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ORIGINAL ARTICLE

Admission hyperglycemia predicts poorer short- and long-term outcomes after primary percutaneous coronary intervention for ST-elevation myocardial infarction

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ABSTRACT

Aims/Introduction: Admission hyperglycemia is associated with poor outcome in patients with myocardial infarction. The present study evaluated the relationship between admission glucose level and other clinical variables in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Materials and Methods: The 959 consecutive STEMI patients undergoing primary PCI were divided into five groups based on admission glucose levels of <100, 100–139, 140–189, 190–249 and ≥250 mg/dL. Their short- and long-term outcomes were compared.

Results: Higher admission glucose levels were associated with significantly higher in-hospital morbidity and mortality, the overall mortality rate at follow up, and the incidence of reinfarction or heart failure requiring admission or leading to mortality at follow up. The odds ratios (95% confidence interval) for in-hospital morbidity, in-hospital mortality, mortality at follow up and re-infarction or heart failure or mortality at follow up of patients with admission glucose levels ≥190 mg/dL, compared with those with admission glucose levels <190 mg/dL, were 2.12 (1.3–3.4, $P = 0.001$), 2.74 (1.4–5.5, $P = 0.004$), 2.52 (1.2–5.1, $P = 0.01$) and 1.70 (1.03–2.8, $P = 0.04$), respectively. Previously non-diabetic patients with admission glucose levels ≥250 mg/dL had significantly higher in-hospital morbidity or mortality (44 vs 70%, $P = 0.03$). Known diabetic patients had higher rates of reinfarction, heart failure or mortality at follow up in the 100–139 mg/dL (8 vs 27%, $P = 0.04$) and 140–189 mg/dL (11 vs 26%, $P = 0.02$) groups.

Conclusions: Admission hyperglycemia, especially at glucose levels ≥190 mg/dL, is a predictor of poor prognosis in STEMI patients undergoing primary PCI.

INTRODUCTION

Elevated glucose levels on admission are associated with poor outcomes in patients with acute myocardial infarction (MI), regardless of comorbid diabetes[1–9]. Most studies include patients diagnosed with both ST-elevation myocardial infarction (STEMI) and non-STEMI[1–5,8], and fibrinolysis is usually the initial treatment[3–9]. Two studies showed that admission hyperglycemia is related to in-hospital mortality in MI patients[10,11], approximately 90% of whom are diagnosed as STEMI and primary percutaneous coronary intervention (PCI) is carried out in 72%. However, coronary angiographic features and long-term outcomes are not available for these studies.

Several randomized trials have shown better outcomes from primary PCI and stent implantation compared with fibrinolysis

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for MI patients[12–14], so we focused on the MI patients undergoing primary PCI in the present study. However, in the era of PCI, few papers have discussed the effects of admission glucose levels in patients with STEMI undergoing PCI. Lazzeri *et al.*[15] have shown that admission hyperglycemia is an independent predictor of mortality among elderly patients (age ≥75 years) undergoing primary PCI in the intensive cardiac care unit. Pres *et al.*[16] showed that elevated admission glucose levels result in increased in-hospital and long-term mortality in STEMI patients complicated by cardiogenic shock, and treated with primary PCI. In two other studies, admission hyperglycemia is associated with larger infarct sizes and more severely impaired epicardial coronary flow when compared with normoglycemic patients[17,18].

However, relevant data on admission glucose levels in STEMI patients undergoing primary PCI remains limited. The present study aimed to investigate the predictive value of admission glucose levels for the clinical features at short- and long-term outcomes in STEMI patients undergoing PCI.

METHODS

Patients

Between November 1992 and December 2008, 1,035 consecutive patients underwent primary PCI for STEMI, which was defined using the criteria of the time[19,20]: (i) characteristic chest pain lasting at least 20 min; (ii) elevated levels of serum cardiac biomarkers at least twofold higher than the upper limit of normal; (iii) ST-segment elevation ≥1 mm, with subsequent evolution of negative T-waves with a depth of ≥1 mm and the development of new Q-waves for at least ≥0.04 s or deeper than one-quarter of the following R wave in voltage. Coronary angiography confirmed the complete occlusion or critical stenosis of the infarct-related arteries in all of the patients. The admission glucose values of these patients were reviewed. Patients who received fibrinolysis therapy or had no available data on glucose levels were excluded. A total of 959 patients were included in the present study. The local ethics committee approved this observational study and all patients provided written informed consent.

