.017	0.020
Peak hs Troponin	4.74	14.74	<0.0002	5.08	10.44	<0.0002	0.006

More uric acid and a higher incidence of STEMI were seen in non-diabetic patients with hyperglycemia, although no statistically significant differences were seen in diabetic patients. When comparing the two hyperglycemia subgroups, hyperglycemia patients without diabetes tended to be younger, men, former smokers, and STEMI more frequently; they were more likely to have hyperglycemia, liver disease, and lung disease less frequently; they showed lower Killip class, heart rate, procalcitonin, c-reactive protein, and triglyceride; they also had higher Left Ventricular Ejection Fraction Value, Hemoglobin,

Hospitalization resulted in 113 fatalities. In-hospital deaths and cardiogenic shock were more prevalent in patients with hyperglycemia, whether they had diabetes or not ($p<0.02$). When compared to non-hyperglycemic patients, those with hyperglycemia displayed a higher arrhythmogenic burden (atrial fibrillation and ventricular arrhythmias) during hospitalization ($p<0.02$). Diabetes patients with hyperglycemia experienced greater in-hospital deaths, heart failure, and cardiogenic shock than patients without diabetes ($p<0.02$).

Higher FBG levels were linked to higher all-cause mortality among non-diabetic individuals than among diabetics, indicating a significant interaction between diabetes status and increasing FBG levels on all-cause mortality ($p <0.002$). As a result, these analyses were divided into groups based on the presence or absence of diabetes, with FBG cutoff levels determined for each group. To determine the cutoff values for FBG levels related to all-cause mortality in patients with and without diabetes, restricted cubic spline analysis was carried out. Until about 5.50 mmol/L (100 mg/dL) of expected FBG level, the risk of all-cause death was very low and the hazard ratio was 1, but it subsequently started to rise quickly in individuals without diabetes (p for overall <0.02 and p for non-linearity <0.237).

The hazard ratio per additional standard deviation higher estimated all-cause death was 1.18 above 5.6 mmol/L. (1.08–1.30). We found a J-shaped relationship between FBG and all-cause mortality in diabetic patients; the plot revealed a significant reduction in risk within the lower range of predicted FBG level, which reached its lowest risk at 10.5 mmol/L (180 mg/dL) and then increased after that (p for overall <0.002 and p for non-linearity <0.002). The hazard ratio for increased projected all-cause death was 1.26 above 10.5 mmol/L. (1.11–1.45). In order to categories patients into four categories, we chose FBG of 5.50 mmol/L for patients without diabetes and 10.50 mmol/L for patients with diabetes as practical cutoff values.

A total of 113 fatalities and 160 MACE were reported over a follow-up duration of 1.2 years, which was the median. Incidences of MACE and all-cause mortality significantly varied among the four groups, according to Kaplan-Meier survival analysis ($p <0.002$). All-cause death was more common in non-diabetic patients with hyperglycemia ($p<0.002$). MACE occurred more frequently in patients with hyperglycemia in both diabetic and non-diabetic patients ($p=0.052$ and $p=0.017$, respectively). All-cause mortality and MACE were more frequently noted in hyperglycemia patients with diabetes when compared to the other hyperglycemic subgroups ($p <0.002$).

To determine the mortality HRs for each FBG category, IPTW Cox models were used. Hyperglycemia was a significant predictor of short-term mortality in a weighted univariable Cox model (non-diabetic patients: HR 2.25, 95% CI 1.34-3.78; diabetic patients: HR 1.71, 95% CI 1.15-2.48). (in-hospital death). Regarding the long-term outcome, hyperglycemia was

identified as an independent predictor of long-term death (non-diabetic patients: 1.22; 95% CI 1.02-1.498; diabetes patients: HR 1.21, 95% CI 1.01-1.57) (all-cause mortality). The results' significance was unaffected by further adjustments for age, gender, ethnicity, hypertension, diagnosis, Killip class, and EF or the clinical factors from the multiple Cox proportional hazard model (c-indices of the model was 0.80). The FBG and both short-term and long-term mortality showed a similar dose-response association (p for trend <0.002 for all).

