Relationship between hyperglycaemia at admission and prognosis in patients with acute myocardial infarction: a retrospective cohort study

Linlin Liu,1 Jun Qian,1 Wenwen Yan,1 Xuebo Liu,1 Ya Zhao,2 Lin Che1

ABSTRACT

Background The optimal threshold of hyperglycaemia at admission for identifying high-risk individuals in patients with acute myocardial infarction (AMI) and its impact on clinical prognosis are still unclear. 

Methods We retrospectively reviewed 2027 patients with AMI admitted from June 2001 to December 2012 in the ‘Medical Information Mart for Intensive Care III’ database. The significant cut-off values of admission blood glucose (Glucose_0) for predicting hospital mortality in patients with AMI with and without diabetes were obtained from the receiver operating characteristic (ROC) curve, then patients were assigned to hyperglycaemia and non-hyperglycaemia groups based on corresponding cut-off values. The primary endpoints were the hospital and 1-year mortality.

Results Among 2027 patients, death occurred in 311 patients (15.3%). According to the ROC curve, the significant cut-off values of Glucose_0 to predict hospital mortality were 224.5 and 139.5 mg/dL in patients with diabetes and without diabetes, respectively. The crude hospital and 1-year mortality of the hyperglycaemia subgroup were higher than the corresponding non-hyperglycaemia group (p<0.01). After adjustment, regardless of the state of diabetes, hyperglycaemia at admission was related to significantly increased hospital mortality in patients with AMI. For patients with AMI without diabetes, hyperglycaemia at admission was positively correlated with the increase of 1-year mortality (HR, 1.47; 95% CI 1.18 to 1.82; p=0.001). Nevertheless, this trend disappeared in those with diabetes (HR, 1.35; 95% CI 0.93 to 1.95; p=0.113).

Conclusion Hyperglycaemia at admission was an independent predictor for mortality during hospitalisation and at 1-year in patients with AMI, especially in patients without diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hyperglycaemia at admission is common in patients with acute myocardial infarction (AMI).
⇒ Hyperglycaemia at admission is a prognostic factor of poor short-term prognosis in patients with AMI.

WHAT THIS STUDY ADDS

⇒ Hyperglycaemia at admission was a high-risk marker of hospital mortality in patients with AMI, regardless of whether there is diabetes.
⇒ The significant cut-off value of admission blood glucose for predicting hospital mortality in diabetic patients with AMI was remarkably higher than that in non-diabetic patients.
⇒ For 1-year mortality, hyperglycaemia at admission was an independent predictor of non-diabetic patients with AMI rather than of diabetic patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For non-diabetic AMI patients with hyperglycaemia on admission, close blood glucose monitoring and more aggressive treatment measures should be taken during hospitalisation.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the highest morbidity and mortality diseases in the world.1 Although timely and effective revascularisation and drug use have improved the clinical outcomes of AMI, the mortality rate of AMI remains high. Additionally, other clinical factors affecting the mortality of patients with AMI are considered. Hyperglycaemia is a universal clinical phenomenon in critically ill patients, and more and more evidence has shown that it is related to the severity and mortality of the disease.2 Diabetes promotes the occurrence and development of AMI. For patients with AMI with diabetes, the prognosis is relatively poor and the mortality rate is high.3 Admission hyperglycaemia is a common phenomenon in patients with AMI. Epidemiological studies have shown that hyperglycaemia is present in approximately 25%–50% of patients with AMI and is considered an effective prognostic factor, regardless of whether they have diabetes or not.4,5 Subsequent research has suggested that high blood sugar levels at admission could predict short-term poor prognosis for patients with AMI without diabetes and that hospital mortality increases with an increase of blood glucose levels, but its prognostic value in patients with AMI remains controversial.6 Until now, no consensus has been reached on the value of admission hyperglycaemia in patients with AMI. The mechanisms of glucose metabolism are different between patients with diabetes and without diabetes, so the serum glucose cut-off value at admission for predicting mortality should be unequal.7 Nevertheless, most studies used the same prognostic threshold whether diabetes...
existed or not, which affected the predictive effect of admission serum glucose to a certain extent, especially in patients with AMI and diabetes.\(^9\)

Hence, this study sought to investigate the significant cut-off value of admission blood glucose for predicting adverse events in patients with AMI with or without diabetes, and to provide clinicians with a trigger point for glucose-lowering therapy.

