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An In-depth Look into Urban and Rural Disparities in Prehospital Delay in Patients with Acute ST-elevation Myocardial Infarction and Its Impact on Prognosis

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An In-depth Look into Urban and Rural Disparities in Prehospital Delay in Patients with Acute ST-elevation Myocardial Infarction and Its Impact on Prognosis

Short title: Prehospital delay in acute STEMI in rural China

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ABSTRACT

Objectives Despite the improvement in prognosis in patients with ST-segment elevation myocardial infarction (STEMI), the difference in prehospital delay between urban and rural areas of China and its impact on prognosis is unclear.

Design Prospective observational study.

Setting This study was conducted in a tertiary hospital. This hospital is the only nationally accredited chest pain center with percutaneous coronary intervention (PCI) capacity in the Pizhou, China.

Participants 394 patients with STEMI without patients with in-hospital STEMI or patients who were lost to follow-up were included.

Primary outcome measures The primary outcome was major adverse cardiovascular events (MACEs), including cardiac death, nonfatal myocardial infarction and heart failure.

Results Among 394 patients enrolled, 261 (66.2%) were men, the median age was 69 years (IQR: 61-77 years), and 269 (68.3%) were from rural areas. S2D time was significantly longer for rural patients than for urban patients (190 min *vs.* 75 min, $P<0.001$). Cox regression analyses revealed that living in rural areas was independently associated with prolonged S2D time (adjusted HR, 0.59; 95% CI, 0.43-0.81; $P=0.001$). During the one-year follow-up, the incidence of MACEs was higher in rural patients (24.5% *vs.* 12.8%, $P=0.008$). The unadjusted OR for MACEs between rural patients and urban patients was 2.22 (95% CI, 1.22-4.01). Adjusting for sex did not attenuate the association (OR, 2.06; 95% CI, 1.13-3.76), but after further adjusting for age, cardiac function classification, S2D time, and performance of primary PCI, we found that the odds were similar for rural and urban patients (OR, 1.19; 95% CI, 0.59-

2.38).

Conclusions Rural patients with STEMI had a longer S2D time, which led to a higher incidence of MACEs. This study provides rationales for taking all the measures to avoid prehospital delay.

Key Words: Acute myocardial infarction; Prehospital delay; Urban and rural areas; Prognosis.

Strengths and limitations of this study:

- This study is the first to investigate the urban and rural disparities in prehospital delay in patients with acute STEMI and its impact on the prognosis of STEMI in China.
- This study explores the seriousness of prehospital delay in rural areas, and suggests measures of future exploration.
- The population in this study came from the developed plain areas of China, and the actual situation of the whole China is not clear.
- The outcomes of patients lost to follow-up might influence our results, but the influence might be slight.

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is the most common acute manifestation of coronary heart disease, with high morbidity and mortality.[1] The Global Registry of Acute Coronary Events (GRACE) showed that STEMI accounted for one-third of coronary events.[2] In China, the proportion of hospitalized STEMI patients has been increasing year by year.[3] Therefore, STEMI is a major public health problem, seriously threatening human life and bringing very large economic burdens to both families and society. In recent years, with the progress of medical treatment and preventive measures, the mortality and complication rates have been reduced in STEMI patients.[4-7] The time from symptom onset to culprit vessel reperfusion has also been greatly reduced since fast heart attack care is promoted globally.[8] In line with the cardiac fast track, the "green pathway for patients with heart attack" policy is implemented in China. With the acceleration of chest pain center construction, the treatment of acute myocardial infarction in China, especially the door-to-balloon (D2B) time, is improving.[9, 10] However, the prehospital delay in patients with STEMI has never been thoroughly investigated in China. Although the number of rural residents has decreased due to industrialization and urbanization in China, there are still a large number of people living in rural areas, especially elderly people.[11] People in rural areas have relatively poor knowledge of the disease, less efficient transportation facilities and lower levels of primary care.[12,13] To provide a theoretical basis for spreading the accredited chest pain center further down to the rural front line and optimizing the management algorithm of chest pain patients, this study aimed to explore the urban and rural disparities in prehospital delays in STEMI patients and their impact on prognosis.

METHODS

Study design and population

In this prospective observational study, all acute STEMI patients who were admitted to the Pizhou Affiliated Hospital of Xuzhou Medical University (Pizhou Hospital) from January 2018 to June 2020 were included. This hospital is the only nationally accredited chest pain center with percutaneous coronary intervention (PCI) capacity in the Pizhou, a region of 2,088 square kilometers and 1.46 million people. STEMI was diagnosed in accordance with the universal definition of myocardial infarction.[14] All the patients were divided into the rural group and the urban group based on their location where STEMI occurred. Patients with in-hospital STEMI or patients who were lost to follow-up were excluded from this study.

Data collection

Sociodemographic characteristics (age, sex, and education level) and clinical characteristics (cardiovascular comorbidities, smoking, drinking, previous medical history, and cardiac function classification) were collected. Based on the highest level of education completed by the participants, the education level was classified as below high school or high school or above. The estimates of delays, including symptom-to-door (S2D) time and D2B time, and transportation distance, were based on data registered in the national chest pain center reporting platform. In our study, prehospital delay was defined as S2D time, *i.e.*, time from symptom onset to arrival at Pizhou Hospital. Therefore, the prehospital delay consists of patient delay (time from symptom onset to first medical contact) and prehospital system delay (time from first medical contact to arrival at the PCI center). The location where STEMI occurred was self-reported by patient. Transportation distance was defined as the distance from the patient's location where the STEMI occurred to Pizhou Hospital. In addition, information on pretreatment with fibrinolysis and the performance of primary PCI (PPCI) was collected. According to the recommendation from the guidelines, a PPCI is not indicated in patients with time from symptom onset >12 h and without ongoing symptoms.[15] The first-visit medical institutions of the patients were categorized into primary healthcare centers and tertiary hospitals according to the Chinese hospital classification system.

Clinical outcomes and follow-up

The primary endpoint was major adverse cardiovascular events (MACEs), which included cardiac death, nonfatal myocardial infarction and heart failure. The secondary endpoints were cardiac death, nonfatal myocardial infarction, heart failure, in-hospital death and all-cause death. The time and cause of death were obtained from the self-report of the patient's relatives or Xuzhou Centers for Disease Control and Prevention database.

All patients received standard of care after discharge. Follow-up was completed via clinic visits or by telephone interviews with patients or their relatives every 3 months after discharge within one year.

Statistical analysis

All the continuous variables investigated in our study were nonnormally distributed and presented as medians and interquartile ranges (IQRs). Differences between groups were tested using the Mann–Whitney U test. The categorical variables were expressed as counts with percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was considered when two-sided P values <0.05.

A multivariable Cox proportional hazards model was constructed from S2D time by rural/urban areas and was adjusted for sex, age, education level, transportation distance and first-visit to a medical institution. These variables were adjusted based on our hypothesis that they would at least partly explain the association between regional differences and S2D time persuasively. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were used to estimate the association.

Multivariable logistic regression was performed to determine the risk factors associated with the incidence of MACEs. Variables with a P value <0.01 in univariate analyses were included in the multivariable logistic regression model. An additional multivariable logistic regression was performed to estimate the association of rural areas and incident MACEs. The odds ratios (ORs) and the corresponding 95% CIs were obtained to assess the association. All analyses were performed using SPSS statistical software version 22.0.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Baseline demographic characteristics

A total of 418 acute STEMI patients were admitted to Pizhou Hospital during our study period. Our final analysis included 394 patients who fulfilled the inclusion and exclusion criteria. Figure 1 depicts the patient flow through the study. In total, the median age was 69 years (IQR: 61-77 years), and 261 (66.2%) of the patients were men. Table 1 shows the baseline characteristics of all 394 patients. Compared with those in the urban group, patients in the rural group were older and more likely to be female and poorly educated. Our study group and the group of patients lost to follow-up were balanced with respect to all the baseline characteristics. (Supplementary Table 1).

