Reperfusion strategy and in-hospital outcomes for ST elevation myocardial infarction in secondary and tertiary hospitals in predominantly rural central China: a multicentre, prospective and observational study

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ABSTRACT

Objectives To assess differences in reperfusion treatment and outcomes between secondary and tertiary hospitals in predominantly rural central China.

Design Multicentre, prospective and observational study.

Setting Sixty-six (50 secondary and 16 tertiary) hospitals in Henan province, central China.

Participants Patients with ST elevation myocardial infarction (STEMI) within 30 days of symptom onset during 2016–2018.

Primary outcome measures In-hospital mortality, and in-hospital death or treatment withdrawal.

Results Among 5063 patients of STEMI, 2553 were treated at secondary hospitals. Reperfusion (82.0% vs 73.0%, p<0.001) including fibrinolytic therapy (70.3% vs 4.4%, p<0.001) were more preformed, whereas primary percutaneous coronary intervention (11.7% vs 68.6%, p<0.001) were less frequent at secondary hospitals. In secondary hospitals, 53% received fibrinolytic therapy 3 hours after onset, and 5.8% underwent coronary angiography 2–24 hours after fibrinolysis. Secondary hospitals had a shorter onset-to-first-medical-contact time (176 min vs 270 min, p<0.001). Adjusted in-hospital mortality (adjusted OR 1.23, 95% CI 0.89 to 1.70, p=0.210) and in-hospital death or treatment withdrawal (adjusted OR 1.18, 95% CI 0.82 to 1.70, p=0.361) were similar between secondary and tertiary hospitals.

Conclusions With fibrinolytic therapy as the main reperfusion strategy, the reperfusion rate was higher in secondary hospitals, whereas in-hospital outcomes were similar compared with tertiary hospitals. Public awareness, capacity of primary and secondary care institutes to treat STEMI, and establishment of deeper cooperation among different-level healthcare institutes need to further improve.

Trial registration number NCT02641262.

INTRODUCTION

With the effect of changing lifestyles and an ageing population, the prevalence of cardiovascular disease is continuously rising in China, with estimates of 290 million individuals being affected by the disease.1–12 Cardiovascular diseases including ST elevation myocardial infarction (STEMI) remain the lead cause of death in China and worldwide,2–4 and cardiovascular mortality in rural China has been higher than that of urban areas since 2009.2 Thrombolysis and primary percutaneous coronary intervention (PCI) have improved the prognosis of patients with STEMI.13–15 However, large gap existed between clinical practice and guideline recommendation in China.8 9 Moreover, significant geographical variations and hospital-level...
differences persist in process of care and outcomes for patients with STEMI in China.\textsuperscript{10,11}

There are limited data available on reperfusion treatment and in-hospital outcomes in rural areas of China, especially in predominantly rural central China. A national study showed that central China had the lowest reperfusion rate among the three areas of China (western, central, or eastern), but the best mortality outcomes.\textsuperscript{10} In rural areas of China, secondary hospitals are often first-visited hospitals for patients of STEMI. However, the proportion of secondary hospitals included in national prospective multicentre STEMI clinical trials was very low, approximately 26% in the China Acute Myocardial Infarction Registry,\textsuperscript{12} and 22% in the ongoing Improving Care for Cardiovascular Disease in China—Acute Coronary Syndrome project.\textsuperscript{13}

Therefore, we used data from the Henan STEMI registry to assess differences in clinical characteristics, reperfusion therapy, time delays and in-hospital outcomes between secondary and tertiary hospitals in Henan, predominantly rural areas of central China.

**METHODS**

**Study design**

The design of Henan STEMI registry has been described previously.\textsuperscript{14} Briefly, it is a multicentre, prospective, and observational study aimed to evaluate the characteristics, management and outcomes of patients with STEMI as seen in routine clinical practice. Only secondary and tertiary hospitals are reperfusion capable, which are located in three levels of Chinese local government-province, prefecture and county. Therefore, this registry included 66 (50 secondary and 16 tertiary) hospitals from 15 prefectures of Henan.