**METHODS**

**Database introduction**

This was a retrospective cohort study from V.1.4 of the large key database ‘Multi-parameter Intelligent Monitoring in Intensive Care Database III’. This database contains comprehensive clinical information about patients who were hospitalised at the Beth Israel Deaconess Medical Center (BIDMC) in Boston,\(^{10}\) Massachusetts, USA, from June 2001 to October 2012. The database has been approved by the Institutional Review Board in advance. So, we were free to collect the original data without having to obtain informed consent. The research protocol complied with the Helsinki Declaration of 1975, which is reported in the prior approval of the institution’s Human Research Committee. Researchers around the world can access this database free of charge, but before entering the database and being eligible to extract the data, they must pass the National Institutes of Health online course called ‘Protection of Human Research Participants’ (certification number: 43259734).

**Study population**

All patients diagnosed with AMI from the database on the basis of the International Classification of Diseases (ICD)-9 diagnosis code (ICD-9 codes from 410.00 to 410.92) were selected retrospectively. The exclusion criteria were as follows: repeated admissions, multiple admissions to the intensive care unit (ICU), age <18 years or missing data, whereas for the repeated hospitalisations of some patients, the first admission information was adopted. Finally, 2027 patients were studied.

Subsequently, we extracted the admission data of these patients, including gender, age, sequential organ failure assessment (SOFA) score, comorbidities, laboratory test indicators, drugs used, hospital mortality, hospital length of stay (LOS), ICU LOS and 1-year mortality, using a structure query language. Additionally, we extracted the detailed records of blood glucose, wherein we defined the first admission blood glucose as admission blood glucose (Glucose_0), and regarded it as the main object of this study.

Considering the mechanism of glucose metabolism, different cut-off values should be used for patients with AMI with and without diabetes. So, patients were separated into diabetic and non-diabetic groups based on the medical history information provided by patients on admission. Significant cut-off values of Glucose_0 for the prediction of hospital mortality in patients with and without diabetes were derived from receiver operating characteristic (ROC) curves, respectively. Then, the diabetic and non-diabetic groups were separated into different subgroups with corresponding Glucose_0 cut-off values for subsequent analysis.

**Study endpoints**

Hospital mortality and 1-year mortality were the primary endpoints and the secondary endpoints included total hospital LOS, ICU LOS and acute kidney injury (AKI), which was a 1.5-fold increase in creatinine levels on admission. Survival time was defined as the interval from the day of admission until death. Survival status at discharge was defined by hospital mortality.

**Statistical analysis**

Continuous variables were reported as mean±SD or median (IQR), and Student’s t-test or Mann-Whitney U test was adopted as needed. The categorical variables were expressed as frequency (percentage), and the \(\chi^2\) test or Fisher’s exact test (as the case may be) was used for analysis.

The ROC curve was adopted to assess the potential of Glucose_0 to predict the hospital mortality of unequal disease groups, and the significant threshold was obtained according to the Youden Index. In addition, due to numerous variables involved in the research, univariate logistic regression was first used to initially screen the influencing factors between survivors and non-survivor groups, and then statistically significant covariates and clinically relevant confounders were incorporated into subsequent multivariate regression models. The variance inflation factor (VIF) was used to test for collinearity issues in the model (VIF >5, indicating multicollinearity). Logistic regression was performed to analyse the effect of admission hyperglycaemia on the hospital mortality. Kaplan-Meier curves were used to visually estimate 1-year survival rate, and the log-rank test was used for between-group comparisons. Cox multivariable regression model was operated to investigate the connection between hyperglycaemia and 1-year mortality in different groups. When \(p\) value was less than 0.05, it indicated there was a statistical difference. Stata (V.13, Stata Corp, College Station, Texas, USA) and statistical software package R were adopted for graphing and data analysis, respectively.