Table 1 Baseline characteristics of the patients in the two groups

Characteristic	Rural group (n=269)	Urban group (n=125)	*P* value
Demographics			
Age, median (IQR), y	70 (63-79)	66 (56-74)	<0.001
Women, n (%)	100 (37.2)	33 (26.4)	0.035
Education level, n (%)			<0.001
Less than high school	248 (92.2)	92 (73.6)	
High school and above	21 (7.8)	33 (26.4)	
Clinical characteristics, n (%)			
Hypertension	109 (40.5)	53 (42.4)	0.724
Diabetes mellitus	49 (18.2)	26 (20.8)	0.543
Dyslipidemia	128 (47.6)	71 (56.8)	0.089
Previous myocardial infarction	6 (2.2)	4 (3.2)	0.732
Previous PCI	8 (3.0)	4 (3.2)	1.000
Current smoker	67 (24.9)	32 (25.6)	0.883
Current drinker	57 (21.2)	24 (19.2)	0.649
Killip class, n (%)			0.394
I	240 (89.2)	115 (92.0)	0.390
II	14 (5.2)	5 (4.0)	0.604
III	8 (3.0)	2 (1.6)	0.514

IV	7 (2.6)	3 (2.4)	1.000

IQR=interquartile range; PCI=percutaneous coronary intervention.

Data regarding delays, transportation distance and performance of PPCI

Table 2 shows that S2D time was significantly longer for patients in the rural group than for those in the urban group (190 min *vs.* 75 min, *P*<0.001). The transportation distance from the patient's location where the STEMI occurred to the tertiary hospital with PPCI capacity (Pizhou Hospital) was longer for patients in the rural group than for those in the urban group (23.3 km *vs.* 4.5 km, *P*<0.001). Patients in the rural group were less likely to go to Pizhou Hospital for their first medical visit than were those in the urban group (27.5% *vs.* 48.8%, *P*<0.001). Patients in the rural group were more likely to miss the PPCI indication (13.4% *vs.* 4.0%, *P*=0.005). The proportion of patients who underwent PPCI was significantly lower in the rural group than in the urban group (75.1% *vs.* 91.2%, *P*<0.001). There was no significant difference in D2B time between the two groups. Notably, thrombolytic therapy was not performed in any of the patients in the entire cohort.

Table 2 Delays, transportation distance and performance of primary percutaneous coronary intervention

Characteristic	Rural group (n=269)	Urban group (n=125)	*P* value
Delays and transportation			
Delay, median (IQR), min			

S2D time	190 (108-432)	75 (47-155)	<0.001
D2B time	80 (63-103)	84 (66-105)	0.432
Transportation, median (IQR), km	23.3 (16.2-29.7)	4.5 (2.6-7.7)	<0.001
Ambulance transfer, n (%)	117 (43.5)	48 (38.4)	0.340
First-visited medical institution, n (%)			<0.001
Primary healthcare center	177 (65.8)	56 (44.8)	<0.001
Tertiary hospital without PPCI capability	18 (6.7)	8 (6.4)	0.914
Tertiary hospital with PPCI capacity (Pizhou Hospital)	74 (27.5)	61 (48.8)	<0.001
Performance of PPCI n (%)			0.001
indication of PPCI missed	36 (13.4)	5 (4.0)	0.005
PPCI performed	202 (75.1)	114 (91.2)	<0.001
With indication, but PPCI not perform	31 (11.5)	6 (4.8)	0.033

IQR=interquartile range; S2D=symptom to door; D2B=door to balloon; PPCI=primary percutaneous coronary intervention.

Cox regression analyses revealed that patients in the rural group had significantly longer S2D times than those in the urban group (crude HR, 0.46; 95% CI, 0.37-0.57; *P* <0.001). An HR of <1 indicates that the S2D time is longer for patients in the rural group (group of interest) than for those in the urban group (reference group). This association remained statistically significant (adjusted HR, 0.59; 95% CI, 0.43-0.81; *P*=0.001) after adjusting for sex, age, education level, transportation distance, and first-visit to a medical institution (Table 3).

Table 3 S2D: Crude and adjusted HRs

Variable	HR	95% CI	P
Crude analysis			
Rural areas	0.46	0.37-0.57	<0.001
Adjusted model			
Rural areas	0.59	0.43-0.81	0.001
Women	0.87	0.69-1.09	0.215
Age	0.98	0.97-0.99	<0.001
Education level (high school and above)	0.99	0.72-1.37	0.953
Transportation distance	0.99	0.98-1.01	0.233
First-visited medical institution other than Pizhou Hospital	0.91	0.73-1.13	0.378

S2D=symptom to door; HR=hazard ratio; CI=confidence interval.

Major adverse clinical events during the one-year follow-up

During the one-year follow-up, MACEs occurred in 66 patients in the rural group (24.5%, 66/269) and 16 patients (12.8%, 16/125) in the urban group (*P*=0.008). As shown in Figure 2, no statistically significant difference was observed in the incidence rates of cardiac death, nonfatal MI, and heart failure between the two groups. The all-cause mortality of the rural group was significantly higher than that of the urban group (17.8% *vs.* 8.8%, *P*=0.019).

Independent predictors of MACEs in the entire study population were older age, Killip class ≥II and prolonged S2D time (Supplementary Table 2).

Table 4 shows that, when rural patients and urban patients were compared, the unadjusted OR for MACEs after STEMI was 2.22 (95% CI, 1.22-4.01). Adjusting for sex did not attenuate the association (OR, 2.06; 95% CI, 1.13-3.76), but further adjusting for age attenuated the association between rural areas and MACEs (OR, 1.66; 95% CI, 0.89-3.08). After additional adjustment for the cardiac function classification, S2D time, and performance of PPCI, the odds were similar for rural and urban patients (OR, 1.19; 95% CI, 0.59-2.38).

Table 4 Association of rural areas with MACEs

MACEs	Urban group (n=125)	Rural group (n=269)	*P* value
Cases	16	66	
Model 0, OR (95% CI)	1 (reference)	2.22 (1.22-4.01)	0.009
Model 1, OR (95% CI)	1 (reference)	2.06 (1.13-3.76)	0.018
Model 2, OR (95% CI)	1 (reference)	1.66 (0.89-3.08)	0.111
Model 3, OR (95% CI)	1 (reference)	1.72 (0.89-3.33)	0.105
Model 4, OR (95% CI)	1 (reference)	1.59 (0.83-3.07)	0.166
Model 5, OR (95% CI)	1 (reference)	1.19 (0.59-2.38)	0.626

MACEs=major adverse cardiovascular events; OR=odds ratio; CI=confidence interval; S2D=symptom to door; PPCI=primary percutaneous coronary intervention.

Model 0: unadjusted

Model 1: adjusted for sex

Model 2: adjusted for variables in model 1 and age

Model 3: adjusted for variables in model 2 and characteristics of the cardiac function classification (Killip class ≥II)

Model 4: adjusted for variables in model 3 and S2D in hours

Model 5: adjusted for variables in model 4 and characteristics of PPCI

DISCUSSION

Our study is the first to investigate the urban and rural disparities in prehospital delay in patients with acute STEMI and their impact on the prognosis of STEMI in China. The major findings are as follows: 1) Although the D2B time was similar between the two groups, the S2D time was significantly prolonged in patients from rural areas compared with those in urban areas; 2) in the rural group, patients had a higher proportion of missed PPCI indications and were less likely to receive PPCI; and 3) a higher one-year incidence rate of MACEs was observed in the rural group than in the urban group. This disparity could be explained by age, cardiac function classification, S2D time, and PPCI performance.