**Participants**

Patients with a primary diagnosis of STEMI admitted within 30 days of symptom onset were consecutively enrolled between September 2016 and August 2018. STEMI was defined in accordance with the universal definition of myocardial infarction (MI),\textsuperscript{15} specifically as persistent ST-segment elevation (≥0.1 mV at J points) in two or more contiguous leads or new onset of left bundle branch block. Furthermore, according to the classification of MI, types 4a and type 5 are excluded from this registry.

Among 5479 patients from 66 hospitals, we excluded 137 cases who did not meet the study criteria to create the study sample of 5342 patients with STEMI (2562 in secondary hospitals, and 2780 in tertiary hospitals). For the main analysis of in-hospital treatments and outcomes, we further excluded 279 cases with prior reperfusion because it may influence the doctor’s treatment choices.

**Patient and public involvement**

No patient involved.
events (MACCE, death or treatment withdrawal, congestive heart failure, reinfarction and ischaemic stroke) among different-level hospitals.

**Statistical analysis**

Categorical variables are presented as number and percentage, and were compared using the χ² or Fisher exact tests among different-level hospitals. Continuous variables are presented as median (IQR) and differences between secondary and tertiary hospitals were compared using the Mann-Whitney U test.

Information about smoking was missing for 23 (0.5%) patients, and we used the multiple imputation method to impute the variable. For the missing data on other risk factors or medical history (≤0.7%), we imputed sample medians. Data on postfibrinolysis angiography and DIDO time were missing in 229 (16.1%) and 47 (10.4%) patients, respectively. No other data were missing.

To examine the association between hospital class and in-hospital outcomes, we used generalised linear mixed model to account for clustering of patients within hospitals. The dependent variables were in-hospital death; in-hospital death or treatment withdrawal; and in-hospital MACCE, respectively. The independent variables were patients’ demographics (age and sex); risk factors or medical history (hypertension, diabetes, current smoker, previous coronary heart disease and previous stroke); clinical characteristics at admission (cardiac arrest, heart rate, systolic blood pressure, anterior MI, cardiogenic shock and prehospital ECG); and symptom onset to FMC time. We transformed continuous variables (age, heart rate, systolic blood pressure and symptom onset to FMC time) into categorical variables according to clinically meaningful cut-off values (tables 1 and 2).

We used two methods for sensitivity analysis. First, we used 7day outcomes instead of the original outcomes. Second, we excluded patients who were transferred out or discharged within 24 hours because they probably left against medical advice and there was very little time for treatment. For these models we report ORs with 95% CIs for secondary hospital versus tertiary hospital. Two-sided p values<0.05 were considered statistically significant. Statistical analyses were performed with SAS 9.4 (SAS Institute).

**RESULTS**

**Baseline characteristics**

A total of 5063 patients were included in the final analysis: 2553 and 2510 came from secondary and tertiary hospitals, respectively (figure 1). Compared with patients with STEMI in tertiary hospitals, those in secondary centres were significantly older, with lower proportions of men, hypertension, dyslipidaemia, diabetes, smoking, and prior stroke. At admission, patients in secondary hospitals were less likely to be transferred from another hospital, to be admitted by ambulance, to bypass the emergency room to catheter lab, and to have prehospital ECG, typical chest pain, and cardiac arrest, and instead, they had a higher prevalence of cardiogenic shock (table 1).

**Treatment delays**

Patients in tertiary hospitals had longer onset-to-FMC, FMC-to-fibrinolysis, onset-to-fibrinolysis and onset-to-PCI time than those in secondary hospitals. First ECG was higher in secondary hospitals. In secondary hospitals, more than half patients received fibrinolysis after 3 hours of symptom onset, and 29.7% of fibrinolysis was performed in ≤30 min, which was higher than that of tertiary hospitals. For patients transferred to tertiary hospitals, few patients (14.2%) achieved a DIDO of ≤30 min in tertiary hospitals (table 2).