**RESULTS**

**Basic clinical information of the study population**

Of 2027 patients with AMI participated in the research (549 patients with diabetes and 1478 patients without diabetes). The mean age of these population was 68±14, of which 64% were men (1298/2027) and 36% were women (729/2027). According to the survival status at discharge, all population were divided into two groups. The clinical information characteristics of these patients are displayed in table 1. It could be seen that compared with the survivors group, individuals in the non-survivor group were older, more often women (46.3%) and the higher prevalence of heart failure (47.6%) and ventricular arrhythmia (24.4%); the creatinine level, white blood cell count, and SOFA score were significantly higher in the non-survivor group (\(p<0.001\)); and the Glucose_0 value (136.0 (114.0–175.0) mg/dL) in the survivor group was obviously lower than in the non-survivor group (164.0 (135.0–252.0) mg/dL) (\(p<0.001\)). In addition, there was no statistical difference in diabetes, chronic obstructive pulmonary disease, diuretic use, platelet count and serum sodium between the two groups.

Then, patients were classified into two groups on the basis of their diabetes status, and further analysis of basic clinical information were conducted (online supplemental table 1). The results presented that in comparison to the diabetic group, the non-diabetic group had fewer comorbidities (hypertension, heart failure, hyperlipidaemia and ventricular arrhythmias), lower use of antidiabetic drugs and lower Glucose_0 (132.0 (111.0–160.0) vs 178.0 (140.0–251.0), (\(p<0.001\)). Surprisingly, no significant difference in survival rates between the two groups was found (\(p=0.508\)).
The relationship between Glucose_0 and endpoints

The ROC curves were adopted to acquire the significant cut-off points for Glucose_0 in the prediction of the hospital mortality in patients with AMI with or without diabetes (figure 1). The significant cut-off values for the diabetes and non-diabetes groups were 224.5 mg/dL (area under curve (AUC)=0.612, a sensitivity of 52%, and a specificity of 72%, p<0.001) and 139.5 mg/dL (AUC=0.674, a sensitivity of 70%, and a specificity of 62%, p<0.001), respectively. Then patients with AMI with diabetes were divided into two subgroups: hyperglycaemic group (Glucose_0 ≥224.5 mg/dL) and non-hyperglycaemic group (Glucose_0 <224.5 mg/dL). Patients without diabetes were also divided into two subgroups: hyperglycaemic (Glucose_0 ≥139.5 mg/dL) and non-hyperglycaemic (Glucose_0 <139.5 mg/dL) and we further analysed the crude relationship between admission hyperglycaemia and clinical outcomes (table 2). The results revealed that with an increase in blood glucose in patients, the hospital and 1-year mortality increased significantly (p<0.01), whether the patients had diabetes or not. The hyperglycaemia in the non-diabetes group was obviously correlated with hospital LOS, ICU LOS and AKI (p<0.001). The hospitalisation time of patients with diabetes with Glucose_0 of ≥224.5 mg/dL (5.2 (3.2–9.9) days) was relatively shorter than that of patients with Glucose_0 of <224.5 mg/dL (6.0 (3.4–10.1) days), but the difference was not statistically significant (p=0.271).

In the diabetes group and the non-diabetes group, a multivariate logistic regression analysis was carried out to determine whether high blood sugar at admission was an independent hazard factor for hospital mortality (figure 2). Other variables such as gender, smoking status, hypertension, heart failure, hyperlipidaemia, ventricular arrhythmia, cerebral infarction, angiotensin-converting enzyme inhibitor (ACEI) use, insulin use, clopidogrel use, creatinine and SOFA score were adjusted, no collinearity was found in the final model of the diabetic and the non-diabetic groups (the maximum values of VIF were 3.28 and 3.27, respectively).

In the diabetes group, Glucose_0 of ≥224.5 mg/dL was distinctly correlated with an increase in hospital mortality