The 2017 European Society of Cardiology Guidelines emphasized the total ischemic time of STEMI, raising the concept of entire rescue time, which consists of S2D time and D2B time.[15] A reduction in D2B time is significantly associated with a decrease in mortality,[16, 17] and measures have been taken to reduce D2B time.[18, 19] With the establishment of chest pain centers in China in the past decade, the D2B time was greatly reduced to within 60-90 min.[10]

However, a further decrease in D2B time from 83 min to 67 min had no association with a reduction in in-hospital mortality.[20] In our study, the D2B time was approximately 80 min, and there was no difference in in-hospital mortality between the two groups. However, the one-year clinical outcome was markedly different. This difference is attributed to the entire myocardial ischemic time. To reduce the entire rescue time, the possibly shortened duration is S2D time.

Indeed, in our study, the S2D time of STEMI patients in the rural group was much longer than that of the urban group. There are four possible reasons accounting for this prehospital delay. 1) Poor family care: Our study showed that STEMI patients from rural areas were older. Such senior patients in rural China lack good family care because their adult children move to cities or coastal areas to seek better employment opportunities.[21] We acknowledge that old age is an independent predictor of MACEs and all-cause mortality,[22] but poor family care is the hurdle to receiving quick first-aid service when older patients are in need. 2) Lacking disease awareness: The most important factor influencing the awareness of disease was educational level, followed by age. From the baseline characteristics of our observation, the rural patients had a lower educational level and older age. Their insufficient understanding and misjudgment of early symptoms of STEMI[23] prolonged the prehospital time and missed the best opportunity for revascularization. 3) Access to medical resources: The accessibility of high-quality medical facilities has a conceivable impact on the treatment of patients. Compared with urban patients, rural patients lack high-quality medical resources.[24] The nearest medical facilities for rural patients with STEMI are village clinics and town hospitals that do not have the capability of PPCI. Patients have to be transported to large tertiary hospitals after diagnosis. In our study, rural patients had higher referral rates than their urban counterparts did. Notably, none of the patients initially underwent thrombolytic therapy before admission to tertiary hospitals. 4) Transportation distance and facilities: The distance between the residence of rural patients and hospitals qualified for PCI was significantly longer than that of urban patients according to our observation. Although the average distance of 23 km is not very long in modern society, the facilities for rural patients to use are insufficient. Less frequent public transportation, less ownership of private vehicles, and less efficient cabs or ambulances are responsible for these delays.

The prolonged S2D time in the rural group could contribute to rural patients missing the PPCI indication and indirectly lead to a lower proportion of patients receiving PPCI. Previous studies have demonstrated that elderly, female and poorly educated patients were less likely to receive reperfusion therapy.[25-27] These are exactly the characteristics of the rural STEMI patients in our study. They often have a bias in understanding the disease and the consequent treatment strategies and therefore present poor compliance to accept invasive treatment.

Early opening of infarcted vessels is the key point for STEMI and is crucial for improving the prognosis of STEMI patients.[28, 29] A previous study demonstrated a 7.5% increase in annual mortality for every 30 min delay in successful reperfusion.[30] Our study showed that the S2D time was significantly longer than that of urban patients, which led to a significantly higher incidence of MACEs and mortality in rural patients than in urban patients. In our study, the in-hospital mortality of the entire study population was 4.31%, which was close to the average level reported previously,[31] suggesting that the in-hospital algorithm and the management of STEMI patients are in line with guideline-directed medical therapy. In this study, no difference in in-hospital mortality between the two groups was found, which might be due to the small sample size.

Prehospital delays are highly associated with the outcomes of patients according to the results of this study. This provides evidence for further optimizing the workflow of emergent management of STEMI patients. While emphasizing the in-hospital management algorithm, we should extend our strength to prehospital management, especially in rural areas of China. Patients' awareness of STEMI symptoms and reperfusion procedures should be raised and treatment compliance should be further improved by strengthening propaganda and education among villagers. This is the first step towards reducing prehospital delays. Second, primary medical institutions should carry out thrombolytic therapy as an emergency treatment. This is an important step to shorten the total ischemic time and improve the prognosis of STEMI patients. Third, in order to alleviate the shortage of first-aid tools and improve the first-aid system in rural areas, more ambulances should be equipped. Moreover, the intelligent construction of village clinics is also a crucial link in the "last mile" of prehospital treatment for acute myocardial infarction in rural areas. Primary medical treatment and emergency treatment will be connected with regional large comprehensive hospitals through installation of wireless electrocardiograph equipment and construction of an online medical network platform to achieve the "sinking of high-quality medical resources to remote areas". When the older patients with hurdle of receiving quick first-aid service, they can call the emergency medical telephone. The nearest village doctor can reach the patient and perform electrocardiogram, which can be transmitted to the PCI hospital diagnosis center wirelessly for rapid diagnosis of the disease. If STEMI is highly suspected, village doctors can promptly pretreat the patients with antiplatelet drugs, and at the same time call an ambulance and send the patients to the PCI center for reperfusion therapy. In this way, barriers of receiving medical service for older patients will be resolved and referral efficiency will be improved. These measures play important roles not only in the treatment of acute myocardial infarction patients but also in the improvement of public health services and other emergent treatments in rural areas.

This study has several limitations. First, it was a single-center observational study, and the overall sample size was relatively small. Further long-term follow-up and a larger sample size are needed to validate the results of this study. Second, the population in this study is from the developed plain area of China. Our results might not represent the actual situation of China as a whole. However, the large "gap" in the management of STEMI patients between urban and rural areas could not be underestimated. Third, the proportion of patients lost to follow-up was 4.5%, which may influence our results. However, the baseline characteristics were balanced between the patients who were followed up and those who lost to follow-up.

CONCLUSIONS

Compared with urban patients, rural patients with acute STEMI had a prolonged prehospital delay, which led to a higher incidence of MACEs. This study provides rationales for taking all the measures to avoid prehospital delay by spreading chest pain units down to the rural front line through an online platform. Strengthening the propagation and education of knowledge regarding chest pain and advanced treatment to rural dwellers and village doctors is also necessary.

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Contributors:

ML Chen, MF Li and Y Yang participated in the design of this study. J Wang, JR Yin and PA Lou record all the cases. CX Shen, CZ Li, ZR Wang and Y Lu collected and performed the statistical analysis. CX Shen wrote the first draft of the manuscript. CZ Li revised the manuscript. ML Chen and MF Li monitored the study. All authors provided input on data analysis, interpretations and participated in multiple revisions of the manuscript, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Competing interests:

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval:

This study was approved by the Clinical Research Ethnics Committee of The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China (XYFY2021-KL141-01) on June 22, 2021.

Data availability statement:

The data that supports the finding of this study are available in the supplementary material of this article.

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Figure legends:

Figure 1. Flow of patients through the study.

STEMI=ST-segment elevation myocardial infarction

Figure 2. Incidence rate of primary and secondary endpoint events at 1 year in the rural group *vs.* the urban group.

MACEs=major adverse cardiovascular events; MI=myocardial infarction.