**Reperfusion treatment**

Compared with tertiary hospitals, patients in secondary centres had a significantly higher proportion of reperfusion (82.0% vs 73.0%, p<0.001) and fibrinolytic therapy (70.3% vs 4.4%, p<0.001), but lower utilisation rate of primary PCI (11.7% vs 68.6%, p<0.001). Of a total of 356 patients hospitalised within 12–24 hour of symptom onset, 83 received reperfusion. There was no difference in the reperfusion rate between different levels of hospitals. In secondary hospitals, 26 (15.6%) patients underwent fibrinolytic therapy between 12 and 24 hours after onset of symptoms. One more patient admitted between 24 and 48 hours of symptom onset in tertiary hospital was treated with primary PCI. Among 1517 patients treated with primary PCI, tertiary hospitals had higher utilisation of transfer PCI and lower proportion of stents. Among the patients who received fibrinolytic therapy in secondary hospitals, 95.1% were treated with specific thrombolytic agents, but 17.2% failed, of which 5.6% were referred to rescue PCI. And 5.8% underwent coronary angiography 2–24 hours after fibrinolysis (table 3).

**In-hospital outcomes**

Before adjustment, patients in secondary hospitals has higher in-hospital mortality (4.6% vs 3.2%, p=0.013) or in-hospital death or treatment withdrawal (8.6% vs 6.9%, p=0.025). However, there was no difference in in-hospital death, or in-hospital death or treatment withdrawal between secondary and tertiary hospitals after adjusting for sociodemographic variables, risk factors, medical history, clinical characteristics at admission and symptom onset to FMC time. Similarly, the adjusted risk of MACCE was similar between the two classes of hospitals (figure 2). Adjusted outcomes calculated with a 7-day timeframe were similar to those of the primary analyses using the entire hospital stay (figure 2). A sensitivity analysis compared the results of the entire cohort with those of the population excluding patients who transferred out or discharged within 24 hours. The results of these two analyses did not differ (figure 2).
### Table 1  Baseline characteristics of patients with STEMI

|                                | Secondary hospital (n=2553) | Tertiary hospital (n=2510) | P value |
|--------------------------------|-----------------------------|-----------------------------|---------|
| **Age, years**                 | 64.2 (54.0–72.0)            | 62.0 (51.4–70.0)            | <0.001  |
| ≥75 years                      | 483 (18.9)                  | 371 (14.8)                  | <0.001  |
| Women                          | 693 (27.1)                  | 541 (21.6)                  | <0.001  |
| **Risk factors**               |                             |                             |         |
| Hypertension                   | 1029 (40.3)                 | 1204 (48.0)                 | <0.001  |
| Dyslipidaemia                  | 1297 (50.8)                 | 1424 (56.7)                 | <0.001  |
| Diabetes                       | 382 (15.0)                  | 503 (20.0)                  | <0.001  |
| Current smoker                 | 870 (34.1)                  | 1133 (45.1)                 | <0.001  |
| **Medical history**            |                             |                             |         |
| Stroke                         | 296 (11.6)                  | 360 (14.3)                  | 0.004   |
| Ischaemic                      | 275 (10.8)                  | 336 (13.4)                  | 0.004   |
| Haemorrhagic                   | 26 (1.0)                    | 32 (1.3)                    | 0.39    |
| Coronary heart disease         | 159 (6.2)                   | 155 (6.2)                   | 0.94    |
| Myocardial infarction          | 127 (5.0)                   | 131 (5.2)                   | 0.69    |
| Percutaneous coronary intervention | 73 (2.9)                   | 89 (3.6)                    | 0.17    |
| Coronary artery bypass graft   | 3 (0.1)                     | 4 (0.2)                     | 0.72    |
| **Clinical characteristic**    |                             |                             |         |
| Transferred in                 | 79 (3.1)                    | 1063 (42.4)                 | <0.001  |
| Hospital approaching method    |                             |                             | <0.001  |
| Self-transport                 | 1984 (77.7)                 | 1630 (64.9)                 |         |
| By ambulance                   | 530 (20.8)                  | 866 (34.5)                  |         |
| On site                        | 39 (1.5)                    | 14 (0.6)                    |         |
| Prehospital ECG               | 340 (13.3)                  | 710 (28.3)                  | <0.001  |
| Bypassing the ER              | 20 (0.8)                    | 114 (4.5)                   | <0.001  |
| **Myocardial ischaemia symptoms** |                         |                             | <0.001  |
| Typical                        | 2038 (79.8)                 | 2215 (88.3)                 |         |
| Atypical                       | 508 (19.9)                  | 284 (11.3)                  |         |
| No symptom                     | 7 (0.3)                     | 11 (0.4)                    |         |
| Cardiac arrest                 | 52 (2.0)                    | 102 (4.1)                   | <0.001  |
| Cardiogenic shock              | 192 (7.5)                   | 125 (5.0)                   | <0.001  |
| Anterior myocardial infarction | 1452 (56.9)                 | 1423 (56.7)                 | 0.90    |
| LBBB                           | 22 (0.9)                    | 20 (0.8)                    | 0.80    |
| Heart rate (beats/min)         |                             |                             | <0.001  |
| <50                            | 149 (5.8)                   | 80 (3.2)                    |         |
| 50–109                         | 2278 (89.2)                 | 2277 (90.7)                 |         |
| ≥110                           | 126 (4.9)                   | 153 (6.1)                   |         |
| Systolic blood pressure (mm Hg)|                             |                             | <0.001  |
| <90                            | 151 (5.9)                   | 95 (3.8)                    |         |
| 90–139                         | 1374 (53.8)                 | 1628 (64.9)                 |         |
| ≥140                           | 1028 (40.3)                 | 787 (31.4)                  |         |
| Length of stay, days           | 10 (6–13)                   | 11 (8–14)                   | <0.001  |

