BMJ Open

Pre- and in-hospital delays to care and associated factors in STEMI patients: an observational study at 101 non-PCI hospitals in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031918
Article Type:	Research
Date Submitted by the Author:	25-May-2019
Complete List of Authors:	Feng, Lin; Peking University First Hospital, ; Peking University Clinical Research Institute, Li , Min; Peking University School of Public Health , Epidemiology and Biostatistics Xie , Wuxiang Zhang, Aihua; The George Institute for Global Health at Peking University Health Science Center Lei, Licheng; Capital Medical University Affiliated Beijing Shijitan Hospital, The Department of Cardiology Li , Xian; The George Institute for Global Health at Peking University Health Science Center Gao, R; Fu Wai Hospital, National Center for Cardiovascular Diseases, Wu, Yangfeng; Peking University School of Public Health, Epidemiology
Keywords:	Myocardial infarction < CARDIOLOGY, delays, associated factors

Pre- and in-hospital delays to care and associated factors in STEMI patients: an observational study at 101 non-PCI hospitals in China

Authors: Lin Feng (BM)[1,2], Min Li (PhD)[3], Wuxiang Xie (PhD)[2], Aihua Zhang (BM)[4], Licheng Lei (MD)[5], Xian Li (MSc)[4], Runlin Gao (MD)[6], Yangfeng Wu (PhD)[2,4 *]

[1] Peking University First Hospital, Beijing, China;

[2] Peking University Clinical Research Institute, Peking University Health Science Center, Beijing, China;

[3] Clinical Epidemiology and EBM Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center for Digestive Disease, Beijing, China;

[4] The George Institute for Global Health at Peking University Health Science Center, Beijing, China;

[5] The Department of Cardiology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China;

[6] The Department of Cardiology, Cardiovascular Institute and Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Bejing, China;

*Corresponding Author: Yangfeng Wu, wuyf@bjmu.edu.cn

Peking University Clinical Research Institute, Peking University Health Science Center, No. 38 Xueyuan Road, Haidian District, 100191, Beijing, China.

Word count: 2889

ABSTRACT

Objectives: to describe the pre- and –in hospital delays to care and factors associated with the delays among ST-segment Elevation Myocardial Infarction (STEMI) patients in non-PCI hospitals in China.

Design, setting and participants: We analyzed data from a large registry-based quality of care improvement trial conducted in 2011 to 2014 among 101 non-PCI hospitals in China. A total of 7,312 STEMI patients were included. Pre-hospital delay was defined as time from onset to door ≥ 120 minutes, first ECG delay as door-to-ECG ≥ 10 minutes and thrombolytic therapy delay as ECG-to-thrombolytic therapy ≥ 10 minutes. Generalized linear models were preformed to identify the factors associated with each delay.

Results: The rates of pre-hospital delay, first ECG delay and thrombolytic therapy delay were 67.1%, 31.4% and 85.8%. Patients who were female, older than 65 years old, illiterate, farmer, onset during late night and forenoon, had heart rate ≥ 100 beats/m at admission were more likely and patients who had history of myocardial infarction, hypertension, or SBP < 90 mmHg at admission less likely to have pre-hospital delay. First ECG delay was more likely to take place in patients arriving on regular hours. Thrombolytic therapy delay was lower in patients who had pre-hospital delay or first ECG delay but higher in those heart rate≥100 beats/m at admission.

Conclusion: Chinese STEMI patients in low medical resource areas suffered severe pre- and in-hospital delays to care. Future efforts should be made to improve the pre-hospital delay among vulnerable population with low social economic status.

Keywords: myocardial infarction; delays; associated factors

Strengths and limitations of this study

- This study provides the insights into the pre- and in-hospital delays to care among STEMI patients in low medical resource areas with a large sample from 101 non-PCI hospitals across China.
- The study used prospective data to investigate influencing factors of first ECG delay and thrombolytic therapy delay in STEMI patients.
- We could not exclude the influence of patient's recall bias for symptom onset time. However, data were collected during patient's admission within a very narrow time after STEMI onset.
- Survivor bias might exist as patients who were dead on arrival or within 10 min of hospital arrival were excluded.
- We did not collect the onset symptoms and hence could hardly study on the possible associations between the symptoms and the delays to care.

INTRODUCTION

Total ischemic time (from symptom onset to effective reperfusion strategy) is an important indicator to the prognosis of patients with ST-segment Elevation Myocardial Infarction (STEMI). [1 2] In general, the total ischemic time comprises three consecutive segments. The time from symptoms onset to the door of hospital represents the time patients spend to respond to the disease onset and seeking medical care. The time from door to having the first ECG in hospital represents the time hospital staffs' responses to the patient's call for help, and with the first ECG done in time the diagnosis of STEMI could be made and appropriate treatments could be initiated. The time from diagnosis to treatment represents doctors' responses to the diagnosis of disease. Delay in each segment can lead to a longer ischemic time, which has been fund associated with higher short-term as well as medium-term to long-term mortality in previous studies. [3-6]

Meanwhile, recent studies indicated that time delays to care among STEMI patients exist universally, showing a worse situation in low and middle income countries than that of high income countries, [7-10] such as 28.7% of ACS patients in Germany but two thirds of STEMI patients in Brazil suffered first ECG delay. [8 9] The delays to care in STEMI patients remain as great challenges to be overcome across all countries.