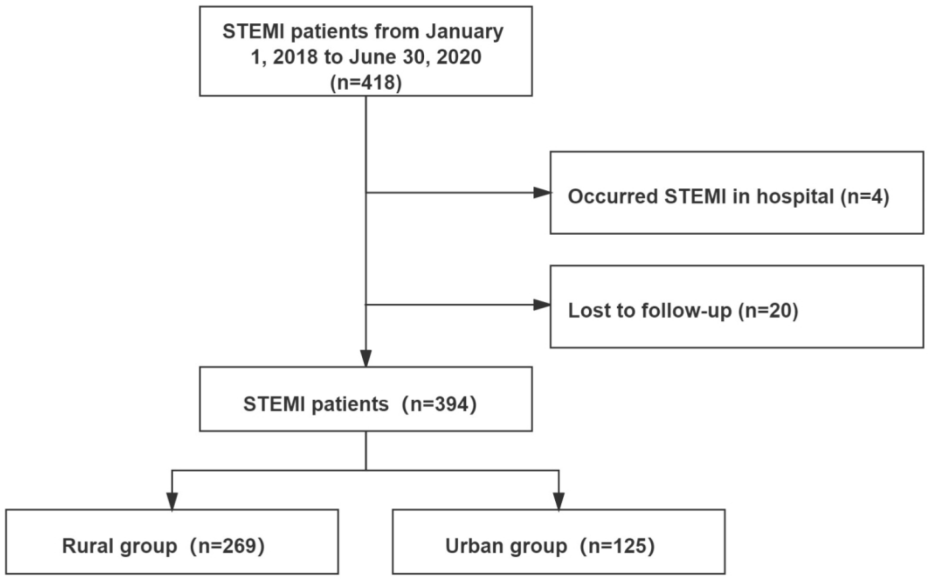

Figure 1. Flow of patients through the study.STEMI=ST-segment elevation myocardial infarction

139x91mm (300 x 300 DPI)

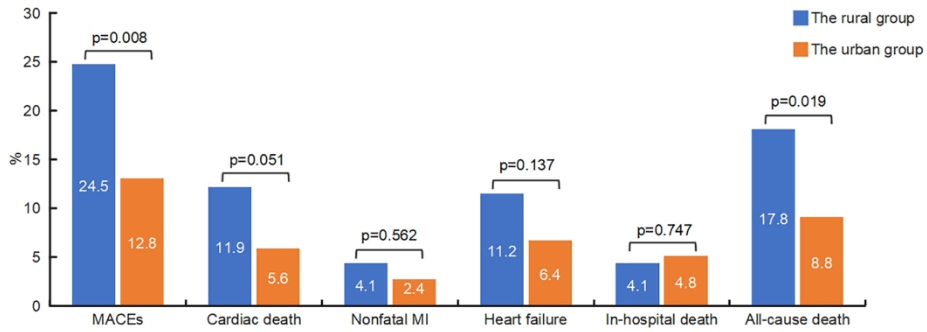

Figure 2. Incidence rate of primary and secondary endpoint events at 1 year in the rural group vs. the urban group.MACEs=major adverse cardiovascular events; MI=myocardial infarction.

180x92mm (300 x 300 DPI)

Supplementary Tables:

Supplementary Table 1 Baseline characteristics of study group and the group lost to follow-up

Characteristic	With follow-up (n=394)	Lost to follow-up (n=20)	*P* Value
Demographics			
Age, median (IQR), y	69 (61-77)	74 (56-81)	0.555
Women, n (%)	133 (33.8)	9 (45.0)	0.301
Education level, n (%)			
Less than high school	340 (86.3)	17 (85.0)	0.746
High school and above	54 (13.7)	3 (15.0)	
Clinical characteristics, n (%)			
Hypertension	162 (41.1)	9 (45.0)	0.731
Diabetes mellitus	75 (19.0)	4 (20.0)	1.000
Dyslipidemia	199 (50.5)	9 (45.0)	0.631
Previous MI	10 (2.5)	2 (10.0)	0.109
Previous PCI	12 (3.0)	1 (5.0)	0.480
Current smoker	99 (25.1)	4 (20.0)	0.793
Current drinker	81 (20.6)	3 (15.0)	0.777
Killip class, n (%)			0.996
I	355 (90.1)	18 (90.0)	1.000
II	19 (4.8)	1 (5.0)	1.000
III	10 (2.5)	1 (5.0)	0.424
IV	10 (2.5)	0 (0.0)	1.000

IQR=interquartile range; MI=myocardial infarction; PCI=percutaneous coronary intervention

Supplementary Table 2 Univariate and multivariable logistic regression analysis to identify independent predictors of MACEs in the entire study population

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.07 (1.05-1.10)	<0.001	1.04 (1.01-1.07)	0.013
Women	2.24 (1.37-3.68)	0.001	1.20 (0.65-2.23)	0.566
Education level-High school and above	0.27 (0.09-0.77)	0.014		
Hypertension	0.96 (0.58-1.57)	0.857		
Diabetes mellitus	1.38 (0.77-2.48)	0.285		
Dyslipidemia	0.98 (0.60-1.59)	0.918		
Previous MI	3.99 (1.13-14.12)	0.032		
Previous PCI	0.34 (0.04-2.66)	0.302		
Current smoking	1.03 (0.59-1.81)	0.910		
Current drinking	1.85 (1.06-3.23)	0.030		
Ambulance transfer	1.43 (0.87-2.32)	0.156		
Killip class ≥II	10.68 (5.18-22.03)	<0.001	6.93 (2.98-16.12)	<0.001
Without indication of PPCI	11.93 (5.81-24.47)	<0.001	1.22 (0.32-4.63)	0.776
PPCI performed	0.14 (0.08-0.23)	<0.001	0.44 (0.19-1.04)	0.062
With indication, but PPCI not performed	2.26 (1.10-4.67)	0.027		

Region-Rural area	2.22 (1.22-4.01)	0.009	0.91 (0.34-2.47)	0.852
S2D time	6.60 (3.95-11.03)	<0.001	3.35 (1.47-7.63)	0.004
Transportation distance	1.03 (1.01-1.05)	0.003	1.00 (0.97-1.04)	0.842
Tertiary hospital with PPCI capacity	0.75 (0.44-1.27)	0.285		

MACEs=Major Adverse Cardiovascular Events; OR=odds ratio; CI=confidence interval; PCI= percutaneous coronary intervention; MI=myocardial infarction; PPCI= primary percutaneous coronary intervention; S2D=symptom to door. Only variables reaching $P<0.01$ at univariate analysis were entered into the multivariable analysis.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed *
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6-7
Bias	9	Describe any efforts to address potential sources of bias Page 6-7
Study size	10	Explain how the study size was arrived at Page 6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions Page 7-8
		(*c*) Explain how missing data were addressed *
		(*d*) If applicable, explain how loss to follow-up was addressed Page 7-8
		(*e*) Describe any sensitivity analyses Page 7-8
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 8-9
		(b) Give reasons for non-participation at each stage *
		(c) Consider use of a flow diagram Page 8 and figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 8-11
		(b) Indicate number of participants with missing data for each variable of interest Page 8-9
		(c) Summarise follow-up time (eg, average and total amount) Page 12
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 11-14
		(*b*) Report category boundaries when continuous variables were categorized Page 11-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page 11-14

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 11-14
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 16-18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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An In-depth Look into Urban and Rural Disparities in Prehospital Delay in Patients with Acute ST-elevation Myocardial Infarction and Its Impact on Prognosis: A Prospective Observational Study

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An In-depth Look into Urban and Rural Disparities in Prehospital Delay in Patients with Acute ST-elevation Myocardial Infarction and Its Impact on Prognosis: A Prospective Observational Study

Short title: Prehospital delay in acute STEMI in rural China

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Numbers of Tables: 4.

Numbers of Figures: 2.

Numbers of Supplementary Tables: 3.

ABSTRACT

Objectives In line with the cardiac fast track, the "green pathway for patients with heart attack" policy in China is implemented to reduce door-to-balloon time in patients with ST-segment elevation myocardial infarction (STEMI). However, the difference in prehospital delay between urban and rural areas of China and its impact on prognosis is unclear.

Design Prospective observational study.

Setting This study was conducted in a tertiary hospital, the only nationally accredited chest pain center with percutaneous coronary intervention (PCI) capacity in Pizhou, China.

Participants 394 patients with STEMI without patients with in-hospital STEMI or patients lost to follow-up were included.

Primary outcome measures Primary outcome was major adverse cardiovascular events (MACEs), including cardiac death, nonfatal myocardial infarction and heart failure.