Data are presented as median (IQR) or n (%).
ECG, electrocardiogram; ER, emergency room; LBBB, left bundle branch block; STEMI, ST elevation myocardial infarction.
**DISCUSSION**

Based on data collected in the multicentre, prospective Henan STEMI registry on real-world reperfusion, treatment delays and in-hospital outcomes of patients with STEMI in predominantly rural central China, we here report that different practice patterns exist between hospital tiers, with thrombolysis mainly used in secondary hospitals and primary intervention in tertiary hospitals.

The reperfusion rate was higher in secondary hospitals, whereas in-hospital outcomes were similar between secondary and tertiary hospitals. There is still a large gap between reperfusion practices and those recommended by guidelines, such as delayed thrombolysis without further angiographic assessment and prolonged prehospital delay.

Our results showed substantial gaps in the use of thrombolytic therapy compared with guidelines. Similar to other developing countries, fibrinolytic therapy remains the main reperfusion therapy in secondary hospitals.\(^1\)\(^9\)\(^2\)\(^0\)

With a vast territory, and limited by medical condition, geographical location and techniques, early fibrinolysis and/or transfer PCI strategy should be the priority in  

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**Table 2  Treatment delays among patients with STEMI**

|                          | Secondary hospital (n=2553) | Tertiary hospital (n=2510) | P value |
|--------------------------|-----------------------------|---------------------------|---------|
| **Among all patients**   |                             |                           |         |
| Onset-to-FMC, min        | 176 (90–365)                | 270 (122–970)             | <0.001  |
| Onset-to-FMC time >12hours | 438 (17.2)                  | 703 (28.0)                | <0.001  |
| FMC-to-ECG≤10 min        | 2260 (88.5)                 | 2108 (84.0)               | <0.001  |
| **Among patients receiving reperfusion** |                         |                           |         |
| Onset-to-FMC, min        | 122 (67–214)                | 180 (93–320)              | <0.001  |
| FMC-to-fibrinolysis time, min | 45 (28–78)              | 73 (47–125)               | <0.001  |
| FMC-to-PCI time, min     | 57 (37–93)                  | 66 (43–95)                | 0.09    |
| FMC-to-fibrinolysis≤30min | 399 (29.7)                  | 9 (11.4)                  | <0.001  |
| FMC-to-PCI≤90 min        | 166 (73.8)                  | 940 (72.8)                | 0.75    |
| Onset-to-fibrinolysis, min | 190 (130–285)            | 235 (174–345)             | <0.001  |
| Onset-to-fibrinolysis>3 hours | 712 (53.0)                | 57 (72.2)                 | <0.001  |
| Onset-to-PCI time, min   | 209 (130–360)               | 260 (165–408.5)           | <0.001  |
| Door-in-Door-out time ≥30min* | 7 (35.0)                  | 55 (14.2)                 | 0.03    |

Data are presented as median (IQR) or n (%).