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**Table 1** Baseline characteristics of survivors and non-survivors

| Variables                  | Survivors (n=1716) | Non-survivors (n=311) | P value |
|---------------------------|--------------------|-----------------------|---------|
| Age (years)               | 66.9±13.8          | 74.0±13.1             | <0.001  |
| Male, n (%)               | 1131 (65.9)        | 167 (53.7)            | <0.001  |
| Smoke, n (%)              | 211 (12.3)         | 25 (8.0)              | 0.031   |
| Hypertension, n (%)       | 847 (49.3)         | 126 (40.5)            | <0.001  |
| Diabetes, n (%)           | 460 (26.8)         | 89 (28.6)             | 0.508   |
| Heart failure, n (%)      | 636 (37.1)         | 148 (47.6)            | <0.001  |
| COPD, n (%)               | 16 (0.9)           | 4 (1.3)               | 0.561   |
| Hyperlipidaemia, n (%)    | 414 (24.1)         | 52 (16.7)             | 0.004   |
| Ventricular arrhythmia, n (%) | 285 (16.6)  | 76 (24.4)             | 0.001   |
| Cerebral infarction, n (%)| 34 (2.0)           | 12 (3.9)              | 0.041   |

**Admission drugs**

| Aspirin, n (%)   | 1456 (84.8) | 207 (66.6) | <0.001 |
| Clopidogrel, n (%) | 1123 (65.4) | 122 (39.2) | <0.001 |
| Statin, n (%)    | 1278 (74.5) | 129 (41.5) | <0.001 |
| β-blocker, n (%) | 1438 (83.8) | 150 (48.2) | <0.001 |
| ACEI, n (%)      | 1148 (66.9) | 66 (21.2)  | <0.001 |
| Diuretic, n (%)  | 940 (54.8)  | 152 (48.9) | 0.055  |
| Insulin, n (%)   | 291 (17.0)  | 83 (26.7)  | <0.001 |

**Laboratory data**

| WBC, 10⁹/L       | 11.3 (9.0–14.3) | 13.1 (10.8–18.4) | <0.001 |
| Platelet count, 10⁹/L | 219 (174–271) | 219 (167–276) | 0.545  |
| Haemoglobin, mg/dL | 11.8 (10.3–13.3) | 11.2 (9.9–12.1) | <0.001 |
| Sodium, mmol/L   | 138 (136–140)  | 138 (135–141) | 0.144  |
| Creatinine, mg/dL | 0.9 (0.8–1.2)  | 1.4 (1.0–2.0) | <0.001 |
| Urea, mg/dL      | 17.0 (13.0–24.0) | 28.0 (18.0–44.0) | <0.001 |
| SOFA score       | 2.0 (1.0–5.0)  | 7.0 (4.0–10.0) | <0.001 |
| Glucose_0, mg/dL | 136.0 (114.0–175.0) | 164.0 (135.0–252.0) | <0.001 |

Data are mean±SD, median (IQR) or n (%).

ACEI, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; Glucose_0, admission blood glucose; SOFA, sequential organ failure assessment; WBC, white blood cell count.

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**Figure 1** ROC curve of Glucose_0 predicting hospital mortality of patients with AMI. (A) The ROC curve of Glucose_0 to predict hospital mortality for patients with AMI with diabetes. (B) The ROC curve of Glucose_0 to predict hospital mortality for patients with AMI without diabetes. AMI, acute myocardial infarction; AUC, area under curve; Glucose_0, admission blood glucose; ROC, receiver operating characteristic.
Original research

(OR, 2.19; 95% CI, 1.18 to 4.06; p = 0.013). Of important, gender (OR, 0.53; 95% CI 0.37 to 0.75; p < 0.001), ventricular arrhythmia (OR, 1.81; 95% CI 1.20 to 2.75; p = 0.005), ACEI use (OR, 0.20; 95% CI 0.13 to 0.30; p < 0.001), SOFA score (OR, 1.30; 95% CI 1.23 to 1.37; p < 0.001) and Glucose_0 of ≥139.5 mg/dL (OR, 2.63; 95% CI 1.83 to 3.78; p < 0.001) were independent predictive factors for hospital mortality in patients with AMI without diabetes.

Survival analysis

The Kaplan-Meier curves demonstrated that 1-year mortality was remarkably different between the hyperglycaemic and non-hyperglycaemic groups (figure 3) whether they had diabetes or not. The log-rank test displayed a statistically remarkable difference in the 1-year mortality between the two subgroups (p < 0.001). The results of the Cox proportional hazard model were presented in table 3. Adjusted for other covariates such as gender, smoking status, hypertension, heart failure, hyperlipidaemia, ventricular arrhythmia, cerebral infarction, ACEI use, insulin use, clopidogrel use, creatinine and SOFA score, hyperglycaemia at admission was a risk factor for predicting 1-year mortality, especially in patients without diabetes with AMI (HR, 1.47; 95% CI 1.18 to 1.82).