Definitions

Admission glucose levels were determined by the first venous blood samples routinely drawn at the emergency room and analyzed at the central laboratory of the hospital. The patients were categorized into five groups based on admission glucose levels of <100, 100–139, 140–189, 190–249 and ≥250 mg/dL[8]. Patients were defined as having previously recognized diabetes if they were under antidiabetic therapy at the time of admission.

To evaluate peak serum cardiac biomarkers, blood samples were obtained every 6 h for 48 h, or until activity returned to normal. Blood samples for lipid profile were drawn after an 8-h fast during the index hospitalization.

Coronary Angiography

All patients underwent coronary artery angiography. Judgment of vessel flow was based on thrombolysis in myocardial infarction (TIMI) flow grade, ranging from 0 to 3, whereby TIMI 0 flow indicated the absence of any antegrade flow beyond a coronary occlusion, whereas TIMI 3 flow indicated normal flow completely filling the distal coronary bed[21].

Outcomes

The clinical outcomes analyzed were short-term outcomes, including length of hospital stay, length of intensive care unit (ICU) stay, and in-hospital mortality and morbidity, as well as long-term outcomes, such as incidence of reinfarction, heart failure requiring hospital admission and mortality at follow up. Clinical follow-up variables, including reinfarction, heart failure requiring admission and mortality data, were obtained from clinic visits, telephone conversations and chart reviews.

Statistical Analysis

Quantitative data were expressed as mean ± standard deviation. The χ^2-test with Yate's correction or Fisher's exact test was used to analyze non-parametric data. Cox regression analysis was used to identify baseline variables independently associated with short- and long-term outcomes. These variables were presented as odds ratios (OR) followed by 95% confidence interval (CI). Statistical significance was set at $P < 0.05$ and significant OR was defined as 95% CI >1. Event-free survival curves (defined as free of reinfarction, heart failure requiring admission, or mortality) were constructed using the Kaplan–Meier method. The significance of differences between curves was assessed by log–rank test.

RESULTS

Risk Factors and Presentations

The patients were predominantly male. Compared with those with lower admission glucose levels, patients with higher admission glucose levels were significantly older, had higher likelihood of previously recognized diabetes and had a previous history of heart failure. Patients with higher admission glucose levels also presented with significantly less typical angina and higher Killip class (III and IV). They also had significantly higher peak creatine kinase levels. However, there were no differences in creatine kinase-MB, cholesterol, high-density lipoprotein, low-density lipoprotein or platelet levels.

The proportion of patients receiving antihypertensive or antidyslipidemic therapy did not differ significantly among the five groups. Nonetheless, the proportion of patients receiving antidiabetic therapy was greater in patients with higher admission glucose levels (Table 1).

Angiographic Data and Interventional Therapy

Patients with higher admission glucose levels tended to have greater incidence of multivessel disease, although this difference

Table 1 | Patient characteristics of the admission glucose groups

Admission glucose level (mg/dL)	<100 (*n* = 72)	100 – 139 (*n* = 345)	140 – 189 (*n* = 237)	190 – 249 (*n* = 114)	≥250 (*n* = 191)	*P*-value
Age (years)	61.2 ± 12.9	58.0 ± 12.6	61.7 ± 12.7	62.2 ± 12.2	63.0 ± 12.0	<0.001
Male	64 (88.9)	306 (88.7)	197 (83.1)	90 (78.9)	130 (68.1)	<0.001
Previously recognized diabetes	13 (18.1)	22 (6.4)	50 (21.1)	63 (55.3)	158 (82.7)	<0.001
History of heart failure	4 (5.6)	6 (1.7)	2 (0.8)	7 (6.1)	9 (4.7)	<0.001
Presentation						
Typical angina	63 (87.5)	321 (93.0)	214 (90.3)	100 (87.7)	155 (81.2)	0.001
Killip III/IV	14 (19.4)	64 (18.6)	61 (25.7)	36 (31.6)	89 (46.6)	<0.001
Laboratory analysis						
Creatine kinase (IU/L)†	1864.3 ± 106.0	2910.0 ± 136.4	2995.2 ± 155.4	2734.2 ± 227.5	3374.8 ± 239.8	0.002
Creatine kinase-MB (IU/L)†	185.9 ± 19.6	269.8 ± 14.1	260.6 ± 12.8	250.5 ± 24.5	278.0 ± 22.2	0.11
Total cholesterol (mg/dL)	177.5 ± 37.5	187.7 ± 41.5	183.4 ± 40.1	178.9 ± 46.2	189.8 ± 48.3	0.09
Triglyceride (mg/dL)	129.4 ± 85.6	132.7 ± 101.9	130.1 ± 95.7	180.2 ± 177.6	184.5 ± 199.9	<0.001
High-density lipoprotein (mg/dL)	42.3 ± 16.0	43.4 ± 12.7	43.1 ± 13.8	40.4 ± 12.9	40.3 ± 13.5	0.22
Low-density lipoprotein (mg/dL)	111.1 ± 34.1	123.0 ± 35.5	117.8 ± 37.7	110.5 ± 39.2	116.7 ± 40.4	0.06
Platelets (K/uL)	235.9 ± 123.8	223.7 ± 68.0	215.0 ± 53.3	226.8 ± 65.6	227.7 ± 82.0	0.24
Medication therapy						
Antihypertensive therapy	22 (30.6)	135 (39.1)	94 (39.7)	35 (30.7)	60 (31.4)	0.14
Antidyslipidemic therapy	11 (15.3)	82 (23.8)	59 (24.9)	20 (17.5)	44 (23.0)	0.30
Antidiabetic therapy	13 (18.1)	22 (6.4)	50 (21.1)	63 (55.3)	158 (82.7)	<0.001