Up to the present, quite a few studies have tried to better understand the reasons behind these delays and showed that sociodemographic factors (female gender, older age, low educational level), medical histories (diabetes, myocardial infarction), ambiguous heart symptoms, use of private transport were related to longer delay in at least one of the three kinds of time delays. [8 11-14] Based on these findings, some national or regional programs

have been initiated to reduce the delays by targeting at controlling these factors, through educational campaign, implementation of pre-hospital ECG, establishing regional collaborative network, etc. and these actions turned out to be effective. [15-18]

However, almost all of those studies focused on pre-hospital delay and the patients who had access to onsite primary percutaneous coronary intervention (PCI) procedure. Those evidences have limited value for non-PCI hospitals in remote areas where fibrinolysis is the main reperfusion option for STEMI patients. As effectiveness of thrombolytic therapy is more time-dependent than PCI, it is of great importance to investigate delays in those settings. Therefore, the aims of the present study are (a) to describe the time delays among STEMI patients in non-PCI hospitals in China, (b) to identify factors associated to these delays, and (c) to make suggestions for reducing these delays and improving care of STEMI patients in the similar settings in China and other countries.

METHODS

Study population

We used data of the STEMI patients from a very large registry-based quality of care improvement trial, the third phase of the Clinical Pathways for Acute Coronary Syndromes (CPACS-3) in China.[19] In brief, patients in CPACS-3 trial were recruited consecutively from 101 regional hospitals without the capacity to perform onsite PCI between Oct. 2011 and Nov. 2014. Patients were all over 18 years old and with a final diagnosis of ACS at discharge or death. The patients who were dead on arrival or within 10 min after hospital arrival were excluded. For the present study, we further excluded patients whose data of

time at either symptoms onset, arrival to hospital, having the first ECG or receiving thrombolytic therapy were missing. From a total 10,294 STEMI patients recruited in CPACS-3 trial, we had 7,312 patients analyzed with complete data. The study flow diagram was shown in Figure 1.

The Peking University IRB reviewed and approved the CPACS-3 trial and all participating patients provided written informed consents. The CPACS-3 study registered on www.clinicaltrails.gov (NCT01398228).

Data collection and verification

A trained hospital staff member, who was not involved in the management of patients with ACS, was responsible for collecting and entering data into a dedicated web-based Data Management System (DMS). Data of each patient was collected from medical records. The data included socio-demographic information, vital signs relating to the presenting ACS, medical history, ECG, biomarker findings, investigations performed, treatments administered prior to admission, during hospitalization, and at death or hospital discharge, final diagnosis and discharge status, major in-hospital clinical events, personal insurance status and the total cost of hospitalization. Data quality was maintained through independent centrally managed in-person and on-line study monitoring activities.

Definitions and outcomes

Pre-hospital delay was defined as the time from symptoms onset to arrival to the door of hospital (onset-to door time) ≥ 120 minutes.[14 20 21] Most of hospitals without PCI facility in China are located in rural area, where pre-hospital emergency system is either not existing or pretty weak. The ambulances serve only as a transportation vehicle but no ECG

equipped or the results not able to be transmitted back to the hospital. Thrombolytic therapy remains an in-hospital practice throughout the whole country up to now. Thus, the first ECG delay was defined as the time from patient's arrival to the door of hospital to the time the patient had the first ECG done (door-to-ECG time) ≥ 10 minutes. [22 23] The diagnosis of STEMI should had been made by then. The thrombolytic therapy delay was defined as the time from patient had the first ECG done to the time the thrombolytic therapy initiated (door-to-needle time) ≥ 10 minutes.[22]

Statistical analysis

The baseline characteristics of our study patients were described as percentages for categorical variables and means with standard deviations (SDs) for continuous variables with a normal distribution or medians with interquartile ranges (IQRs) for continuous variables with skewed distribution. The generalized estimating equations (GEE) were used to test the associates of the time delays (pre-hospital delay, first ECG delay, thrombolytic therapy delay), with an exchangeable correlation structure to account for clustering effect (the correlation within hospitals). Missing data of covariates (all categorical variables) were handled as separated groups in multivariate analyses. We used SAS 9.4 (SAS Institute Inc., Cary, NC, USA) to perform data analyses. The significant level α was set at 0.05.

RESULTS

The characteristics of our included patients were summarized in Table 1. Their ages ranged from 19 to 102 years old and had a mean age of 63.4 years old. Most patients were males

(71.2%), more than half were famers (67.2%), and almost all covered by medical insurances (94.1%). Almost a third of them were illiterate. The vital signs, cardiovascular risk factors and history of cardiovascular diseases were shown in Table 1.

Table 1. Characteristics of included patients

Characteristics	All STEMI patients (N=7312)*
Male, No. (%)	5205 (71.2)
Age, Mean (SD), year	63.37 (12.42)
Farmer, No. (%)	4715 (67.2) (n=7013)
Illiteracy, No. (%)	1604 (27.7) (n=5799)
Medical insurance, No. (%)	5140 (94.1) (n=5462)
Cardiovascular risk factors	
Smoking, No. (%)	2488 (34.7) (n=7170)
Hypertension, No. (%)	4588 (62.8)
Dyslipidemia, No. (%)	279 (3.8)
Diabetes, No. (%)	851 (11.6)
Cardiovascular disease history	
Myocardial infarction, No. (%)	460 (6.3)
Angina, No. (%)	805 (11.0)
Stroke, No. (%)	635 (8.7)
TIA, No. (%)	111 (1.5)
Heart failure, No. (%)	160 (2.2)
Symptom onset time	

00:00-05:59, No. (%)	1315 (18.0)
06:00-11:59, No. (%)	2681 (36.7)
12:00-17:59, No. (%)	1896 (25.9)
18:00-23:59, No. (%)	1420 (19.4)
Vital signs at admission	
SBP < 90mmHg, No. (%)	407 (5.6) (n=7252)
Heart rates ≥ 100 b/m, No. (%)	832 (11.6) (n=7192)

STEMI, ST-segment elevation myocardial infarction; SD, standard deviation; TIA, transient ischemic attack; SBP, systolic blood pressure.

* Total number are shown for variable for which data were not completely reported.

The delays to care

For all STEMI patients, 67% had experienced the pre-hospital delay and 31% experienced the first ECG delay. The patients receiving thrombolytic therapy had significantly less pre-hospital and first ECG delays, comparing with patients not receiving the therapy. Among the patients receiving thrombolytic therapy, 86% initiated the treatment after 10 minutes of the first ECG done.

