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Admission hyperglycemia as an independent predictor of long-term prognosis in acute myocardial infarction patients without diabetes: A retrospective study

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ABSTRACT

Aims/Introduction: The predictive value of admission hyperglycemia in the long-term prognosis of acute myocardial infarction patients is still controversial. We aimed to investigate this value based on the diabetes status.

Materials and Methods: We carried out a multicenter, retrospective study of 1,288 acute myocardial infarction patients enrolled in 11 hospitals between March 2014 and June 2019 in Chengdu, China. The patients were classified into those with diabetes and those without diabetes, each was further divided into: hyperglycemia and non-hyperglycemia subgroups, according to the optimal cut-off value of the blood glucose to predict all-cause mortality during follow up. The end-points were all-cause death and major adverse cardiovascular and cerebrovascular events, including all-cause death, non-fatal myocardial infarction, vessel revascularization and non-fatal stroke.

Results: In the follow-up period of 15 months, we observed 210 (16.3%), 6 (0.5%), 57 (4.4%) and 34 (2.6%) cases of death, non-fatal myocardial infarction, revascularization and non-fatal stroke, respectively. The optimal cut-off values of admission blood glucose for patients with diabetes and patients without diabetes to predict all-cause mortality during follow up were 14.80 and 6.77 mmol/L, respectively. We divided patients with diabetes (n = 331) into hyperglycemia (n = 92) and non-hyperglycemia (n = 239), and patients without diabetes (n = 897) into hyperglycemia (n = 425) and non-hyperglycemia (n = 472). The cumulative rates of all-cause death and major adverse cardiovascular and cerebrovascular events among the patients in each hyperglycemia group was higher than that in the corresponding non-hyperglycemia group (P < 0.001). In patients without diabetes, admission hyperglycemia was an independent predictor of all-cause mortality and major adverse cardiovascular and cerebrovascular events.

Conclusion: Admission hyperglycemia was an independent predictor for long-term prognosis in acute myocardial infarction patients without diabetes.

INTRODUCTION

Acute myocardial infarction (AMI) is a serious type of coronary heart disease and an important cause of death from cardiovascular disease. Despite the tendency to standardize the diagnosis and treatment of AMI patients in recent years, mortality is still high[1]. Quick identification of high-risk patients, strengthening the treatment and nursing, and improving prognosis are still issues that require attention.

Admission hyperglycemia has been commonly identified in AMI patients[2]. It is related to the stress response of AMI patients as a result of an excessive secretion of steroid

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hormones, adrenaline, glucagon and free fatty acids[3]. Furthermore, acute hyperglycemia could provoke a prothrombotic state[4], enhance inflammation and oxidative response, damage the endothelial cells and microcirculation function, and then cause a massive myocardial infarction[5].

Previous studies[6–8] showed admission hyperglycemia to be an independent predictor of short-term and long-term death in patients with AMI, regardless of whether the patient has diabetes. However, later studies[9,10] showed that admission hyperglycemia was an independent predictor of AMI in patients without diabetes. As a result, the prognostic value of admission hyperglycemia on long-term prognosis remains elusive, especially in AMI patients with diabetes.

Although the diabetes status should be considered when analyzing blood glucose, most studies currently use the same admission hyperglycemia standard for all AMI patients, without distinguishing between patients with and without diabetes. In addition, the discussions in previous studies were based on the acute hyperglycemia threshold, admission hyperglycemia or blood glucose quartile/tertile on admission[9,11]. Regarding AMI patients, there has been no accurate threshold of admission hyperglycemia to predict mortality. Therefore, in the present study, we used different cut-off values in patients with and without diabetes to discuss their predictive value in the long-term prognosis of AMI patients.

METHODS

Study design and population

The present study was a retrospective, multicenter, observational cohort study. We observed 1,288 consecutive AMI patients that were admitted to 11 general hospitals between January 2014 and June 2019 in the city of Chengdu, China (http://www.medresman.org). AMI was defined according to the current guidelines[12], including ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). The patients were excluded based on the following criteria: (i) they were aged <18 years; (ii) no date on plasma glucose on admission was available; (iii) they were lost to follow-up; or (iv) they had severe valvular heart disease, severe or decompensated heart failure, severe renal failure, or tumors.