Results Among 394 patients enrolled, 261 (66.2%) were men, the median age was 69 years (IQR: 61-77 years), and 269 (68.3%) were from rural areas. Symptom-to-door (S2D) time was significantly longer for rural patients than for urban patients (*P*<0.001). Cox regression analyses revealed living in rural areas was independently associated with prolonged S2D time (adjusted HR 0.59; 95% CI 0.43-0.81; *P*=0.001). HR of <1 indicates the S2D time is longer for patients in the rural group (group of interest). During one-year follow-up, the incidence of MACEs was higher in rural patients (*P*=0.008). The unadjusted OR for MACEs between rural and urban patients was 2.22 (95% CI 1.22-4.01). Adjusting for sex didn't attenuate the association (OR 2.06; 95% CI 1.13-3.76), but after further adjusting for age, cardiac function classification, S2D time, and performance of primary PCI, we found odds were similar for rural and urban patients (OR 1.19; 95% CI 0.59-2.38).

Conclusions Rural patients with STEMI had a longer S2D time, which led to a higher incidence of MACEs. This study provides rationales for taking all the measures to avoid prehospital delay.

Key Words: Acute myocardial infarction; Prehospital delay; Urban and rural areas; Prognosis.

Strengths and limitations of this study:

- We constructed 6 models to determine the association between rural area and incidence of MACE, and to extrapolate the potential disparity between rural and urban areas.
- A multivariable Cox proportional hazards model was constructed from symptom-to-door (S2D) time by rural/urban areas, in which the occurrence of ST-segment elevation myocardial infarction was defined as the event, and the S2D time was considered as the survival time.
- The limitation of this study is that the results of this single-center observational study might not represent the actual situation of China as a whole.
- Since the baseline characteristics were balanced between the patients who were followed up and those who lost to follow-up, the rate of loss to follow-up may only have a slight influence on the results.

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is the most common acute manifestation of coronary heart disease, with high morbidity and mortality.[1] The Global Registry of Acute Coronary Events (GRACE) showed that STEMI accounted for one-third of coronary events.[2] In China, the proportion of hospitalized STEMI patients has been increasing year by year.[3] Therefore, STEMI is a major public health problem, seriously threatening human life and bringing very large economic burdens to both families and society. In recent years, with the progress of medical treatment and preventive measures, the mortality and complication rates have been reduced in STEMI patients.[4-7] The time from symptom onset to culprit vessel reperfusion has also been greatly reduced since fast heart attack care is promoted globally.[8] In line with the cardiac fast track, the "green pathway for patients with heart attack" policy is implemented in China. With the acceleration of chest pain center construction, the treatment of acute myocardial infarction in China, especially the door-to-balloon (D2B) time, is improving.[9, 10] However, the prehospital delay in patients with STEMI has never been thoroughly investigated in China. Although the number of rural residents has decreased due to industrialization and urbanization in China, there are still a large number of people living in rural areas, especially elderly people.[11] People in rural areas have relatively poor knowledge of the disease, less efficient transportation facilities and lower levels of primary care.[12],[13] To provide a theoretical basis for spreading the accredited chest pain center further down to the rural front line and optimizing the management algorithm of chest pain patients, this study aimed to explore the urban and rural disparities in prehospital delays in STEMI patients and their impact on prognosis.

METHODS

Study design and population

In this prospective observational study, all acute STEMI patients who were admitted to the Pizhou Affiliated Hospital of Xuzhou Medical University (Pizhou Hospital) from January 2018 to June 2020 were included. This hospital is the only nationally accredited chest pain center with percutaneous coronary intervention (PCI) capacity in the Pizhou, a region of 2,088 square kilometers and 1.46 million people. STEMI was diagnosed in accordance with the universal definition of myocardial infarction.[14] All the patients were divided into the rural group and the urban group based on their location where STEMI occurred. Based on the 2014 Administrative Planning approval document of Pizhou City, Jiangsu Province, China, their location was classified into urban or rural areas. In detail, Yunhe subdistrict, Donghu subdistrict, Paoche subdistrict and Daiwei subdistrict were designated as urban areas, and the remaining areas of Pizhou were rural areas. Patients with in-hospital STEMI or patients who were lost to follow-up were excluded from this study.

Data collection

Sociodemographic characteristics (age, sex, and education level) and clinical characteristics (cardiovascular comorbidities, smoking, drinking, previous medical history, and cardiac function classification) were collected. Based on the highest level of education completed by the participants, the education level was classified as below high school or high school or above. The estimates of delays, including symptom-to-door (S2D) time and D2B time, and transportation distance, were based on data registered in the national chest pain center reporting platform. In our study, prehospital delay was defined as S2D time, *i.e.*, time from symptom onset to arrival at Pizhou Hospital. Therefore, the prehospital delay consists of patient delay (time from symptom onset to first medical contact) and prehospital system delay (time from first medical contact to arrival at the PCI center). The location where STEMI occurred was self-reported by patient. Transportation distance was defined as the distance from the patient's location where the STEMI occurred to Pizhou Hospital. In addition, information on pretreatment with fibrinolysis and the performance of primary PCI (PPCI) was collected. The first-visit medical institutions of the patients were categorized into primary healthcare centers and tertiary hospitals according to the Chinese hospital classification system.

Clinical outcomes and follow-up

The primary endpoint was major adverse cardiovascular events (MACEs), which included cardiac death, nonfatal myocardial infarction and heart failure. The secondary endpoints were cardiac death, nonfatal myocardial infarction, heart failure, in-hospital death and all-cause death. The time and cause of death were obtained from the self-report of the patient's relatives or Xuzhou Centers for Disease Control and Prevention database.

All patients received standard of care after discharge. Follow-up was completed via clinic visits or by telephone interviews with patients or their relatives every 3 months after discharge within one year. If a patient had an outcome event during follow-up, all his/her medical records were acquired and adjudicated.

Statistical analysis

All the continuous variables investigated in our study were nonnormally distributed and presented as medians and interquartile ranges (IQRs). Differences between groups were tested using the Mann–Whitney U test. The categorical variables were expressed as counts with percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was considered when two-sided P values <0.05.

A multivariable Cox proportional hazards model was constructed from S2D time by rural/urban areas. At the first step, the association between S2D time and all variables that were considered to have a potential influence on S2D time was tested univariate analysis. Then, those variables with a *P* value <0.05 in univariate analysis were adjusted in the multivariable Cox proportional hazards model (enter method). Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were used to estimate the association (Supplementary Method).

Multivariable logistic regression was performed to determine the risk factors associated with the incidence of MACEs. Variables with a *P* value <0.01 in univariate analyses were included in the multivariable logistic regression model. An additional multivariable logistic regression was performed to estimate the association of rural areas and incident MACEs. The odds ratios (ORs) and the corresponding 95% CIs were obtained to assess the association. All analyses were performed using SPSS statistical software version 22.0.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Baseline demographic characteristics

A total of 418 acute STEMI patients were admitted to Pizhou Hospital during our study period. Our final analysis included 394 patients who fulfilled the inclusion and exclusion criteria. Figure 1 depicts the patient flow through the study. In total, the median age was 69 years (IQR: 61-77 years), and 261 (66.2%) of the patients were men. Table 1 shows the baseline characteristics of all 394 patients. Compared with those in the urban group, patients in the rural group were older and more likely to be female and poorly educated. Our study group and the group of patients lost to follow-up were balanced with respect to all the baseline characteristics. (Supplementary Table 1).