No matter patients received or not thrombolytic therapy, onset-to-door time was the dominant time segment, accounting for two thirds of the total ischemic time among those who received thrombolytic therapy. Patients who did not received thrombolytic therapy suffered more than twice longer onset-to-door time as their counterparts who received thrombolytic therapy. (See Table 2)

Table 2. Time duration and delay in different segments from onset to care among STEMI

patients (min)

	Onset-to-door time	Door-to-ECG time	ECG-to-Needle time	Total
All STEMI patients				
Time duration, median (IQR)	210 (110-660)	5 (0-17)	-	260 (145-710)*
Delay, % (No. of Participants/Total)	67.1 (4903/7312)	31.4 (2299/7312)	-	-
Patients with thrombolytic therapy				
Time duration, median (IQR)	140 (70-240)	4 (0-10)	38 (20-65)	210 (135-320)
Delay, % (No. of Participants/Total)	54.6 (1669/3057)	23.6 (722/3057)	85.8 (2623/3057)	
Patients with non-thrombolytic therapy				
Time duration, median (IQR)	360 (130-1364)	6 (0-24)	-	395 (157-1419)†
Delay, % (No. of Participants/Total)	76.0 (3234/4255)	37.1 (1577/4255)	-	

STEMI, ST-segment elevation myocardial infarction; ECG, Electrocardiograph; IQR, inter quartile range.

*, representing onset-to-needle time among those received thrombolytic therapy but onset-to-ECG time among those not;

†, representing onset-to-ECG time;

Factors associated with the delays

A number of patient-level factors were associated with pre-hospital delay. The patients who were female, order than 65 years, illiterate, farmers, symptom onset during 00:00-05:59 and 06:00-11:59, with a faster heart rate were more likely to experience a pre-hospital delay. While, patients who had a history of myocardial infarction or hypertension, with a cardiac shock at presentation were less likely to experience a pre-hospital delay. (See Table 3)

Few patient level factors were found associated with the first ECG delay and thrombolytic therapy delay. Only patients who arrived on regular hours independently associated with higher first ECG delay rate. The first ECG delay was decreasing during the study period. (See Table 3)

Thrombolytic therapy delay was less likely to take place among patients who experienced pre-hospital delay or first ECG delay. Patients who presented with faster heart rate were more likely to experience a delay in thrombolytic therapy. (See Table 3)

Table 3. Multivariate analyses of factors associated with pre-hospital delay, first ECG delay and thrombolytic therapy delay, using generalized estimating equations.

	Pre-hospital delay (N=7312)	First ECG delay (N=7312)	Thrombolytic therapy delay (N=3057)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female	1.20(1.05-1.38)	1.03(0.90-1.18)	1.07(0.80-1.43)

≥65 years old	1.54(1.37-1.73)	1.04(0.92-1.18)	0.97(0.77-1.23)
Illiteracy	1.44(1.17-1.77)	1.12(0.92-1.35)	0.86(0.59-1.25)
Farmer	1.61(1.36-1.90)	1.02(0.85-1.23)	1.21(0.90-1.63)
Medical insurance	1.14(0.73-1.79)	1.21(0.88-1.67)	0.69(0.32-1.45)
Smoking	1.00(0.86-1.15)	0.90(0.74-1.09)	1.07(0.81-1.42)
History of disease, %			
Myocardial infarction	0.67(0.52-0.87)	1.20(0.94-1.53)	1.16(0.70-1.92)
Angina	0.91(0.78-1.06)	0.82(0.67-1.00)	0.84(0.60-1.17)
Stroke	1.19(0.99-1.42)	0.92(0.74-1.14)	1.30(0.83-2.03)
Heart failure	1.25(0.84-1.88)	0.95(0.64-1.41)	0.74(0.24-2.25)
TIA	0.68(0.45-1.05)	1.01(0.56-1.82)	1.06(0.46-2.42)
Diabetes	0.98(0.85-1.13)	1.00(0.84-1.18)	1.19(0.86-1.64)
Hypertension	0.89(0.79-0.99)	1.01(0.90-1.14)	1.03(0.83-1.29)
Dyslipidemia	1.04(0.80-1.35)	1.03(0.74-1.43)	0.68(0.40-1.15)
Time cycles (every 6 months)	0.97(0.91-1.05)	0.87(0.76-0.99)	1.01(0.87-1.17)
Symptom onset time			
00:00-05:59	2.04(1.80-2.32)	-	-
06:00-11:59	1.47(1.28-1.68)	-	-
12:00-17:59	ref	-	-

18:00-23:59	1.00(0.89-1.13)	-	-
Vital signs at admission			
SBP < 90 mmHg	0.57(0.46-0.71)	0.78(0.59-1.04)	0.85(0.56-1.28)
Heart rates ≥ 100 beats/m	1.71(1.48-1.99)	1.05(0.90-1.23)	1.61(1.04-2.50)
Arrived on regular hours	-	1.12(1.00-1.25)	0.94(0.77-1.15)
Pre-hospital delay	-	1.14(0.99-1.32)	0.78(0.64-0.95)
First ECG delay	-	-	0.56(0.41-0.78)
CPACS-3 intervention*	1.08(0.86-1.36)	0.78(0.51-1.18)	1.03(0.65-1.63)

ECG, electrocardiograph; OR, odds ratio; TIA, transient ischemic attack; SBP, systolic blood pressure.

*, the intervention of the third phase of the Clinical Pathways for Acute Coronary Syndromes study.