The study was approved by the local ethics committee. The study is registered in the Chinese Clinical Trials Registry in China (ChiCTR1900025138).

The patients were divided into two groups: those with diabetes and those without diabetes, according to the diagnosis on discharge. Patients with diabetes had a history of diabetes or were newly diagnosed with diabetes by the oral glucose tolerance test, fasting glucose test or glycated hemoglobin ≥6.5% during hospitalization[13].

The first fasting plasma glucose value on admission of the AMI patients was recorded. The receiver operating characteristic (ROC) curve showed that the optimal critical value of plasma glucose on admission to predict long-term mortality for patients with and without diabetes was 14.80 mmol/L (the area under the ROC curve was 0.634, the sensitivity was 50%, the specificity was 78%, P-value < 0.001; Figure 1a) and 6.77 mmol/L (the area under the ROC curve was 0.660, the sensitivity was 68%, the specificity was 57%, P-value < 0.001, Figure 1b), respectively. The patients with diabetes were divided into two subgroups: the hyperglycemia group with blood glucose on admission ≥14.80 mmol/L (n = 239), and the non-hyperglycemia group with blood glucose at admission <14.80 mmol/L (n = 92). The patients without diabetes were divided into the hyperglycemia group with blood glucose on admission ≥6.77 mmol/L (n = 425), and the non-hyperglycemia group with blood glucose at admission <6.77 mmol/L (n = 472). The demographic, clinical, biochemical and angiographic data were exported from the hospital medical records system.

Study end-points

The end-points were all-cause death, cardiogenic or non-cardiogenic, and the occurrence of major adverse cardiovascular and

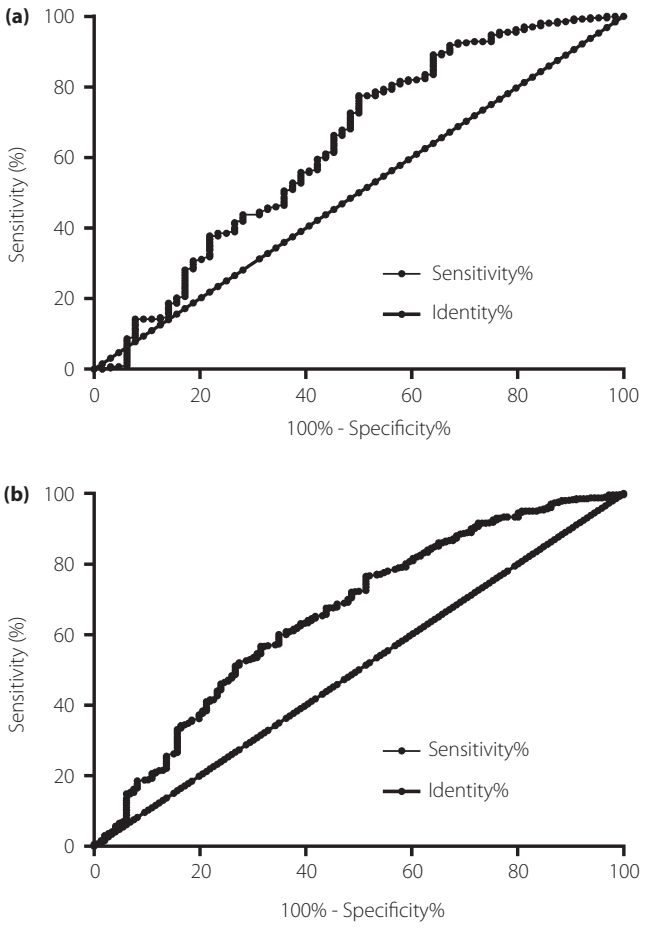

Figure 1 | (a) The receiver operating characteristic curve of plasma glucose on admission to predict long-term mortality for acute myocardial infarction patients with diabetes. (b) The Cox regression analysis of death for acute myocardial infarction (AMI) patients without diabetes. (c) The Cox regression analysis of major adverse cardiovascular and cerebrovascular events for AMI patients with diabetes.