Values are presented as *n* (%) or as mean ± standard deviation (*n* = 959). †Values are presented as mean ± standard error.

Table 2 | Coronary angiographic features of the admission glucose groups

Admission glucose level (mg/dL)	<100 (*n* = 72)	100 – 139 (*n* = 345)	140 – 189 (*n* = 237)	190 – 249 (*n* = 114)	≥250 (*n* = 191)	*P*-value
No. diseased vessels						
Single-vessel disease	24 (33.3)	125 (36.2)	74 (31.2)	34 (29.8)	45 (23.6)	0.05
Multiple-vessel disease	48 (66.7)	220 (63.8)	163 (68.8)	80 (70.2)	146 (76.4)	
Coronary artery intervention						
Initial success of primary PCI	65 (90.3)	325 (94.2)	219 (92.4)	103 (91.2)	155 (82.4)	<0.001
Post-PCI TIMI flow grade	2.8 ± 0.7	2.9 ± 0.6	2.8 ± 0.7	2.7 ± 0.8	2.5 ± 1.0	<0.001
Intra-aortic balloon pump	10 (13.9)	49 (14.2)	42 (17.7)	20 (17.7)	60 (31.4)	<0.001
Emergency CABG	1 (1.4)	3 (0.9)	0 (0)	0 (0)	3 (1.6)	0.29
LVEF, by heart echo	54.1 ± 12.9	57.8 ± 11.7	56.2 ± 13.1	52.6 ± 12.7	51.2 ± 13.6	<0.001

Values are presented as *n* (%) or as mean ± standard deviation (*n* = 959). CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

was only borderline significant ($P = 0.05$). They had significantly lower rates of initial success of primary PCI and poorer post-PCI TIMI flow grades, were significantly more likely to require intra-aortic balloon pump (IABP) implantation, and tended to have poorer left ventricular ejection fraction (Table 2).

Outcomes

Higher admission glucose levels were associated with significantly higher in-hospital morbidity, including those as a result of cardiogenic shock, ventricular arrhythmia requiring defibrillation, sepsis and acute renal failure requiring hemodialysis, but were not associated with differences in bleeding complications requiring blood transfusion and cardiac rupture/tamponade. Higher admission glucose levels were also associated with significantly increased risk of in-hospital mortality and morbidity, and longer durations of ICU stay and length of hospitalization.

In terms of long-term outcomes, there was no significant association between hyperglycemia on admission and the incidence of reinfarction or heart failure requiring hospital admission. However, the overall mortality rate at follow up and the incidence of reinfarction or heart failure requiring admission or leading to mortality at follow up were significantly higher among patients with higher admission hyperglycemia (Table 3).