Association of receiving thrombolytic therapy with pre-hospital delay and first ECG delay

Patients who suffered pre-hospital delay or first ECG delay were less likely to receive thrombolytic therapy at hospital. Even further adjusted for potential confounders, pre-hospital delay and first ECG delay separately linked to 32% and 28% reductions of receiving thrombolytic therapy among our patients. (See Table 4)

Table 4. Association of receiving thrombolytic therapy with pre-hospital delay and first ECG delay

	Thrombolytic therapy rate (%) (No. of Participants/Total)	Crude RR* (95% CI)	Adjusted RR† (95% CI)
Pre-hospital delay			
Yes	34.0 (1669/4903)	0.62(0.58-0.67)	0.68(0.64-0.73)
No	57.6 (1388/2409)		
First ECG delay			
Yes	31.4 (722/2299)	0.71(0.66-0.76)	0.72(0.66-0.78)
No	46.6 (2335/5013)		

ECG, electrocardiograph; RR, risk ratio.

*, crude RR calculated from model only included pre-hospital delay and first ECG delay;

†, further adjusted for sex, age, education level, occupation, medical insurance, smoking, histories of myocardial infarction, angina, stroke, heart failure, transient ischemic attack, diabetes, hypertension, dyslipidemia, time cycles (every 6 months), vital signs at admission, arrived on regular hours, CPACS-3 intervention.

DISCUSSION

Main results

In the present study, we found that two thirds of STEMI patients in non-PCI hospitals in China had the pre-hospital delay after their disease onsets in their seeking for medical care; and about one third of them had their first ECG delayed after they arrived at hospitals,

according to the criteria from ESC and ACC/AHA guidelines or previous researches.[14 20 21] Among patients who received their thrombolytic therapy as high as 86% of them received the treatment after 10 minutes of the disease diagnosis.

Compared with STEMI patients from large medical centers in metropolitan areas of China[14] and other developed countries[13 24], where the median onset-to-door time was about 113 to 150 minutes, the median time found in our study was much longer, about 210 minutes. But our results were similar to that was reported in the Middle East[10] and shorter than that in India[25]. The first ECG delay in our study was much better than that in Brazil (67%)[8] and India (55%)[7] but worse than that in developed countries like Japan (18.4%)[26] and Germany (28.7%)[9]. As previous studies including ours have demonstrated the significant association of ischemic time with the short and long term mortality among patients with STEMI, our findings in this study highlighted the urgent needs to reduce the delays to care for STEMI patients in the similar settings in China and other developing countries.

Our further analyses showed that the pre-hospital and first ECG delays were significantly associated with the risk of not receiving thrombolytic therapy. In fact, only 43% of our study patients received thrombolytic therapy. Since these patients admitted to non-PCI hospitals of China often lived far away from large tertiary medical centers equipped with PCI facilities, thrombolytic therapy was the only revascularization treatment they could have in the first line. Reducing the pre-hospital and first ECG delay should have great potential to permit more patients with thrombolytic therapy, which in turn will save many more lives in these remote areas. In our study, half of the patients not receiving

thrombolytic therapy arrived at hospital beyond 6 hours after their disease onsets and hence lost the best opportunity to receive the treatment. If the median time could be reduced to 3 hours, probably the most of these patients would still have chance for the thrombolytic therapy.

The study on the factors associated with the delays to care could help to find solutions to reduce the delays. Like previous studies, the onset-to-door time took the most part of the total ischemic time, and we should pay more attention to reduce the pre-hospital delay. In our study, patients who were female, older than 75 years old, illiterate, and farmer were found more likely to have the pre-hospital delay. This implies that efforts should be made to improve the medical access for the vulnerable patients with low social economic status. A recent study among Indian STEMI patients supports our findings and found that the difficulty of arranging money was an important factor leading to the pre-hospital delay.[7] Furthermore, the elderly and illiterate patients might misinterpret the symptoms of STEMI with symptoms of ageing, aggravating their pre-hospital delays.[21]

Patients with history of myocardial infarction, hypertension, or presented with shock at admission were found less likely to have the pre-hospital delay. We believe this is because these patients had more knowledge of myocardial infarction and realized the importance of in-time medical rescue. We believe the reason for patients who presented with shock at admission were found less likely to have pre-hospital delay was due to the severity of the symptom, which alarmed the patient itself, family members or a companion person that helped to access medical care in time. In contrast, we believe the reason for patients who presented with tachycardia at admission more likely to have pre-hospital delay was

actually an inverse causal relationship, i.e. the tachycardia was a result of pre-hospital delay.

Similar to previous studies,[7 13 14 27] we also found patients suffered pre-hospital delay had their symptom onset most during 00:00 to 05:59. Most people are in sleep during this time, and most patients would not want to bother others at this time if they believe the disease was not severe. Those patients might be prone to going to the hospital the next day avoiding troublesome visits at late night. The phenomenon might be exaggerated by the fact that the most of our study patients were living in rural areas. The barriers for patients living in rural areas seeking for medical service include long distance, poor transport facilities and costs concerns. The evidence that patients who had shorter onset-to-door time were with less stroke or heart failure history supported this explanation to some extent.

As the first ECG delay reflects more medical staff rather than patients' responses to the disease, no patient side factor was found associated with the first ECG delay in our study. But first ECG delay was found more likely to take place in patients arriving on regular hours. The same results were also found among NSTE-ACS patients in CRUSADE Quality Improvement Initiative study.[28] Although the reasons are still unknown, this relationship may reflect the insufficiency of medical staff and the consequential long waiting time in regular hours.