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cerebrovascular events (MACCE), including non-fatal myocardial infarction, target vessel revascularization and non-fatal stroke. Myocardial infarction was defined as the symptoms of a cardiac ischemia and a troponin level above the 99th centile, whereas revascularization was defined as the revascularization of any lesion, including percutaneous coronary intervention (PCI) or coronary artery bypass grafting. Finally, stroke was defined as a new cerebral infarction or cerebral hemorrhage diagnosed by neurologists.

Follow up

The patients were followed up at outpatient clinics or using a telephone questionnaire on the date of discharge, then at 1, 6 and 12 months later, and annually thereafter. The information about death and MACCE was obtained from the hospital records or the patient's guardians by telephone contact. The baseline and follow-up data were collected by specially trained doctors.

Statistical analysis

SPSS software version 20.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. Continuous data are expressed as the mean ± standard deviation or median (interquartile range) and compared, as appropriate, using the Student's *t*-test or Mann-Whitney *U*-test. Categorical variables were expressed as percentages, and comparisons were carried out using the χ^2-test or Fisher's exact test. The optimal cut-off value for blood glucose was determined by the Youden Index in the ROC curve. The Youden Index is equal to the sum of sensitivity and specificity minus 1. Then, the optimal cut-off point for plasma glucose is the plasma glucose value that corresponds to the maximum Youden Index. The time-to-event data were plotted using the Kaplan–Meier method and compared between the groups using the log-rank test. To assess whether acute hyperglycemia was associated with a worse long-term prognosis, Cox regression analyses were carried out. The factors of age, sex, prior cardiovascular disease Killip class, heart rate, C-reaction protein, serum creatinine, STEMI, PCI and admission hyperglycemia were included in the multivariate survival analyses. A Cox regression model was used to test the interactions while adjusting for other risk factors, to determine whether the relationship between acute hyperglycemia and long-term mortality varied between different subgroups. All the statistical tests were two-tailed, and a P-value < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 1.288 AMI patients (848 STEMI and 440 NSTEMI) were included in the study, among which 72.3% (906/1,288) were men and 27.7% (382/1,288) were women. The average age was 67 ± 13 years, and the median plasma glucose level on admission was 7.33 mmol/L (25th to 75th centiles, 5.83–9.78 mmol/L).

The baseline characteristics and angiographic findings are listed in Table 1. Among the patients with diabetes, those in the hyperglycemia group had more women and a higher Killip grade ($P < 0.05$) compared with the non-hyperglycemia group. Among the patients without diabetes, those in the hyperglycemia group were older, included more women and STEMI cases, and had a higher Killip grade than that in the non-hyperglycemia group ($P < 0.05$). The symptom of sweating at onset was more common in patients with hyperglycemia ($P < 0.05$); these patients also had higher C-reactive protein, serum creatinine, triglyceride, total cholesterol and low-density lipoprotein cholesterol levels compared with non-hyperglycemia patients ($P < 0.05$). In contrast, the smoking rate was higher in the non-hyperglycemia group than that in the hyperglycemia group ($P < 0.05$). The subgroups of both patients with and without diabetes had similar admission systolic blood pressure, brain natriuretic polypeptide levels, high-density lipoprotein cholesterol levels and lipoprotein(a) levels ($P > 0.05$). Additionally, the length of stay, hospitalization costs, multiple coronary arteries lesions, left main lesions or anterior descending lesions did not differ between the two subgroups ($P > 0.05$).

All-cause death and MACCE occurrence at follow up

At the 15-month (8 months, 22 months) follow up, 210 (16.3%), 6 (0.5%), 57 (4.4%) and 34 (2.6%) cases of death, non-fatal MI, revascularization and non-fatal stroke occurred, respectively. The Kaplan–Meier survival curves showed that the cumulative incidence of all-cause death, cardiogenic death and MACCE was higher in the hyperglycemic subgroup, both in the patients with and without diabetes ($P < 0.001$; Figure 2a–f).