*Data were missing in 10.4% of the records.

FMC, first medical contact; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

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**Figure 1  Study profile.** CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.
secondary hospitals without PCI capability in Henan.21–24 However, there is still much room for improvement in thrombolytic therapy. First, the proportion of early fibrinolytic therapy was low. Our finding showed that more than half of the patients received fibrinolytic therapy after 3 hours of symptom onset; 15.6% of patients in secondary hospitals even received it beyond 12 hours of symptom onset; and only 29.7% of patients undergoing fibrinolysis within 30 min of FMC. Second, there was no emphasis on timely evaluation with coronary angiography after fibrinolysis. Current guidelines recommend that patients with STEMI should be transferred to a PCI-capable hospital for coronary angiography between 2 and 24 hours after successful fibrinolysis.5–7 However, in the present study, only 5.8% underwent early angiography in accordance with the guidelines in secondary hospitals, which was lower than in other countries.20,25 Furthermore, only 5.6% of the patients who failed fibrinolysis underwent rescue PCI. These gaps reflect the insufficient public knowledge of STEMI,26 poor ability of primary healthcare to identify and treat STEMI,27 inability of most secondary hospitals to provide 24/7 PCI service,28 and inadequate medicare payment systems,27,29 which need further improvement.

Although primary PCI is the mainstay reperfusion method in tertiary hospitals in central China, the proportion of early fibrinolytic therapy was low. Our finding showed that more than half of the patients received fibrinolytic therapy after 3 hours of symptom onset; 15.6% of patients in secondary hospitals even received it beyond 12 hours of symptom onset; and only 29.7% of patients undergoing fibrinolysis within 30 min of FMC. Second, there was no emphasis on timely evaluation with coronary angiography after fibrinolysis. Current guidelines recommend that patients with STEMI should be transferred to a PCI-capable hospital for coronary angiography between 2 and 24 hours after successful fibrinolysis.5–7 However, in the present study, only 5.8% underwent early angiography in accordance with the guidelines in secondary hospitals, which was lower than in other countries.20,25 Furthermore, only 5.6% of the patients who failed fibrinolysis underwent rescue PCI. These gaps reflect the insufficient public knowledge of STEMI,26 poor ability of primary healthcare to identify and treat STEMI,27 inability of most secondary hospitals to provide 24/7 PCI service,28 and inadequate medicare payment systems,27,29 which need further improvement.

Although primary PCI is the mainstay reperfusion method in tertiary hospitals in central China, the proportion of primary PCI is lower compared with developed
Moreover, our results showed that the early reperfusion rate was lower in tertiary hospitals compared with secondary hospitals, despite tertiary hospitals having more advanced facilities and greater availability of specialists, possibly due to the following reasons. First, prolonged prehospital delay resulted in a lower percentage of patients meeting reperfusion criteria. In our study, prehospital delays were observed in both secondary and tertiary hospitals, especially in tertiary hospitals. The median onset-to-FMC time was nearly greater than 3 hours in both hospitals, significantly higher than that of other studies. Prehospital delays mainly results from the healthcare system and patients. Our study found low percentage of ambulance transport and longer DIDO time. Second, patients in secondary hospitals were not timely transferred to tertiary hospitals after thrombolysis. Therefore, it is in urgent need in tertiary hospitals to establish an integrated regional network including the central coordination of emergency medical system, patient referral from primary healthcare facilities to PCI hospitals, interhospital transfer and coordinated clinical pathway in PCI hospitals. This is just the purpose of the China Chest Pain Center project. It has been showed that accreditation of chest pain centre is associated with better management and in-hospital outcomes. In 2020, the establishment of chest pain care units in primary healthcare institutions has been initiated to improve the ability of primary care physicians to recognise chest pain and STEMI diagnosis.