Recent STREAM trial demonstrated that thrombolytic therapy (median time from randomization to bolus recorded was 9 min) was as effective as primary PCI beyond 1 hour among STEMI patients who presented within 3 hours after symptom onset.[29] Based on the results from the STREAM trial, European Society of Cardiology recommended time

from STEMI diagnosis to the start of fibrinolysis to be within 10 min.[22] According to the new ESC guidelines, only 14% of patients who received fibrinolysis achieved the 10 min target. We consider this target time may be ideal but quite unrealistic in rural China now, considering there are many barriers that prevent from initiating the thrombolytic therapy in such a short time. Particularly, the new type of fibrinolytic agents (Tenecteplase), which was used in the STREAM trial, is not available yet in China. Hopefully, the ECG-to-needle time can be shortened as the recombinant human TNK tissue-type plasminogen activator (rhTNKtPA) has been approved by China FDA recently, which is applied in bolus at once and easy for administration. Meanwhile, due to the possible severe bleedings, the patient inform consent often takes a long time, particularly when the doctor-patient relationship is not good and the medical insurance could not cover the entire costs. However, even with the old criteria that door-to-needle time should be within 30 minutes,[23] there were still 68% STEMI patients in present study started their thrombolytic therapy beyond this criterion. Door-to-needle delays were also reported severe in other similar settings like India (87%)[7] and rural Canada (42%)[30] according to the old criteria.

One of the interesting findings from our study was that among patients receiving thrombolytic therapy, the treatment delay was lower in patients who had pre-hospital delay or first ECG delay, reflecting medical team's "time catch-up" effort after the patient was confirmed STEMI diagnosis by ECG examination. Physicians were apt to react more rapidly to make up previous delays, as the effects of the treatment are time-dependent, especially for thrombolytic therapy. Nevertheless, we should understand that physicians' "catch-up effect" only had limited value for shortening total ischemic time, as the major

segment was the onset-to-door time. More emphases should be put onto reducing the pre-hospital delay.

Strengths and limitations

The strengths of our study include: 1) A large sample from non-PCI hospitals across China. The results could be extended to other places of China and the world with the similar settings. 2) The data were collected prospectively, under strict supervision by an experienced project management team and a steering committee composed of international expertise in cardiology, epidemiology and biostatistics.

The present study also has several limitations. First, we could not exclude the influence of patient's recall bias for symptom onset time. However, data were collected during patient's admission within a very narrow time after their symptom onset. Another limitation is that survivor bias might exist as patients who were dead on arrival or within 10 min of hospital arrival were excluded. Additionally, we did not collect the onset symptoms and hence could hardly study on the possible associations between the symptoms and the delays to care.

CONCLUSIONS

In conclusion, the present study demonstrated that STEMI patients in non-PCI hospitals in China suffered severe time delays to care. Among the three types of delay, pre-hospital delay should be emphasized although the other two still have rooms for improvement. Future efforts should be made to improve the pre-hospital delay among vulnerable populations with low social economic status.

Implication

Establishment of pre-hospital rescue system facilitated with ECG examination and results transmission equipment as well as population-wide health education of in-time seeking medical care and chest pain might offer solutions to improve the current clinical practice and enhance the quality of care among STEMI patients.

Author contributions

LF, ML and YW conceived this study. YW obtained research funding. LF conceived and conducted statistical analyses. WX and XL provided statistical advice and statistical validation. AZ supervised the conduct of the study and data collection. LF, ML, LL, WX and YW interpreted the results. LF drafted the manuscript and all authors contributed substantially to its revision. YW takes responsibility for the paper as a whole.

Acknowledgements

The CPACS-3 Study Steering Committee (sorted by the first letter of the family name): Kalipso Chalkidou (National Institute for Health and Clinical Excellence), Runlin Gao* (Cardiovascular Institute and Fuwai Hospital), Dayi Hu (Peking University People's Hospital), Yong Huo (Peking University First Hospital), Yahui Jiao (NHFPC of China), Lingzhi Kong (NHFPC of China), Anushka Patel (The George Institute for Global Health), Eric Peterson (Duke Clinical Research Institute), Fiona Turnbull (The George Institute for Global Health), Mark Woodward (The George Institute for Global Health), Yangfeng Wu* (The George Institute for Global Health at PUHSC).

*Co-principal investigators.

Funding

CPACS-3 study is an investigator sponsored study supported by Sanofi. The George Institute for Global Health at PUHSC sponsored the study and owns the data. However, the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Conflict of interest

None declared.

REFERENCES

1. Solhpour A, Chang KW, Arain SA, et al. Ischemic time is a better predictor than door-to-balloon time for mortality and infarct size in ST-elevation myocardial infarction. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions* 2016;87(7):1194-200. doi: 10.1002/ccd.26230 [published Online First: 2015/09/04]

2. Chughtai H, Ratner D, Pozo M, et al. Prehospital delay and its impact on time to treatment in ST-elevation myocardial infarction. *The American journal of emergency medicine* 2011;29(4):396-400. doi: 10.1016/j.ajem.2009.11.006 [published Online First: 2010/09/10]

3. Nallamothu B, Fox KA, Kennelly BM, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart (British Cardiac Society)* 2007;93(12):1552-5. doi: 10.1136/hrt.2006.112847 [published Online First: 2007/06/27]

4. Berger PB, Ellis SG, Holmes DR, Jr., et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation* 1999;100(1):14-20. [published Online First: 1999/07/07]

5. Foo CY, Bonsu KO, Nallamothu BK, et al. Coronary intervention door-to-balloon time and outcomes in ST-elevation myocardial infarction: a meta-analysis. *Heart (British Cardiac Society)*

2018;104(16):1362-69. doi: 10.1136/heartjnl-2017-312517 [published Online First: 2018/02/14]

6. Benamer H, Bataille S, Tafflet M, et al. Longer pre-hospital delays and higher mortality in women with STEMI: the e-MUST Registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2016;12(5):e542-9. doi: 10.4244/eijv12i5a93 [published Online First: 2016/08/09]

7. George L, Ramamoorthy L, Satheesh S, et al. Prehospital delay and time to reperfusion therapy in ST elevation myocardial infarction. *Journal of emergencies, trauma, and shock* 2017;10(2):64-69. doi: 10.4103/0974-2700.201580 [published Online First: 2017/04/04]

8. Duraes AR, Bitar YS, Freitas ACT, et al. Gender differences in ST-elevation myocardial infarction (STEMI) time delays: experience of a public health service in Salvador-Brazil. *American journal of cardiovascular disease* 2017;7(5):102-07. [published Online First: 2017/11/29]