Independent predictors of all-cause death and MACCE

The Cox regression analysis for patients with diabetes showed that the independent predictors of all-cause death were old age and PCI (Figure 3a), whereas the independent predictors of MACCE were old age, STEMI and PCI (Figure 3b). In contrast, the Cox regression analysis for patients without diabetes showed that the independent predictors of all-cause death and MACCE were old age, Killip class ≥2, admission hyperglycemia and PCI (Figure 3c,d).

DISCUSSION

The present study was carried out to analyze the predictive value of acute hyperglycemia in the prognosis of AMI patients with and without diabetes. We showed that a blood glucose ≥6.77 mmol/L was an independent predictor of all-cause death and MACCE in AMI patients without diabetes. In contrast, admission hyperglycemia was not an independent predictor in AMI patients with diabetes.

The study of Mohamed *et al.*[2] classified a blood glucose level >7.78 mmol/L as acute hyperglycemia, whereas the study of Li *et al.*[14] grouped the patients according to a threshold of 11.11 mmol/L. These studies lacked a unified definition of admission hyperglycemia, and admission hyperglycemia should

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Table 1 | Baseline characteristics

	Patients without diabetes			Patients with diabetes		
	Hyperglycemia group (n = 425)	Non-hyperglycemia group (n = 472)	P-value	Hyperglycemia group (n = 239)	Non-hyperglycemia group (n = 92)	P-value
Demographic						
Age (years)	67.7 ± 13.2	65.4 ± 14.0	0.011	70.3 ± 11.3	68.7 ± 11.8	0.262
Male (%)	70.6%	82.4%	<0.001	53.3%	70.3%	0.003
Social benefit						
Hospital stay (days)	9 (7,11)	8 (7,11)	0.799	10 (9,12)	9 (7,14)	0.139
Hospitalization cost (10,000 yuan)	4.11 (0.98,5.16)	3.27 (1.34,4.28)	0.320	4.44 (1.71,7.00)	3.60 (1.59,4.73)	0.569
Medical history						
Smoking (%)						
Never smoking	50.9%	42.7%	0.025	56.2%	56.9%	0.887
Quit smoking	10.4%	9.8%		9.0%	10.5%	
Continue smoking	38.7%	47.6%		34.8%	32.6%	
Coronary heart disease (%)	10.4%	10.2%	0.900	14.1%	15.6%	0.737
Percutaneous coronary intervention (%)	2.6%	2.8%	0.883	4.3%	8.4%	0.200
Hypertension (%)	48.5%	43.0%	0.102	65.2%	68.4%	0.586
Clinical characteristic						
Clinical signs (%)						
Chest pain	93.0%	96.1%	0.043	87.9%	93.6%	0.092
Dyspnea	6.5%	4.1%	0.114	7.7%	6.0%	0.580
Syncope	4.1%	3.5%	0.627	5.5%	3.9%	0.516
Nausea and vomiting	9.4%	7.2%	0.228	11.0%	9.9%	0.765
Profuse sweating	36.4%	27.3%	0.004	24.2%	27.0%	0.599
Systolic blood pressure (mmHg)	130.65 ± 28.43	130.74 ± 23.94	0.960	131.23 ± 28.54	133.00 ± 26.38	
Heart rate (b.p.m.)	84 (72,101)	78 (67,90)	0.198	70 (67,94)	83 (78,94)	0.983
Killip class (%)						
I	60.0%	65.1%	<0.001	48.9%	64.1%	0.003
II	19.3%	23.9%		22.2%	23.8%	
III	4.8%	3.9%		11.1%	6.1%	
IV	16.0%	7.0%		17.8%	6.1%	
Killip class >2	40.0%	34.9%	0.117	51.1%	35.9%	0.013
Laboratory values at hospital admission						
BNP (ng/L)	693.10 (199.33–1,326.03)	392.02 (122.10–746.80)	0.893	347.37 (151.83–1,012.78)	217.99 (47.83–1,163.50)	0.601
Serum creatinine (μmol/L)	97.00 (75.95–119.23)	76.40 (65.70–94.9)	0.019	92.35 (76.23–109.65)	105.10 (81.80–151.23)	0.582
Triglyceride (mmol/L)	1.23 (0.96–1.49)	1.15 (0.90–1.74)	0.023	2.41 (2.16–2.73)	1.55 (1.20–2.42)	0.419
Total cholesterol (mmol/L)	4.38 (3.85–4.92)	4.12 (3.50–4.84)	0.001	4.65 (3.74–4.90)	4.11 (3.72–5.54)	0.074
LDL-C (mmol/L)	2.60 (2.05–3.21)	2.88 (2.30–3.29)	0.005	2.59 (2.06–2.87)	2.62 (2.11–3.68)	0.09
HDL-C (mmol/L)	1.15 (0.88–1.42)	1.14 (0.90–1.30)	0.104	1.10 (1.03–1.11)	1.11 (0.79–1.23)	0.249
Lp(a) (mg/L)	159.00 (85.50–305.65)	85.97 (35.10–270.30)	0.940	213.70 (25.92–259.83)	71.25 (36.22–213.20)	0.687
CRP (mg/L)	24.90 (6.38–54.99)	9 (3.10–35.60)	0.012	6.82 (2.70–39.06)	4.20 (2.39–17.30)	0.629
STEMI (%)	75.1%	66.9%	0.008	62.0%	65.3%	0.573
PCI (%)	70.6%	72.2%	0.583	69.6%	77.0%	0.163
Coronary artery						
Multiple coronary arteries lesion (%)	41.2%	40.4%	0.866	44.7%	44.7%	0.999
Left main or anterior descending lesion (%)	53.3%	56.3%	0.465	43.4%	56.7%	0.094