Table 3 | Clinical outcomes of the admission glucose groups

Admission glucose level (mg/dL)	<100 (*n* = 72)	100 – 139 (*n* = 345)	140 – 189 (*n* = 237)	190 – 249 (*n* = 114)	≥250 (*n* = 191)	*P*-value
Short-term outcomes						
In-hospital morbidity	19 (26.4)	96 (27.8)	71 (30.0)	39 (34.2)	93 (48.7)	<0.001
Cardiogenic shock	13 (18.1)	48 (13.9)	45 (19.0)	30 (26.3)	70 (36.6)	<0.001
Ventricular arrhythmia required defibrillation	5 (6.9)	43 (12.5)	17 (7.2)	4 (3.5)	23 (12.0)	0.02
Sepsis	0 (0)	11 (3.2)	9 (3.8)	8 (7.0)	19 (9.9)	0.001
Bleeding complications requiring blood transfusion	3 (4.2)	20 (5.8)	11 (4.6)	6 (5.3)	21 (11.0)	0.06
Cardiac rupture/tamponade	0 (0)	2 (0.6)	1 (0.4)	1 (0.9)	2 (1.0)	0.86
Acute renal failure requiring hemodialysis	0 (0)	3 (0.9)	3 (0.9)	0 (0)	7 (3.7)	0.03
In-hospital mortality	6 (8.3)	10 (2.9)	12 (5.1)	11 (9.6)	41 (21.5)	<0.001
In-hospital morbidity or mortality	22 (30.6)	98 (28.4)	74 (31.2)	42 (36.8)	93 (48.7)	<0.001
Length of intensive care unit stay (day)	2.9 ± 1.8	3.6 ± 4.6	2.6 ± 3.1	4.9 ± 6.0	4.9 ± 7.9	0.004
Length of total hospital stay (day)	7.6 ± 6.3	7.7 ± 5.9	8.2 ± 6.4	10.0 ± 8.7	9.6 ± 9.8	0.005
Long-term outcomes						
Reinfarction	2 (2.8)	10 (2.9)	4 (1.7)	8 (7.0)	6 (3.1)	0.12
HF required hospital admission	6 (8.3)	15 (4.3)	16 (6.8)	10 (8.8)	20 (10.5)	0.09
Mortality at follow up	1 (1.4)	12 (3.5)	14 (5.9)	10 (8.8)	25 (13.1)	0.002
Reinfarction or HF or mortality	7 (9.7)	33 (9.6)	34 (14.3)	20 (17.5)	42 (22.0)	0.001
Follow up (months)†	66.2 ± 5.9	64.5 ± 2.7	65.9 ± 3.2	63.0 ± 4.8	53.3 ± 3.6	0.07

Values are presented as numbers (%) or mean ± standard deviation (*n* = 959). †Values are presented as mean ± standard error. HF, heart failure.

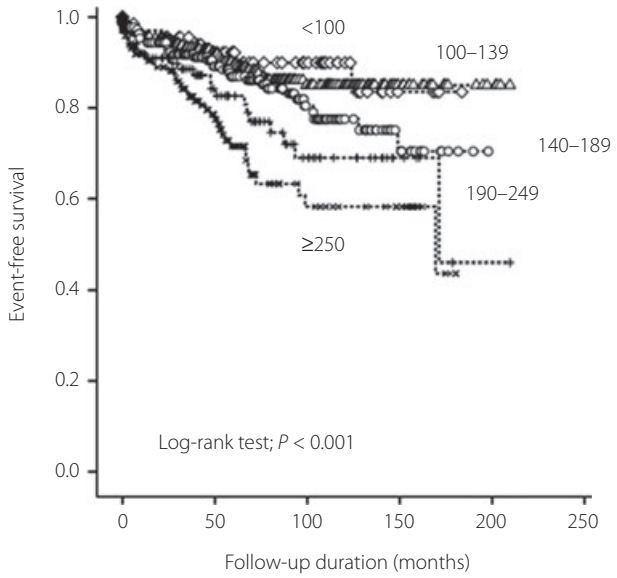

Figure 1 | Event-free survival curves in different admission glucose groups.

The Kaplan–Meier curves of event-free survival showed that patients with higher admission glucose levels had higher rates of reinfarction, heart failure requiring admission and mortality at follow up ($P < 0.001$, log–rank test; Figure 1). After adjusting for sex, age, Killip class >1, current smoking, diabetes, hypertension, multivessel disease, chronic kidney disease and culprit artery TIMI flow after coronary intervention, admission glucose level ≥190 mg/dL was able to predict higher in-hospital morbidity (OR 2.12, 95% CI 1.3–3.4, $P = 0.001$), in-hospital mortality (OR 2.74, 95% CI 1.4–5.5, $P = 0.004$), in-hospital morbidity or mortality (OR 1.97, 95% CI 1.3–3.1, $P = 0.003$), mortality at follow up (OR 2.52, 95% CI 1.2–5.1, $P = 0.01$), and risk of reinfarction, heart failure requiring admission and mortality at follow up (OR 1.70, 95% CI 1.03–2.8, $P = 0.04$; Table 4).