The results of subgroup analyses of the risk of all-cause death based on demographic, clinical, and FBG categories were similar across all subgroups (p for interaction >0.04 for all). The risk of all-cause mortality and MACE among patients with and without diabetes exhibited comparable patterns for continuous levels of FBG, according to multivariable-adjusted limited cubic splines. After eliminating participants who passed away while hospitalized, Multivariable-adjusted limited cubic spline analysis was reapplied, and the results showed a similar shaped connection between FBG and all-cause mortality among patients with and without diabetes. The outcomes of multivariable analysis without IPTW were consistent with those of the primary analyses.

Discussion

We looked at the mortality risks associated with different diabetes states when FBG levels rose. FBG is a crucial glycemic indicator for identifying a subset of "high-risk" individuals who would likely benefit from secondary preventive medical treatment. Our results showed that the connection between FBG and all-cause mortality followed a J shape in patients with diabetes and a non-linear shape in people without diabetes when FBG was treated as a restricted cubic spline term. When FBG levels were 5.50 mmol/L for patients without diabetes and 10.50 mmol/L for those with diabetes, the mortality risk significantly increased. Our results showed that entry hyperglycemia was independently related with short- and long-term outcomes in AMI patients, regardless of diabetes status, based on FBG categories.

According to certain studies, persistent hyperglycemia is a more reliable and powerful independent risk predictor than admission blood glucose. When hyperglycemia (blood glucose 8.9 mmol/L) lasts for more than 24 hours following the onset of symptoms, it is linked to both pre-discharge left ventricular dysfunction and impaired myocardial perfusion, even while the infarct-related artery is still open [8]. According to a different study, high glucose at admission has a less correlation with 30-day MACE than persistent hyperglycemia in myocardial infarction [9]. Regarding 30-day mortality, a prior study found that fasting glucose was superior to admission glucose [10]. The improved ability of FBG to predict outcomes over random glucose levels is likely due to variables such differences in calorie intake and the interval since the last meal. In a recent study, FBG was found to be an independent risk factor for the Gensini score in AMI patients and random blood glucose was found to positively correlate with the Gensini score in AMI patients [11]. Our findings show that microvascular dysfunction may be promoted by acute and persistent blood glucose rise rather than an underlying "diabetic state," which may lead to worse results. Both the initial glucose level and the 24-hour shift in glucose were significant predictors of death within 180 days [12]. Therefore, we thought that FBG levels at admission might more accurately reflect the blood glucose rise that is still present and be a better indicator of clinical outcomes in AMI patients. There is no precise definition for admission hyperglycemia in patients with AMI or

appropriate cutoff values for blood glucose to predict adverse outcomes. Hemoglobin A1c, glucose-HbA1c-ratio, and stress hyperglycemia ratio (SHR, HbA1c, and GHR) were previously described as indicators of clinical outcomes in AMI and other disease processes. However, because thresholds were chosen at random, their ideal values were not made clear [4].

The link between hyperglycemia and adverse outcomes has been explained in a number of ways, including how diabetes or high blood sugar levels affect the pro-inflammatory/oxidative and pro-thrombotic characteristics of arterial plaque lesions [13]. Both diabetes and non-diabetic hyperglycemia patients showed a greater rate of all-cause and MACE in terms of long-term prognosis. Similar to this, patients with diabetes who also had hyperglycemia experienced significantly greater rates of heart failure [14] and macrovascular sequelae (stroke and re-AMI). According to a recent study, patients who underwent thrombus aspiration as part of the primary percutaneous intervention (pPCI) for STEMI had poorer clinical outcomes than those who were normoglycemic [15].

Conclusion

The results showed that admission hyperglycemia is a significant predictor of short and long-term outcomes in AMI patients, independent of diabetes status, according to diabetes status and specific fasting blood glucose levels. Understanding potential differences in the relative contribution of disturbed glucose metabolism to mortality risk following AMI due to diabetes status requires subgroup-specific measures of the relative increase in mortality risk. To determine how these differences might be included in clinical guidelines for the use of diabetes status-specific treatment recommendations across the spectrum of FBG, additional research is required.