BNP, brain natriuretic polypeptide; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein(a); PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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not be confused with impaired fasting glucose, abnormal glucose tolerance and diabetes mellitus. More importantly, there is no reason behind using the same cut-off value for patients with and without diabetes, as they have different basal blood glucose values and different levels of acute increase under stress. In the present study, we divided the AMI patients into two groups: those with diabetes and those without diabetes, and the optimal critical value of blood glucose to predict the long-term death of the AMI patients was calculated in each of the two groups. Then, each of the two groups was further divided into two subgroups according to the optimal cut-off value: a hyperglycemia group and a non-hyperglycemia group. Suleiman *et al.*[15] found the immediate blood glucose and fasting blood glucose levels to be independent predictors for AMI prognosis, but the predictive value of fasting hyperglycemia was higher than immediate hyperglycemia. In the present study, we used the blood glucose level as the fasting blood glucose on admission, and the diagnosis of diabetes used the diagnosis at the time of discharge, so that it would not be mixed with undiagnosed diabetes. Therefore, our research method was more scientific and reasonable regarding blood glucose to predict the clinical outcome of AMI patients. In our research, the ability of admission glucose to predict long-term mortality was modest for both patients with and without diabetes, as the area under the ROC curve was just 0.634 and 0.660 respectively; this might be influenced by the limited sample size. However, the research methods and questions raised in this study might provide insights for future research.

Hao *et al.*[16] recently reported that admission hyperglycemia could be an independent predictor for the prognosis of AMI patients. However, the study did not analyze the difference in the predictive value between the groups of patients with and without diabetes. Another study[9] found that admission hyperglycemia had a predictive value for hospital mortality in patients with AMI, but the predicted value was different between patients with and without diabetes. Unlike the above-mentioned analysis, the present study distinguished between patients with and without diabetes, and long-term follow up was carried out. The results showed that there was indeed a difference in the impact of admission hyperglycemia between the patients with and without diabetes, as it was strongly associated with a poor long-term prognosis in patients without diabetes, whereas it did not have this impact on patients with diabetes. One possible explanation is that the occurrence of AMI with diabetes might itself contribute to a poor long-term prognosis, with the result being a masked effect of admission hyperglycemia in diabetes patients[17,18]. In AMI patients without diabetes, admission hyperglycemia is an indicator of severe myocardial infarction and cardiac dysfunction[19,20]. Compared with diabetes patients whose blood glucose levels are basically elevated, an elevated blood glucose in patients without diabetes might be due to greater ischemia or hemodynamic damage[20]. A second possibility is that the hyperglycemia group in AMI patients without diabetes had a more extensive myocardial infarction, as they have a significantly higher C-reactive protein and tend to have higher brain natriuretic polypeptide. The third possibility is that diabetes patients were more likely to be treated with insulin. Studies have shown that appropriate insulin therapy can increase coronary perfusion. Insulin has been shown to activate endothelial nitric oxide synthase and increase the production of nitric oxide[21]. In addition, insulin might have other beneficial effects on patients with ischemia, such as reducing myocardial cell apoptosis[22].