9. Post F, Giannitsis E, Riemer T, et al. Pre- and early in-hospital procedures in patients with acute coronary syndromes: first results of the "German chest pain unit registry". *Clinical research in cardiology : official journal of the German Cardiac Society* 2012;101(12):983-91. doi: 10.1007/s00392-012-0487-4 [published Online First: 2012/07/26]

10. Shehab A, AlHabib KF, Bhagavathula AS, et al. Clinical presentation, Quality of care, Risk factors and Outcomes in Women with Acute ST-Elevation Myocardial Infarction (STEMI): An Observational Report from Six Middle Eastern Countries. *Current vascular pharmacology* 2018;16:000-00. doi: 10.2174/1570161116666180315104820 [published Online First: 2018/03/16]

11. Sullivan AL, Beshansky JR, Ruthazer R, et al. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. *Circulation Cardiovascular*

quality and outcomes 2014;7(1):86-94. doi: 10.1161/circoutcomes.113.000396 [published Online First: 2014/01/16]

12. McKinley S, Dracup K, Moser DK, et al. International comparison of factors associated with delay in presentation for AMI treatment. *Eur J Cardiovasc Nurs* 2004;3(3):225-30. doi: 10.1016/j.ejcnurse.2004.06.004 [published Online First: 2004/09/08]

13. Park YH, Kang GH, Song BG, et al. Factors related to prehospital time delay in acute ST-segment elevation myocardial infarction. *Journal of Korean medical science* 2012;27(8):864-9. doi: 10.3346/jkms.2012.27.8.864 [published Online First: 2012/08/10]

14. Peng YG, Feng JJ, Guo LF, et al. Factors associated with prehospital delay in patients with ST-segment elevation acute myocardial infarction in China. *The American journal of emergency medicine* 2014;32(4):349-55. doi: 10.1016/j.ajem.2013.12.053 [published Online First: 2014/02/12]

15. Naegeli B, Radovanovic D, Rickli H, et al. Impact of a nationwide public campaign on delays and outcome in Swiss patients with acute coronary syndrome. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2011;18(2):297-304. doi: 10.1177/1741826710389386 [published Online First: 2011/04/01]

16. Quinn T, Johnsen S, Gale CP, et al. Effects of prehospital 12-lead ECG on processes of care and mortality in acute coronary syndrome: a linked cohort study from the Myocardial Ischaemia National Audit Project. *Heart (British Cardiac Society)* 2014;100(12):944-50. doi: 10.1136/heartjnl-2013-304599 [published Online First: 2014/04/16]

17. Mooney M, McKee G, Fealy G, et al. A review of interventions aimed at reducing pre-hospital delay

time in acute coronary syndrome: what has worked and why? *Eur J Cardiovasc Nurs* 2012;11(4):445-53. doi: 10.1016/j.ejcnurse.2011.04.003 [published Online First: 2011/05/14]

18. Duan T, Xiang D, Qin W, et al. [Impact of establishing regional collaborative network on reperfusion time and prognosis of patients with ST-segment elevated myocardial infarction admitting to community hospitals without percutaneous coronary intervention capacity]. *Zhonghua xin xue guan bing za zhi* 2014;42(8):641-5. [published Online First: 2014/11/13]

19. Wu Y, Li S, Patel A, et al. Effect of a Quality of Care Improvement Initiative in Patients With Acute Coronary Syndrome in Resource-Constrained Hospitals in China: A Randomized Clinical Trial. *JAMA Cardiol* 2019 doi: 10.1001/jamacardio.2019.0897 [published Online First: 2019/04/18]

20. Ladwig KH, Fang X, Wolf K, et al. Comparison of Delay Times Between Symptom Onset of an Acute ST-elevation Myocardial Infarction and Hospital Arrival in Men and Women <65 Years Versus >/=65 Years of Age.: Findings From the Multicenter Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction (MEDEA) Study. *The American journal of cardiology* 2017;120(12):2128-34. doi: 10.1016/j.amjcard.2017.09.005 [published Online First: 2017/11/11]

21. Wah W, Pek PP, Ho AF, et al. Symptom-to-door delay among patients with ST-segment elevation myocardial infarction in Singapore. *Emergency medicine Australasia : EMA* 2017;29(1):24-32. doi: 10.1111/1742-6723.12689 [published Online First: 2016/10/12]

22. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017;00:1-66. doi:

10.1093/eurheartj/ehx393

23. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127(4):e362-425. doi: 10.1161/CIR.0b013e3182742cf6

24. Fujii T, Masuda N, Suzuki T, et al. Impact of transport pathways on the time from symptom onset of ST-segment elevation myocardial infarction to door of coronary intervention facility. *Journal of cardiology* 2014;64(1):11-8. doi: 10.1016/j.jjcc.2013.11.008 [published Online First: 2014/01/09]

25. Isezuo S, Subban V, Krishnamoorthy J, et al. Characteristics, treatment and one-year outcomes of patients with acute coronary syndrome in a tertiary hospital in India. *Indian heart journal* 2014;66(2):156-63. doi: 10.1016/j.ihj.2013.12.023 [published Online First: 2014/05/13]

26. Noguchi M, Ako J, Morimoto T, et al. Modifiable factors associated with prolonged door to balloon time in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Heart and vessels* 2018;33(10):1139-48. doi: 10.1007/s00380-018-1164-y [published Online First: 2018/05/08]

27. Goldberg RJ, Steg PG, Sadiq I, et al. Extent of, and factors associated with, delay to hospital presentation in patients with acute coronary disease (the GRACE registry). *The American journal of cardiology* 2002;89(7):791-6. [published Online First: 2002/03/23]