References

1. Paolisso P, Foà A, Bergamaschi L, Angeli F, Fabrizio M, Donati F, *et al*. Impact of admission hyperglycemia on short and long-term prognosis in acute myocardial infarction: MINOCA versus MIOCA. Cardiovasc Diabetol. 2021; 20:1–10
2. Sia CH, Chan MHH, Zheng H, Ko J, Ho AFW, Chong J, *et al*. Optimal glucose, HbA1c, glucose-HbA1c ratio and stress-hyperglycemia ratio cut-of values for predicting 1-year mortality in diabetic and non-diabetic acute myocardial infarction patients. Cardiovasc Diabetol. 2021; 20:1–14
3. Ferreira JA, Baptista RM, Monteiro SR, Gonçalves FM, Monteiro PF, Gon- çalves LM. Admission hyperglycemia and all-cause mortality in diabetic and non-diabetic patients with acute myocardial infarction: a tertiary center analysis. Intern Emerg Med. 2021; 16:2109–19.
4. Kim EJ, Jeong MH, Kim JH, Ahn TH, Seung KB, Oh DJ, *et al*. Clinical impact of admission hyperglycemia on in-hospital mortality in acute myocardial infarction patients. Int J Cardiol. 2017; 236:9–15.
5. Cid-Alvarez B, Gude F, Cadarso-Suarez C, Gonzalez- Babarro E, Rodriguez Alvarez MX, Garcia-Acuna JM, *et al*. Admission and fasting plasma glucose for estimating risk of death of diabetic and nondiabetic patients with acute coronary syndrome: nonlinearity of hazard ratios and time dependent comparison. Am Heart J. 2009; 158:989–97.
6. Marenzi G, Cosentino N, Milazzo V, De MM, Cecere M, Mosca S, *et al*. Prog- nostic value of the acute-to-chronic glycemic ratio at admission in acute myocardial infarction: a prospective study. Diabetes Care. 2018; 41:847–53
7. Yan CC, Gang ZM, Chao CL, Ye T, Mei ZY, Zhu F, *et al*. Admission

hyperglycemia as an independent predictor of long-term prognosis in acute myocardial infarction patients without diabetes: a retrospective study. J Diabetes Investig. 2021; 12:1244–51.
8. Chakrabarti AK, Singh P, Gopalakrishnan L, Kumar V, Elizabeth Doherty M, Abueg C, *et al*. Admission hyperglycemia and acute myocardial infarction: outcomes and potential therapies for diabetics and nondiabetics. Cardiol Res Pract. 2012; 1:1–6.
9. Grant PJ, Cosentino F. The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2019; 40:3215–7.
10. Arnold SV, Spertus JA, Jones PG, McGuire DK, Lipska KJ, Xu Y, *et al*. Predicting adverse outcomes after myocardial infarction among patients with diabetes mellitus. Circ Cardiovasc Qual Outcomes. 2016; 9:372–9.
11. Nauta ST, Akkerhuis KM, Deckers JW, Van Domburg RT. Short- and long term mortality after myocardial infarction in patients with and without diabetes: changes from 1985 to 2008. Diabetes Care. 2012; 35:2043–7.
12. Thygesen K, Alpert JS, Jafe AS, Simoons ML, Chaitman BR, White HD. Third universal defnition of myocardial infarction. J Am Coll Cardiol. 2012; 60:1581–98.
13. Kosuge M, Kimura K, Ishikawa T, Shimizi T, Hibi K, Toda N, *et al*. Persistent hyperglycemia is associated with left ventricular dysfunction in patients with acute myocardial infarction. Circ J. 2005; 69:23–8.
14. van der Horst ICC, Nijsten MWN, Vogelzang M, Zijlstra F. Persistent hyperglycemia is an independent predictor of outcome in acute myocardial infarction. Cardiovasc Diabetol. 2007; 6:2–9.
15. Suleiman M, Hammerman H, Boulos M, Kapeliovich MR, Suleiman A, Agmon Y, *et al*. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. Circulation. 2005; 111:754–60.