In accordance with a previous study[23], we observed that, in both patients with and without diabetes, the hyperglycemia group included more women and its patients had a higher Killip grade compared with the non-hyperglycemia group, suggesting that older women and those with a poor cardiac function among AMI patients were more likely to develop admission hyperglycemia. The possible explanation is that older adults have a metabolic dysfunction and a weakened regulation ability, and they are more likely to develop metabolic disorders in response to stress. Similar to previous studies[8,23], the present results show that women are more likely to have admission hyperglycemia after AMI (mean age 72 ± 11 years). Although the mechanism is still unclear, most women develop AMI after menopause. The occurrence of hyperglycemia is likely to be related to the reduction of sex hormones, but the mechanism remains to be further investigated.

We also found that the proportion of STEMI and high C-reactive protein levels were higher in the hyperglycemia group compared with those in the non-hyperglycemia group, suggesting that the hyperglycemia group had a more severe disease with a stronger inflammatory response. The dramatic fluctuations in blood glucose lead to an increased level of inflammatory factors, an enhanced oxidative stress response and damaged endothelial cells, which can reduce the left ventricular function[24] and thus result in a poor clinical prognosis. In addition, previous studies found that high concentrations of free fatty acids can lead to an increased stress blood glucose[3]. In the present study, we observed that the level of triglycerides was higher in the hyperglycemia group compared with that in the non-hyperglycemia group, among patients without diabetes. In contrast, in patients with diabetes, no difference was observed between these factors in the hyperglycemic and non-hyperglycemic groups, which might be due to the small sample size or caused by diabetes itself.

Patients with AMI should be classified into different degrees of risk according to the admission blood glucose level, which should consider whether the patients have diabetes; thus, the predicted values should be different between patients with and without diabetes. This was not previously investigated. Furthermore, admission hyperglycemia was associated with increased infarct size and decreased left ventricular ejection fraction in AMI patients[25]. AMI patients with admission hyperglycemia should undergo hypoglycemic therapy, which can evidently improve the prognosis[26].