To further determine the association of admission hyperglycaemia with long-term outcome in patients with AMI without diabetes, subgroup analyses were performed (online supplemental table 2). The results revealed a stable positive correlation between admission hyperglycaemia and 1-year mortality in most stratifications, except for cerebral infarction (HR, 2.30; 95% CI 0.75 to 7.05; p = 0.145).

DISCUSSION

This research was designed to analyse the predictive potential of Glucose_0 on prognosis in patients with AMI with and without diabetes, and to determine risk stratifications through the significant cut-off values. We found that hospital mortality in the hyperglycaemia group was remarkably higher than that in the non-hyperglycaemia group, whether combined with diabetes or not. Notably, Glucose_0 of ≥139.5 mg/dL was one of the predicting factors of 1-year mortality in patients with AMI without diabetes. By comparison, hyperglycaemia on admission was not a predictor of 1-year mortality in those patients who had diabetes.

Admission hyperglycaemia is an important and often overlooked condition that can have potentially fatal consequences. Some studies defined hyperglycaemia as fasting blood glucose of ≥126 mg/dL or random blood glucose of ≥200 mg/dL. Capes’s meta-analysis showed that among patients with MI, patients without diabetes with fasting plasma glucose greater than or equal to the range of 6.1–8.0 mmol/L had a 3.9 times higher risk of death than patients without high blood glucose level. In short, there is no definitive conclusion about the definition of admission hyperglycaemia. We avoided the effect of drug intervention on blood glucose values after admission by adopting the blood glucose value in the first blood analysis at admission. Nonetheless, we adopted
different thresholds according to the different status of diabetes to eliminate the interference of chronic high glucose in patients with diabetes. These steps provided suggestions for clinicians about when to start treatment in the face of patients with AMI with diabetes or not.

Some potential mechanisms may explain our research results. Hyperglycaemia increases cell adhesion factor, causes leucocyte aggregation in capillaries, shortens fibrinogen half-life, increases fibrinogen peptide A and coagulation factor VII, increases platelet aggregation, increases platelet thrombosis,14 and reduces endothelium-dependent vasodilation, thereby increasing MI area, significantly reducing cardiac function and increasing mortality.15 We noticed that the admission blood glucose and white blood cell count of non-survivors were significantly higher than those of survivors. This was consistent with previous studies, indicating that hyperglycaemia is related to inflammation.16 Besides, hyperglycaemia is also related to an increase in free fatty acids and prolonged QT interval, which lead to the occurrence of ventricular arrhythmia and the elimination of ischaemic preconditioning.17 18 We observed that the proportion of ventricular arrhythmias in the non-survivors was higher, which was consistent with previous research conclusions that hyperglycaemia was positively correlated with malignant arrhythmias.19

We obtained significant cut-off values of admission serum glucose for predicting hospital mortality in patients with AMI with or without diabetes from the ROC curve. Setting different blood glucose targets for patients with and without diabetes in clinical trials of hyperglycaemia in patients with AMI should be taken into consideration, which was consistent with previous study from Li et al.20 Therefore, we distinguished patients with AMI with or without diabetes. The significant cut-off value of non-diabetes (139.5 mg/dL) was markedly lower than that of the diabetes group (224.5 mg/dL), and with an increase in blood glucose level, the hospital mortality of the two groups increased distinctly. Briefly, 1-year mortality, ICU LOS and AKI were also significantly correlated with hyperglycaemia. In the diabetes group, the hospital LOS was prolonged in patients with Glucose_0 of <224.5 mg/dL, but there was no statistical difference. Patients in non-hyperglycaemic group should be under long-term observation when using hypoglycaemic drugs, so as to avoid hypoglycaemia and worse prognosis. We also found that patients without diabetes had significantly higher survival rate than patients with diabetes (p=0.508), although there was no statistical difference, which might be related to the fact that some patients with undiagnosed diabetes or impaired glucose tolerance on admission were included in the non-diabetes group.