Table 1 Baseline characteristics of the patients in the two groups

Characteristic	Rural group (n=269)	Urban group (n=125)	*P* value
Demographics			
Age, median (IQR), y	70 (63-79)	66 (56-74)	<0.001
Women, n (%)	100 (37.2)	33 (26.4)	0.035
Education level, n (%)			<0.001
Less than high school	248 (92.2)	92 (73.6)	
High school and above	21 (7.8)	33 (26.4)	
Clinical characteristics, n (%)			
Hypertension	109 (40.5)	53 (42.4)	0.724
Diabetes mellitus	49 (18.2)	26 (20.8)	0.543
Dyslipidemia	128 (47.6)	71 (56.8)	0.089
Previous myocardial infarction	6 (2.2)	4 (3.2)	0.732
Previous PCI	8 (3.0)	4 (3.2)	1.000

Current smoker	67 (24.9)	32 (25.6)	0.883
Current drinker	57 (21.2)	24 (19.2)	0.649
Killip class, n (%)			0.394
I	240 (89.2)	115 (92.0)	0.390
II	14 (5.2)	5 (4.0)	0.604
III	8 (3.0)	2 (1.6)	0.514
IV	7 (2.6)	3 (2.4)	1.000

IQR=interquartile range; PCI=percutaneous coronary intervention.

Data regarding delays, transportation distance and performance of PPCI

Table 2 shows that S2D time was significantly longer for patients in the rural group than for those in the urban group (190 min *vs.* 75 min, *P*<0.001). The transportation distance from the patient's location where the STEMI occurred to the tertiary hospital with PPCI capacity (Pizhou Hospital) was longer for patients in the rural group than for those in the urban group (23.3 km *vs.* 4.5 km, *P*<0.001). Patients in the rural group were less likely to go to Pizhou Hospital for their first medical visit than were those in the urban group (27.5% *vs.* 48.8%, *P*<0.001). Patients in the rural group were more likely to miss the PPCI indication (13.4% *vs.* 4.0%, *P*=0.005). The proportion of patients who underwent PPCI was significantly lower in the rural group than in the urban group (75.1% *vs.* 91.2%, *P*<0.001). There was no significant difference in D2B time between the two groups. Notably, thrombolytic therapy was not performed in any of the patients in the entire cohort.

Table 2 Delays, transportation distance and performance of primary percutaneous coronary intervention

Characteristic	Rural group (n=269)	Urban group (n=125)	*P* value
Delays and transportation			
Delay, median (IQR), min			
S2D time	190 (108-432)	75 (47-155)	<0.001
D2B time	80 (63-103)	84 (66-105)	0.432
Transportation, median (IQR), km	23.3 (16.2-29.7)	4.5 (2.6-7.7)	<0.001
Ambulance transfer, n (%)	117 (43.5)	48 (38.4)	0.340
First-visited medical institution, n (%)			<0.001
Primary healthcare center	177 (65.8)	56 (44.8)	<0.001
Tertiary hospital without PPCI capability	18 (6.7)	8 (6.4)	0.914
Tertiary hospital with PPCI capacity (Pizhou Hospital)	74 (27.5)	61 (48.8)	<0.001
Performance of PPCI n (%)			0.001
indication of PPCI missed	36 (13.4)	5 (4.0)	0.005
PPCI performed	202 (75.1)	114 (91.2)	<0.001
With indication, but PPCI not perform	31 (11.5)	6 (4.8)	0.033

IQR=interquartile range; S2D=symptom to door; D2B=door to balloon; PPCI=primary percutaneous coronary intervention.

Cox regression analyses revealed that patients in the rural group had significantly longer S2D times than those in the urban group (crude HR, 0.46; 95% CI, 0.37-0.57; *P* <0.001). An

HR of <1 indicates that the S2D time is longer for patients in the rural group (group of interest) than for those in the urban group (reference group). Variables including sex, age, education level, transportation distance, and first-visit to a medical institution other than Pizhou Hospital were significantly associated with S2D time (Supplemental table 2). After adjusting for these variables, the association between rural area and S2D time remained statistically significant (adjusted HR, 0.59; 95% CI, 0.43-0.81; *P*=0.001) (Table 3).

Table 3 S2D: Crude and adjusted HRs

Variable	HR	95% CI	P
Crude analysis			
Rural areas	0.46	0.37-0.57	<0.001
Adjusted model			
Rural areas	0.59	0.43-0.81	0.001
Women	0.87	0.69-1.09	0.215
Age	0.98	0.97-0.99	<0.001
Education level (high school and above)	0.99	0.72-1.37	0.953
Transportation distance	0.99	0.98-1.01	0.233
First-visited medical institution other than Pizhou Hospital	0.91	0.73-1.13	0.378

S2D=symptom to door; HR=hazard ratio; CI=confidence interval.

Major adverse clinical events during the one-year follow-up

During the one-year follow-up, MACEs occurred in 66 patients in the rural group (24.5%, 66/269) and 16 patients (12.8%, 16/125) in the urban group (*P*=0.008). As shown in Figure 2, no statistically significant difference was observed in the incidence rates of cardiac death, nonfatal MI, and heart failure between the two groups. The all-cause mortality of the rural group was significantly higher than that of the urban group (17.8% *vs.* 8.8%, *P*=0.019). Independent predictors of MACEs in the entire study population were older age, Killip class ≥II and prolonged S2D time (Supplementary Table 3).

Table 4 shows that, when rural patients and urban patients were compared, the unadjusted OR for MACEs after STEMI was 2.22 (95% CI, 1.22-4.01). Adjusting for women did not attenuate the association (OR, 2.06; 95% CI, 1.13-3.76), but further adjusting for age attenuated the association between rural areas and MACEs (OR, 1.66; 95% CI, 0.89-3.08). After additional adjustment for the cardiac function classification, S2D time, and performance of PPCI, the odds were similar for rural and urban patients (OR, 1.19; 95% CI, 0.59-2.38).

Table 4 Association of rural areas with MACEs

MACEs	Urban group (n=125)	Rural group (n=269)	*P* value
Cases	16	66	
Model 0, OR (95% CI)	1 (reference)	2.22 (1.22-4.01)	0.009
Model 1, OR (95% CI)	1 (reference)	2.06 (1.13-3.76)	0.018
Model 2, OR (95% CI)	1 (reference)	1.66 (0.89-3.08)	0.111
Model 3, OR (95% CI)	1 (reference)	1.72 (0.89-3.33)	0.105

Model 4, OR (95% CI)	1 (reference)	1.59 (0.83-3.07)	0.166
Model 5, OR (95% CI)	1 (reference)	1.19 (0.59-2.38)	0.626

MACEs=major adverse cardiovascular events; OR=odds ratio; CI=confidence interval; S2D=symptom to door; PPCI=primary percutaneous coronary intervention.

Model 0: unadjusted

Model 1: adjusted for women

Model 2: adjusted for variables in model 1 and age

Model 3: adjusted for variables in model 2 and characteristics of the cardiac function classification (Killip class ≥II)

Model 4: adjusted for variables in model 3 and S2D in hours

Model 5: adjusted for variables in model 4 and characteristics of PPCI

DISCUSSION

Our study is the first to investigate the urban and rural disparities in prehospital delay in patients with acute STEMI and their impact on the prognosis of STEMI in China. The major findings are as follows. Although the D2B time was similar between the two groups, the S2D time was significantly prolonged in patients from rural areas compared with those in urban areas; in the rural group, patients had a higher proportion of missed PPCI indications and were less likely to receive PPCI; and a higher one-year incidence rate of MACEs was observed in the rural group than in the urban group. This disparity could be explained by age, cardiac function classification, S2D time, and PPCI performance.

The 2017 European Society of Cardiology Guidelines emphasized the total ischemic time of STEMI, raising the concept of entire rescue time, which consists of S2D time and D2B time. According to the recommendation from the 2017 European Society of Cardiology guidelines, a PPCI is not indicated in patients with time from symptom onset >12 h and without clinical and/or electrocardiographic evidence of ongoing ischaemia.[15] A reduction in D2B time is significantly associated with a decrease in mortality,[16, 17] and measures have been taken to reduce D2B time.[18, 19] With the establishment of chest pain centers in China in the past decade, the D2B time was greatly reduced to within 60-90 min.[10] However, a further decrease in D2B time from 83 min to 67 min had no association with a reduction in in-hospital mortality.[20] In our study, the D2B time was approximately 80 min, and there was no difference in in-hospital mortality between the two groups. However, the one-year clinical outcome was markedly different. This difference is attributed to the entire myocardial ischemic time. To reduce the entire rescue time, the possibly shortened duration is S2D time.