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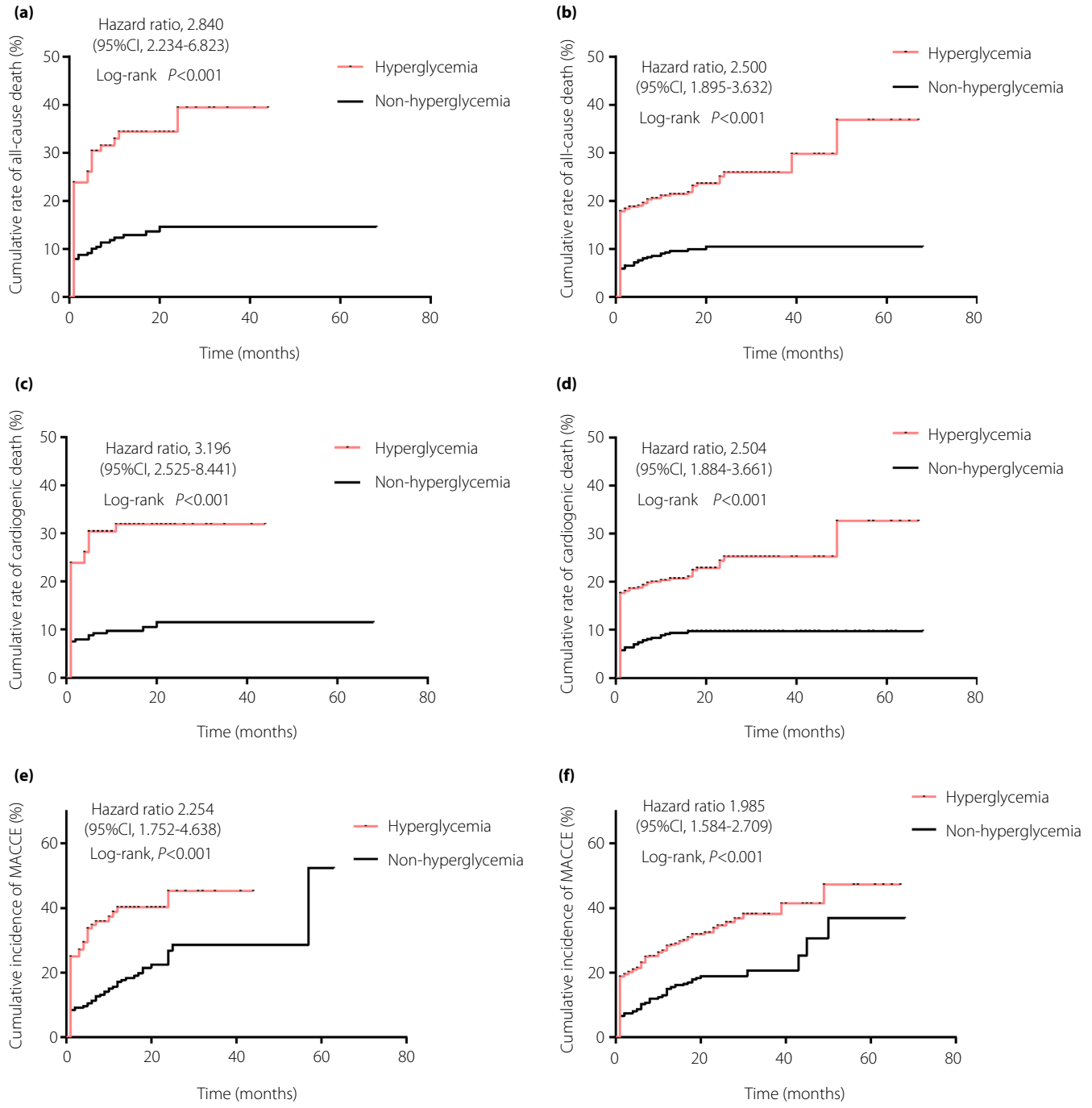

Figure 2 | (a) The cumulative rate of all-cause death in acute myocardial infarction (AMI) patients with diabetes. (b) The cumulative rate of all-cause death in AMI patients without diabetes. (c) The cumulative incidence of cardiogenic death in AMI patients with diabetes. (d) The cumulative incidence of cardiogenic death in AMI patients without diabetes. (e) The cumulative incidence of major adverse cardiovascular and cerebrovascular events (MACCE) in AMI patients with diabetes. (f) The cumulative incidence of MACCE in AMI patients without diabetes. CI, confidence interval.

The present study had some limitations. First, this was a retrospective study with a relatively small sample size, which might introduce a data bias. Second, we were unable to consider the duration, type or treatment of diabetes. In addition, there was a possibility that the blood glucose was checked differently in each hospital.