**Figure 3** Kaplan-Meier survival curves for 1-year mortality. (A) Kaplan-Meier survival curves for 1-year mortality in patients with AMI with diabetes. (B) Kaplan-Meier survival curves for 1-year mortality in patients with AMI without diabetes. AMI, acute myocardial infarction; Glucose_0, admission blood glucose.

**Table 3** Effect of hyperglycaemia at admission on 1-year mortality in Cox regression analysis

| Variable | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|----------|------------------------|---------|----------------------|---------|
| (Glucose_0, mg/dL) | HR | HR (95% CI) | | HR | HR (95% CI) | |
| Diabetes | <224.5 (n=376) | Ref. | Ref. | | | |
| ≥224.5 (n=173) | 1.83 | 1.83 (1.31 to 2.56) | < 0.001 | 1.35 | 1.35 (0.93 to 1.95) | 0.113 |
| Non-diabetes | <139.5 (n=850) | Ref. | Ref. | | | |
| ≥139.5 (n=628) | 2.32 | 2.32 (1.88 to 2.86) | < 0.001 | 1.47 | 1.47 (1.18 to 1.82) | 0.001 |

Adjusted gender, smoking status, hypertension, heart failure, hyperlipidaemia, ventricular arrhythmia, cerebral infarction, angiotensin-converting enzyme inhibitor use, insulin use, clopidogrel use, creatinine and sequential organ failure assessment score. Glucose_0, admission blood glucose; Ref, reference.
After multivariate regression analysis, Glucose_0 of ≥224.5 mg/dL and Glucose_0 of ≥139.5 mg/dL were independent predictors of hospital mortality in patients with AMI who had been diagnosed with diabetes or not, respectively. Admission hyperglycaemia can lead to an increase in cardiovascular events, including non-lethal and fatal, and also is an important predictor of mortality independently of diabetic status in patients with AMI.21 22 It is undesirable for patients with diabetes to adopt the same threshold as that of patients without diabetes, which reduces the reduction in the plasma glucose level much lower than the basic plasma glucose level of an individual patient with diabetes (this may be the patient’s relative hypoglycaemia).23 At the same time, a rapid reduction in blood sugar level may also contribute to poor cardiovascular outcomes.24 Some other studies have shown that hyperglycaemia is a risk factor for failed myocardial tissue reperfusion and increased mortality after primary angioplasty.25 This may be due to the decreased plasma fibrinolytic capacity and increased platelet aggregation under hyperglycaemia. Furthermore, this study also revealed that after adjusting the mixed factors, Cox regression analysis displayed that hyperglycaemia at admission was associated with worse long-term endpoint in patients without diabetes with AMI, but not in patients with diabetes. On the one hand, it might result from poor diet control, inadequate insulin therapy and inconsistent blood glucose monitoring in patients without diabetes. On the other hand, elevated blood glucose was often associated with large MIs and unstable haemodynamics in patients without diabetes compared with patients with diabetes.26 27 Therefore, we suggest that admission hyperglycaemia in patients without diabetes with AMI should be given adequate attention and managed strictly.

We had to admit that this study had certain limitations. First, it was a single-centre small sample study that could only infer the association between hospitalised hyperglycaemia and hospital mortality. Further research is required to confirm the causal relationship. Second, we did not track glycated haemoglobin or glucose tolerance tests in the analysis, resulting in some undiagnosed patients with diabetes being mixed into the non-diabetic group. This inescapably led to certain deviations in the results, but it did not affect the validity of the results. However, the results should be interpreted with caution and confirmed by in-depth studies in the future. Finally, when combined with the AUC of the two groups, the efficiency of blood glucose at admission in predicting hospital mortality was not high, which might have been affected by the small sample size of a single centre.

CONCLUSIONS

Overall, the predictive value of hyperglycaemia at admission was similar among patients with and without diabetes with AMI for hospital mortality. However, in terms of the long-term prognosis, hyperglycaemia at admission was an independent predictor of patients with AMI without diabetes, rather than those with diabetes. Therefore, especially for patients without diabetes with AMI, timely and effective hypoglycaemic treatment strategies and nursing measures are very important.

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ORCID iD Linlin Liu http://orcid.org/0000-0002-2425-8845

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