Indeed, in our study, the S2D time of STEMI patients in the rural group was much longer than that of the urban group. There are four possible reasons accounting for this prehospital delay. Poor family care: Our study showed that STEMI patients from rural areas were older. Such senior patients in rural China lack good family care because their adult children move to cities or coastal areas to seek better employment opportunities.[21] We acknowledge that old age is an independent predictor of MACEs and all-cause mortality,[22] but poor family care is the hurdle to receiving quick first-aid service when older patients are in need. Lacking disease awareness: The most important factor influencing the awareness of disease was educational level, followed by age.[23] From the baseline characteristics of our observation, the rural patients had a lower educational level and older age. Their insufficient understanding and misjudgment of early symptoms of STEMI[24] prolonged the prehospital time and missed the best opportunity for revascularization. Access to medical resources: The accessibility of high-quality medical facilities has a conceivable impact on the treatment of patients. Compared with urban patients, rural patients lack high-quality medical resources.[25] The nearest medical facilities for rural patients with STEMI are village clinics and town hospitals that do not have the capability of PPCI. Patients have to be transported to large tertiary hospitals after diagnosis. In our study, rural patients had higher referral rates than their urban counterparts did. Notably, none of the patients initially underwent thrombolytic therapy before admission to tertiary hospitals. Transportation distance and facilities: The distance between the residence of rural patients and hospitals qualified for PCI was significantly longer than that of urban patients according to our observation. Although the average distance of 23 km is not very long in modern society, the facilities for rural patients to use are insufficient. Less frequent public transportation, less ownership of private vehicles, and less efficient cabs or ambulances are responsible for these delays.

The prolonged S2D time in the rural group could contribute to rural patients missing the PPCI indication and indirectly lead to a lower proportion of patients receiving PPCI. Previous studies have demonstrated that elderly, female and poorly educated patients were less likely to receive reperfusion therapy.[26, 27] These are exactly the characteristics of the rural STEMI patients in our study.

Early opening of infarcted vessels is the key point for STEMI and is crucial for improving the prognosis of STEMI patients.[28, 29] A previous study demonstrated a 7.5% increase in annual mortality for every 30 min delay in successful reperfusion.[30] Our study showed that the S2D time was significantly longer than that of urban patients, which led to a significantly higher incidence of MACEs and mortality in rural patients than in urban patients. In our study, the in-hospital mortality of the entire study population was 4.31%, which was close to the average level reported previously,[31] suggesting that the in-hospital algorithm and the management of STEMI patients are in line with guideline-directed medical therapy. In this study, no difference in in-hospital mortality between the two groups was found, which might be due to the small sample size.

Prehospital delays are highly associated with the outcomes of patients according to the results of this study. This provides evidence for further optimizing the workflow of emergent management of STEMI patients. While emphasizing the in-hospital management algorithm, we should extend our strength to prehospital management, especially in rural areas of China. Patients' awareness of STEMI symptoms and reperfusion procedures should be raised and treatment compliance should be further improved by strengthening propaganda and education among villagers. This is the first step towards reducing prehospital delays. Second, primary medical institutions should carry out thrombolytic therapy as an emergency treatment. This is an important step to shorten the total ischemic time and improve the prognosis of STEMI patients. Third, in order to alleviate the shortage of first-aid tools and improve the first-aid system in rural areas, more ambulances should be equipped. Moreover, the intelligent construction of village clinics is also a crucial link in the "last mile" of prehospital treatment for acute myocardial infarction in rural areas. Primary medical treatment and emergency treatment will be connected with regional large comprehensive hospitals through installation of wireless electrocardiograph equipment and construction of an online medical network platform to achieve the "sinking of high-quality medical resources to remote areas". When the older patients with hurdle of receiving quick first-aid service, they can call the emergency medical telephone. The nearest village doctor can reach the patient and perform electrocardiogram, which can be transmitted to the PCI hospital diagnosis center wirelessly for rapid diagnosis of the disease. If STEMI is highly suspected, village doctors can promptly pretreat the patients with antiplatelet drugs, and at the same time call an ambulance and send the patients to the PCI center for reperfusion therapy. In this way, barriers of receiving medical service for older patients will be resolved and referral efficiency will be improved. These measures play important roles not only in the treatment of acute myocardial infarction patients but also in the improvement of public health services and other emergent treatments in rural areas.

This study has several limitations. First, it was a single-center observational study, and the overall sample size was relatively small. Further long-term follow-up and a larger sample size are needed to validate the results of this study. Second, the population in this study is from the developed plain area of China. Our results might not represent the actual situation of China as a whole. However, the large "gap" in the management of STEMI patients between urban and rural areas could not be underestimated. Third, the proportion of patients lost to follow-up was 4.8%, which may influence our results. However, the baseline characteristics were balanced between the patients who were followed up and those who lost to follow-up.

CONCLUSIONS

Compared with urban patients, rural patients with acute STEMI had a prolonged prehospital delay, which led to a higher incidence of MACEs. This study provides rationales for taking all the measures to avoid prehospital delay by spreading chest pain units down to the rural front line through an online platform. Strengthening the propagation and education of knowledge regarding chest pain and advanced treatment to rural dwellers and village doctors is also necessary.

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Contributors:

ML Chen, MF Li and Y Yang participated in the design of this study. J Wang, JR Yin and PA Lou record all the cases. CX Shen, CZ Li, ZR Wang and Y Lu collected and performed the statistical analysis. CX Shen wrote the first draft of the manuscript. CZ Li revised the manuscript. ML Chen and MF Li monitored the study. All authors provided input on data analysis, interpretations and participated in multiple revisions of the manuscript, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Competing interests:

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval:

This study was approved by the Clinical Research Ethnics Committee of The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China (XYFY2021-KL141-01) on June 22, 2021.

Data availability statement:

The data that supports the finding of this study are available from the corresponding author upon reasonable request.

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Figure legends:

Figure 1. Flow of patients through the study.

STEMI=ST-segment elevation myocardial infarction

Figure 2. Incidence rate of primary and secondary endpoint events at 1 year in the rural group *vs.* the urban group.

MACEs=major adverse cardiovascular events; MI=myocardial infarction.

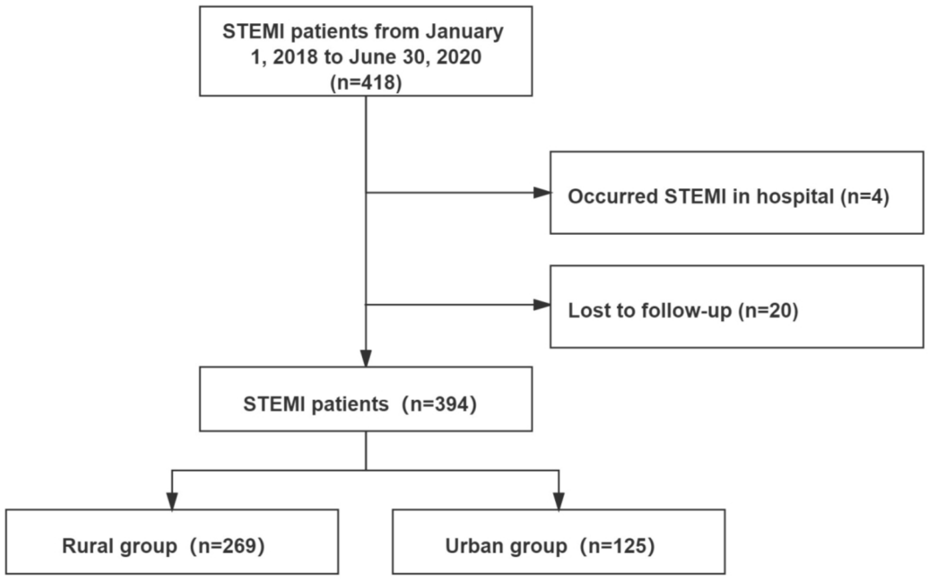

Figure 1. Flow of patients through the study.STEMI=ST-segment elevation myocardial infarction