Our finding showed that in-hospital outcomes were similar in secondary and tertiary hospitals, although the reperfusion use rate was higher in secondary hospitals. Several reasons underlie this situation. First, the main risk factors for death, such as the elderly, women and cardiogenic shock, were more common in secondary hospitals than in tertiary hospitals; Second, most secondary hospitals without PCI capability administered delayed thrombolysis without further angiographic assessment; finally, the first two reasons make tertiary hospitals with PCI capability unable to give full play to the advantages of intervention.

In this study, we identified substantial gaps between reperfusion practices and guidelines in predominantly rural central China, including prolonged prehospital delays, delayed thrombolysis without further angiographic assessment and low PCI use. The main reasons are poor public awareness of STEMI, low quality of primary and secondary healthcare, poor coordination between primary, secondary and tertiary healthcare institutes and inadequate medicare payment systems. To improve the quality care for STEMI in rural China, it is necessary to further increase public awareness, the capacity of primary and secondary healthcare institutes, and establish deeper cooperation among different-level healthcare institutes, such as establishment of medical alliance, chest pain centre and chest pain care unit.

The Henan STEMI registry is distinguished that it is a large multicentre, prospective regional STEMI registry, including both secondary and tertiary hospitals in predominantly rural central China; our finding will help policy makers and healthcare professionals comprehensively get the knowledge of real-world practice care, treatment delays and outcomes in secondary and tertiary hospitals in central China, and facilitate the translation of study findings to improvement of quality care for STEMI in China and other countries in a similar situation.

Limitations
Several limitations of our study should be discussed. First, the centres in our study (as for most registries) were not randomly selected but volunteered to participate. Therefore, the practice patterns at such centres might not necessarily represent practice at all hospitals in Henan, central China. However, the geographical diversity (16 of the total 18 prefectures) gives an indication of the usefulness of the data. Second, the data collection burden for investigators may be the greatest barrier to the registry that may lead to some enrolment bias. We have carefully considered each element to limit the burden and have quality control measures in the registry. Third, we used a multivariable model to adjust for demographic and clinical covariates, but residual measured and unmeasured confounding cannot be excluded. However, the sensitivity analysis results confirmed that our results were relatively stable.

CONCLUSION
Different classed of hospital have different reperfusion methods. Fibrinolytic therapy was the main reperfusion therapy in secondary hospitals, and more than half of the patients had delayed thrombolysis and only a few underwent timely angiographic evaluation. The reperfusion rate was higher in secondary hospitals, whereas in-hospital outcomes were similar between secondary and tertiary hospitals. Improvement of quality of care for STEMI should underscore raising public awareness, enhancing the quality of medical care in primary and secondary healthcare institutes, and establishment of deeper cooperation among different-level healthcare institutes. Our findings provide evidence for policymakers and healthcare professionals in China and other developing countries.

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Acknowledgements We would like to thank all of the members of Scientific Committee, and Executive Committee for their contribution to the Henan STEMI registry. We also want to thank all of the study investigators and coordinators for their great work, and thank Prof. Xi Li, associate research fellow in National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, for his guidance in manuscript preparation.
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Contributors
CG and YZ conceived and designed the study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YZ wrote the first draft or the article, with further contributions from GC, JZ, DO, XW, ZZ, ML and DH. YZ, SW and CG provided expert clinical opinion and interpretation of the data. SW did statistical analysis, with support from YZ and CG. All authors made critical revisions and approved the final version of the article.

Funding
This work was supported by the Project of Scientific and Technological Support Plan of Health and Family Planning Commission of Henan Province in 2016 [grant number: 201602210] and Shanghai Tasyi Pharmaceutical Co. Ltd [grant number: not applicable].

Disclaimer
The funding organisations for this study had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Ethics approval
The medical ethics committee of Henan Provincial People's Hospital approved the Henan STEM registry with a waiver for informed consent [No. 2015 (34)].

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available upon reasonable request.

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