In the present study, 68.1% of patients had no previously documented diabetes. Compared with those with previously known diabetes, those without previously documented diabetes had worse in-hospital morbidity rates in the group with admission glucose levels ≥250 mg/dL (44% vs 73%, $P = 0.03$; Figure 2a) although there was no difference in the in-hospital mortality rate (Figure 2b). The in-hospital morbidity or mortality rate was also higher in patients without previously known diabetes if admission glucose levels were ≥250 mg/dL (44% vs 70%, $P = 0.03$), compared with known diabetics with similar admission glucose levels (Figure 2c).

In regard to long-term outcomes, the overall mortality rates at follow up for patients with and without previously known diabetes did not differ significantly (Figure 2d). However, known diabetic patients had greater rates of reinfarction, heart failure requiring admission, or mortality at follow-up when the admission glucose levels were 100–139 mg/dL (8% vs 27%, $P = 0.04$) and 140–189 mg/dL (11% vs 26%, $P = 0.02$; Figure 2e).

DISCUSSION

The present study focuses on STEMI patients undergoing primary PCI, and shows that admission hyperglycemia can predict unfavorable short- and long-term outcomes. Patients with

Table 4 | Odds ratios and 95% confidence intervals for hyperglycemia (admission glucose ≥190 mg/dL)

	Short-term outcomes									Long-term outcomes					
	In-hospital morbidity			In-hospital mortality			In-hospital morbidity or mortality			Mortality at follow up			ReMI/HF/mortality at follow up		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Glucose ≥190 mg/dL	2.12	1.3 – 3.4	0.001	2.74	1.4 – 5.5	0.004	1.97	1.3 – 3.1	0.003	2.52	1.2 – 5.1	0.01	1.70	1.03 – 2.8	0.04

Adjusted for sex, age, Killip class >1, current smoking, diabetes, hypertension, chronic kidney disease, multivessel disease and culprit artery thrombolysis in myocardial infarction flow >1 before coronary intervention. CI, confidence interval; HF, heart failure; OR, odds ratio; ReMI, reinfarction.

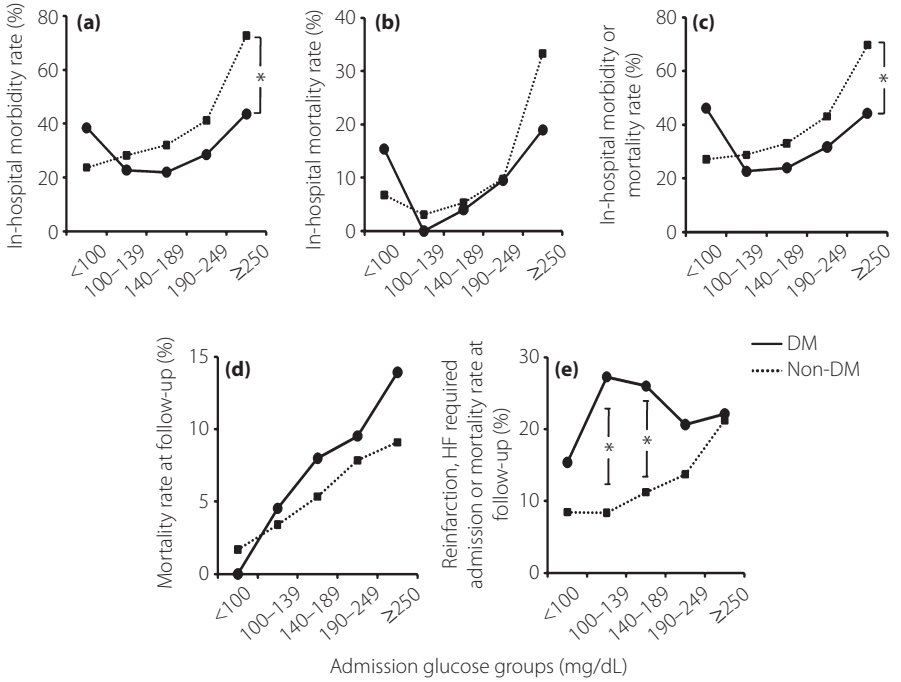

Figure 2 | Relationships between admission glucose level and (a) in-hospital mortality rate, (b) in-hospital morbidity or mortality rates, (c) mortality rate at follow up, (d) reinfarction or heart failure (HF) requiring admission, or mortality rate at follow up, and (e) patients with and without previously recognized diabetes (DM). *$P < 0.05$ for comparison between DM and non-DM.

higher admission glucose levels tend to have a higher prevalence of coexisting risk factors, such as old age, previously recognized diabetes, atypical presentation, poor Killip class and unfavorable coronary angiographic features, all of which contribute to poor clinical outcomes. Admission glucose levels (≥190 mg/dL) can therefore be a simple and useful prognosticating tool for such patients.