28. Diercks DB, Peacock WF, Hiestand BC, et al. Frequency and consequences of recording an electrocardiogram >10 minutes after arrival in an emergency room in non-ST-segment elevation acute coronary syndromes (from the CRUSADE Initiative). *The American journal of cardiology* 2006;97(4):437-42. doi: 10.1016/j.amjcard.2005.09.073 [published Online First:

2006/02/08]

29. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *The New England journal of medicine* 2013;368(15):1379-87. doi: 10.1056/NEJMoa1301092 [published Online First: 2013/03/12]

30. Vlahaki D, Fiaani M, Milne WK. A door-to-needle time of 30 minutes or less for myocardial infarction thrombolysis is possible in rural emergency departments. *Cjem* 2008;10(5):429-33. [published Online First: 2008/10/02]

Figure 1. Study flow diagram of included patient

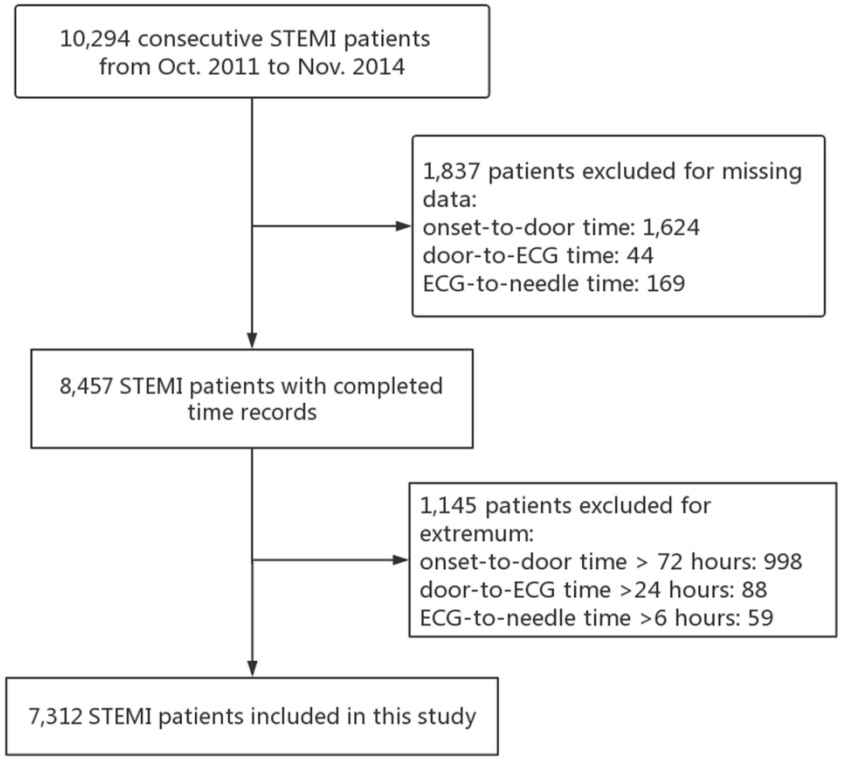

Figure 1. Study flow diagram of included patients.

Figure 1. Study flow diagram of included patient

351x349mm (100 x 100 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	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	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
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	6 and figure 1
		(b) Give reasons for non-participation at each stage	figure 1
		(c) Consider use of a flow diagram	figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	9 table 2
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	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
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	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
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	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Pre- and in-hospital delays to care and associated factors in STEMI patients: an observational study in 101 non-PCI hospitals in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031918.R1
Article Type:	Original research
Date Submitted by the Author:	23-Sep-2019
Complete List of Authors:	Feng, Lin; Peking University First Hospital, ; Peking University Clinical Research Institute, Li , Min; Peking University School of Public Health , Epidemiology and Biostatistics Xie , Wuxiang ; Peking University Clinical Research Institute, Peking University Health Science Center Zhang, Aihua; The George Institute for Global Health at Peking University Health Science Center Lei, Licheng; Capital Medical University Affiliated Beijing Shijitan Hospital, The Department of Cardiology Li , Xian; The George Institute for Global Health at Peking University Health Science Center Gao, R; Fu Wai Hospital, National Center for Cardiovascular Diseases, Wu, Yangfeng; Peking University School of Public Health, Epidemiology
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Myocardial infarction < CARDIOLOGY, delays, associated factors

Pre- and in-hospital delays to care and associated factors in STEMI patients: an observational study in 101 non-PCI hospitals in China

Authors: Lin Feng (BM)[1,2], Min Li (PhD)[3], Wuxiang Xie (PhD)[2], Aihua Zhang (BM)[4], Licheng Lei (MD)[5], Xian Li (MSc)[4], Runlin Gao (MD)[6], Yangfeng Wu (PhD)[2,4 *]

[1] Peking University First Hospital, Beijing, China;

[2] Peking University Clinical Research Institute, Peking University Health Science Center, Beijing, China;

[3] Clinical Epidemiology and EBM Center, Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center for Digestive Disease, Beijing, China;

[4] The George Institute for Global Health at Peking University Health Science Center, Beijing, China;

[5] The Department of Cardiology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China;

[6] The Department of Cardiology, Cardiovascular Institute and Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Bejing, China;

*Corresponding Author: Yangfeng Wu, wuyf@bjmu.edu.cn

Peking University Clinical Research Institute, Peking University Health Science Center, No. 38 Xueyuan Road, Haidian District, 100191, Beijing, China.

Word count: 3281

ABSTRACT

Objectives: To describe the pre- and in-hospital delays to care and factors associated with the delays among ST-segment Elevation Myocardial Infarction (STEMI) patients in non-PCI hospitals in China.

Design, setting and participants: We analyzed data from a large registry-based quality of care improvement trial conducted in 2011 to 2014 among 101 non-PCI hospitals in China. A total of 7,312 STEMI patients were included. Pre-hospital delay was defined as time from symptom onset to hospital arrival > 120 minutes, first ECG delay as time from arrival to first ECG > 10 minutes, thrombolytic therapy delay as time from first ECG to thrombolytic therapy > 10 minutes and in-hospital delay as time from arrival to thrombolytic therapy > 30 minutes. The logistic regressions with generalized estimating equations were preformed to identify the factors associated with each delay.