139x91mm (300 x 300 DPI)

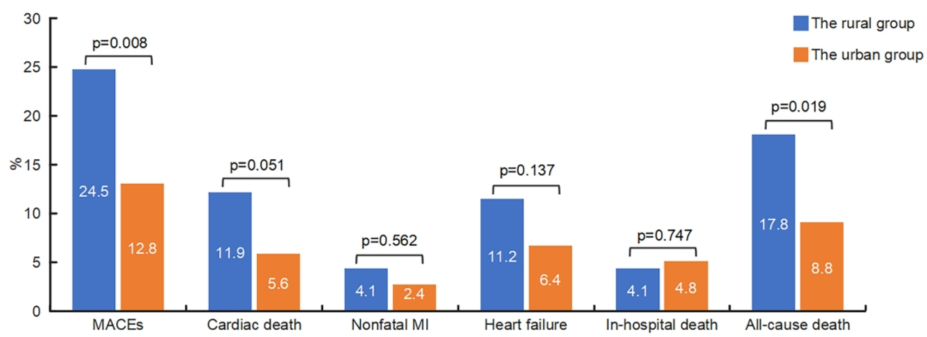

Figure 2. Incidence rate of primary and secondary endpoint events at 1 year in the rural group vs. the urban group.MACEs=major adverse cardiovascular events; MI=myocardial infarction.

180x92mm (300 x 300 DPI)

Because S2D time is nonnormally distributed, linear regression cannot be performed to determine the risk factors associated with S2D time. Therefore, a multivariable Cox proportional hazards model was constructed from S2D time by rural/urban areas and was adjusted for confounding factors. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were used to estimate the association. In the multivariable Cox proportional hazards model, the occurrence of STEMI was defined as the event, so the status of each patient was assigned a value of 1, and the S2D time was considered as the survival time. An HR<1 indicated low risk of event and long survival time (S2D time). HR>1 indicates a high risk of outcome events and a short survival time (S2D time).

Supplementary Tables:

Supplementary Table 1 Baseline characteristics of study group and the group lost to follow-up

Characteristic	With follow-up (n=394)	Lost to follow-up (n=20)	*P* Value
Demographics			
Age, median (IQR), y	69 (61-77)	74 (56-81)	0.555
Women, n (%)	133 (33.8)	9 (45.0)	0.301
Education level, n (%)			
Less than high school	340 (86.3)	17 (85.0)	0.746
High school and above	54 (13.7)	3 (15.0)	
Clinical characteristics, n (%)			
Hypertension	162 (41.1)	9 (45.0)	0.731
Diabetes mellitus	75 (19.0)	4 (20.0)	1.000
Dyslipidemia	199 (50.5)	9 (45.0)	0.631
Previous MI	10 (2.5)	2 (10.0)	0.109
Previous PCI	12 (3.0)	1 (5.0)	0.480
Current smoker	99 (25.1)	4 (20.0)	0.793
Current drinker	81 (20.6)	3 (15.0)	0.777
Killip class, n (%)			0.996
I	355 (90.1)	18 (90.0)	1.000
II	19 (4.8)	1 (5.0)	1.000
III	10 (2.5)	1 (5.0)	0.424
IV	10 (2.5)	0 (0.0)	1.000

IQR=interquartile range; MI=myocardial infarction; PCI=percutaneous coronary intervention

Supplementary Table 2 The univariate Cox regression analyses to identify potential predictors of prolonged S2D time.

	Univariate analysis	
	HR (95% CI)	P Value
Age	0.98 (0.97-0.99)	<0.001
Women	0.69 (0.56-0.85)	0.001
Education level-High school and above	1.66 (1.24-2.21)	0.001
Hypertension	1.13 (0.92-1.38)	0.242
Diabetes mellitus	0.98 (0.76-1.27)	0.886
Dyslipidemia	1.16 (0.95-1.41)	0.144
Previous MI	0.96 (0.51-1.81)	0.910
Previous PCI	1.21 (0.68-2.16)	0.509
Current smoking	1.10 (0.88-1.38)	0.413
Current drinking	1.00 (0.78-1.27)	0.969
Ambulance transfer	1.02 (0.83-1.24)	0.885
Transportation distance	0.98 (0.97-0.98)	<0.001

First-visited medical institution other than Pizhou Hospital	0.75 (0.61-0.92)	0.007

S2D=symptom to door; HR=hazard ratio; CI=confidence interval; MI=myocardial infarction; PCI= percutaneous coronary intervention.

Supplementary Table 3 Univariate and multivariable logistic regression analysis to identify independent predictors of MACEs in the entire study population

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.07 (1.05-1.10)	<0.001	1.04 (1.01-1.07)	0.013
Women	2.24 (1.37-3.68)	0.001	1.20 (0.65-2.23)	0.566
Education level-High school and above	0.27 (0.09-0.77)	0.014		
Hypertension	0.96 (0.58-1.57)	0.857		
Diabetes mellitus	1.38 (0.77-2.48)	0.285		
Dyslipidemia	0.98 (0.60-1.59)	0.918		
Previous MI	3.99 (1.13-14.12)	0.032		
Previous PCI	0.34 (0.04-2.66)	0.302		
Current smoking	1.03 (0.59-1.81)	0.910		
Current drinking	1.85 (1.06-3.23)	0.030		
Ambulance transfer	1.43 (0.87-2.32)	0.156		
Killip class ≥II	10.68 (5.18-22.03)	<0.001	6.93 (2.98-16.12)	<0.001

Without indication of PPCI	11.93 (5.81-24.47)	<0.001	1.22 (0.32-4.63)	0.776
PPCI performed	0.14 (0.08-0.23)	<0.001	0.44 (0.19-1.04)	0.062
With indication, but PPCI not performed	2.26 (1.10-4.67)	0.027		
Region-Rural area	2.22 (1.22-4.01)	0.009	0.91 (0.34-2.47)	0.852
S2D time	6.60 (3.95-11.03)	<0.001	3.35 (1.47-7.63)	0.004
Transportation distance	1.03 (1.01-1.05)	0.003	1.00 (0.97-1.04)	0.842
Tertiary hospital with PPCI capacity	0.75 (0.44-1.27)	0.285		

MACEs=Major Adverse Cardiovascular Events; OR=odds ratio; CI=confidence interval; MI=myocardial infarction; PCI= percutaneous coronary intervention; PPCI= primary percutaneous coronary intervention; S2D=symptom to door. Only variables reaching *P*<0.01 at univariate analysis were entered into the multivariable analysis.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed *
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6-7
Bias	9	Describe any efforts to address potential sources of bias Page 6-7
Study size	10	Explain how the study size was arrived at Page 6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 7-8
		(*b*) Describe any methods used to examine subgroups and interactions Page 7-8
		(*c*) Explain how missing data were addressed *
		(*d*) If applicable, explain how loss to follow-up was addressed Page 7-8
		(*e*) Describe any sensitivity analyses Page 7-8
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 8-9
		(b) Give reasons for non-participation at each stage *
		(c) Consider use of a flow diagram Page 8 and figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 8-11
		(b) Indicate number of participants with missing data for each variable of interest Page 8-9
		(c) Summarise follow-up time (eg, average and total amount) Page 12
Outcome data	15*	Report numbers of outcome events or summary measures over time Page 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 11-14
		(*b*) Report category boundaries when continuous variables were categorized Page 11-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page 11-14

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 11-14
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 16-18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.