Among patients without prior diabetes, hyperglycemia might reflect previously undiagnosed diabetes, stress hyperglycemia or a combination of both. In the present study, patients without previously known diabetes, but with admission glucose levels >250 mg/dL, had a worse short-term outcome than those previously diagnosed with diabetes. This is consistent with findings of previous studies[3,8,22]. Previously undiagnosed and untreated diabetes leads to a greater risk of vascular damage. Hyperglycemia might not cause obvious symptoms or signs for years, thus leading to delays in treatment. However, cardiovascular risk is known to increase even in the early stages of impaired glucose tolerance[23], and might develop years before a confirmed diagnosis of diabetes[24].

In contrast, stress hyperglycemia at the time of hospital admission can also play an important role in the clinical outcomes of MI patients[25–27]. Some patients without previously known diabetes, but presenting with admission hyperglycemia, show normal glucose levels after the acute phase of MI. Acute hyperglycemia in MI has been independently associated with impaired left ventricular function, inducing arrhythmias, increased platelet activation, amplified inflammatory immune reactions and poor cardiac functional outcomes[26]. Thus, stress hyperglycemia might be one explanation for the worse short-term outcomes of patients with higher glucose levels, but without previously recognized diabetes.

Patients with previously diagnosed diabetes also have worse long-term outcomes compared with those without previously diagnosed diabetes. The diagnosis of diabetes itself is associated with adverse outcomes in acute coronary syndrome[28,29], suggesting that overall vascular damage in patients with previous diabetes is worse than that in patients without a history of diabetes because of the longer duration of hyperglycemia in the former. These results echo findings by Ishihara *et al.*[30], who showed that admission hyperglycemia predicts worse short-term mortality, whereas a previous diagnosis of diabetes is associated with increased long-term mortality in MI patients undergoing PCI. Overall, these findings further emphasize the importance of early diagnosis and aggressive management of diabetes, as good glycemic control can greatly affect long-term outcomes in STEMI patients undergoing PCI.

Anti-diabetic therapy might be a factor influencing admission glucose level. In the present study, the proportion of patients receiving antidiabetic therapy was greater in the group with admission glucose levels ≥100 mg/dL, showing that patients with higher admission glucose levels tend to have previously known diabetes. The proportion of patients receiving anti-diabetic therapy is also slightly higher in the group of admission glucose levels <100 mg/dL compared with the 100–139 mg/dL group. Patients with admission glucose levels <100 mg/dL tended to have poorer short-term outcomes, particularly patients receiving antidiabetic therapy. Hypoglycemia seems to cause worse short-term outcomes, for which antidiabetic drugs might be an underlying reason. Previous studies have also shown this J-curve phenomenon. In addition to the influence of antidiabetic drugs, stress-induced hepatic gluconeogenesis dysfunction or relative adrenal insufficiency might also have contributed to hypoglycemia in such patients[7,9,31].

The present study had certain limitations. The diagnostic criteria of previous diabetes was based on the use of antidiabetic medication, which could be a factor influencing admission glucose level, but we did not clarify it clearly. Although patients with and without a previous history of diabetes were compared, glycated hemoglobin levels and the duration of diabetes were not evaluated. In addition, although admission hyperglycemia was associated with poor outcomes, the effect of treating hyperglycemia after admission was not assessed. Further studies are required for more in-depth examination of these factors. Despite these limitations, these findings remain valid and might be corroborated by further investigations.

In conclusion, admission glucose level above 190 mg/dL is an indicator of poor short- and long-term prognosis in STEMI patients undergoing primary PCI. Patients with admission hyperglycemia ≥250 mg/dL and undiagnosed diabetes have poorer short-term outcomes, whereas patients with admission hyperglycemia and previously confirmed diabetes have worse long-term outcomes. Early diagnosis and intensive treatment of diabetes should be emphasized in order to decrease cardiovascular complications, and improve clinical outcomes in such patients.

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