In conclusion, this work showed that admission hyperglycemia was significantly associated with a worse long-term

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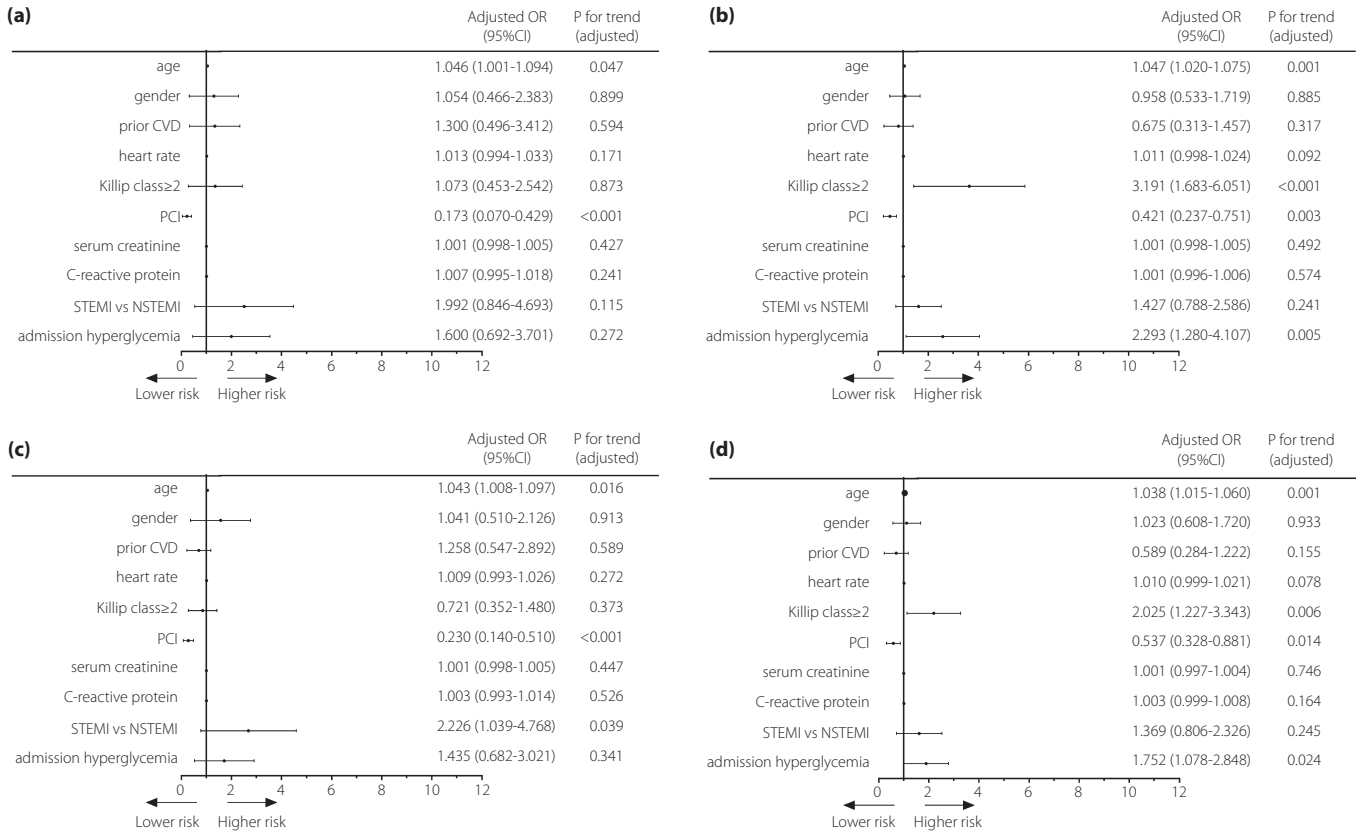

Figure 3 | (a) The Cox regression analysis of death for acute myocardial infarction (AMI) patients with diabetes. (b) The Cox regression analysis of death for AMI patients without diabetes. (c) The Cox regression analysis of major adverse cardiovascular and cerebrovascular events for AMI patients with diabetes. (d) The Cox regression analysis of major adverse cardiovascular and cerebrovascular events for AMI patients without diabetes. NSTEMI, non-ST-segment elevation myocardial infarction; OT, odds ratio; PCI, percutaneous coronary intervention; Prior CVD, prior cardiovascular disease; STEMI, ST-segment elevation myocardial infarction.

prognosis among AMI patients without diabetes. For these patients, blood glucose should be tested after admission, and more active treatment and nursing strategies should be adopted.

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DISCLOSURE

The authors declare no conflict of interest.

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