Results: The rates of pre-hospital delay, first ECG delay, thrombolytic therapy delay and in-hospital delay were 67.1%, 31.4%, 85.8% and 67.8%. Patients who were female, older than 65 years old, illiterate, farmer, onset during late night and forenoon, had heart rate ≥ 100 beats/m at admission were more likely and patients who had history of myocardial infarction, hypertension, or SBP < 90 mmHg at admission were less likely to have pre-hospital delay. First ECG delay was more likely to take place in patients arriving on regular hours. Thrombolytic therapy delay rate was lower in patients who had pre-hospital delay or first ECG delay but higher in those heart rate ≥ 100 beats/m at admission. In-hospital delay rate was lower in patients with history of dyslipidemia and those arrived on regular hours.

Conclusion: Chinese STEMI patients in low medical resource areas suffered severe pre- and in-hospital delays to care. Future efforts should be made to improve the pre-hospital delay among vulnerable population with low social economic status.

Keywords: myocardial infarction; delays; associated factors

Strengths and limitations of this study

- This study provides the insights into the pre- and in-hospital delays to care among STEMI patients in low medical resource areas with a large sample from 101 non-PCI hospitals across China.
- The study used prospective data to investigate influencing factors of first ECG delay and thrombolytic therapy delay in STEMI patients.
- We could not exclude the influence of patient's recall bias for symptom onset time. However, data were collected during patient's admission within a very narrow time after STEMI onset.
- Survivor bias might exist as patients who were dead on arrival or within 10 min of hospital arrival were excluded.
- We did not collect the onset symptoms and hence could hardly study on the possible associations between the symptoms and the delays to care.

INTRODUCTION

Total ischemic time (time from symptom onset to thrombolytic therapy) is an important indicator to the prognosis of patients with ST-segment Elevation Myocardial Infarction (STEMI). [1 2] In general, the total ischemic time comprises three consecutive segments. The time from symptoms onset to the hospital arrival represents the time patients spend to respond to the disease onset and seeking medical care. The time from hospital arrival to having the first electrocardiograph (ECG) in hospital represents the time hospital staffs' responses to the patient's medical presentations, and with the first ECG done in time the working diagnosis of STEMI could be made and appropriate treatments could be initiated. The time from diagnosis to treatment represents doctors' responses to the diagnosis of disease. Delay in each segment can lead to a longer ischemic time, which has been fund associated with higher short-term as well as medium-term to long-term mortality in previous studies. [3-5]

Meanwhile, recent studies indicated that time delays to care among STEMI patients exist universally, showing a worse situation in low and middle income countries than that of high income countries, [6-9] such as 28.7% of ACS patients in Germany but two thirds of STEMI patients in Brazil suffered first ECG delay. [7 8] The delays to care in STEMI patients remain as great challenges to be overcome across all countries.

Up to the present, quite a few studies have tried to better understand the reasons behind these delays and showed that sociodemographic factors (female gender, older age, low educational level), medical histories (diabetes, myocardial infarction), ambiguous heart symptoms, use of private transport were related to longer delay in at least one of the four

kinds of time delays. [7 10-12] Based on these findings, some national or regional programs have been initiated to reduce the delays by targeting at controlling these factors, through educational campaign, implementation of pre-hospital ECG, establishing regional collaborative network, etc. and these actions turned out to be effective. [13-16]

However, almost all of those studies focused on pre-hospital delay and the patients who had access to onsite primary percutaneous coronary intervention (PCI) procedure. Those evidences have limited value for non-PCI hospitals in remote areas where fibrinolysis is the main reperfusion option for STEMI patients. Therefore, the aims of the present study are (a) to describe the time delays among STEMI patients in non-PCI hospitals in China, (b) to identify factors associated to these delays, and (c) to make suggestions for reducing these delays and improving care of STEMI patients in the similar settings in China and other countries.

METHODS

Study population

We used data of the STEMI patients from a very large registry-based quality of care improvement trial, the third phase of the Clinical Pathways for Acute Coronary Syndromes (CPACS-3) in China.[17] In brief, patients in CPACS-3 trial were recruited consecutively from 101 regional hospitals without the capacity to perform onsite PCI between Oct. 2011 and Nov. 2014. Patients were all over 18 years old and with a final diagnosis of ACS at discharge or death. The patients who were dead on arrival or within 10 min after hospital arrival were excluded. For the present study, we further excluded patients whose data of

time at either symptoms onset, hospital arrival, having the first ECG or receiving thrombolytic therapy were missing. From a total 10,294 STEMI patients recruited in CPACS-3 trial, we had 7,312 patients analyzed with complete data. The study flow diagram was shown in Figure 1.

The Peking University IRB reviewed and approved the CPACS-3 trial and all participating patients provided written informed consents. The CPACS-3 study registered on www.clinicaltrails.gov (NCT01398228).

Data collection and verification

A trained hospital staff member, who was not involved in the management of patients with ACS, was responsible for collecting and entering data into a dedicated web-based Data Management System (DMS). Data of each patient was collected from medical records. The data included socio-demographic information, vital signs relating to the presenting ACS, medical history, ECG findings, biomarker findings, investigations performed, treatments administered prior to admission, during hospitalization, and at death or hospital discharge, final diagnosis and discharge status, major in-hospital clinical events, personal insurance status and the total cost of hospitalization. Data quality was maintained through independent centrally managed in-person and on-line study monitoring activities.

Definitions and outcomes

Symptom onset time was defined as when patient first noted ischemic symptoms lasting ≥ 10 min;[18] hospital arrival time was defined as when patient arrived at emergency or outpatient department for help. Pre-hospital delay was defined as the time from symptoms onset to hospital arrival (symptoms onset-to-hospital arrival time) > 120 minutes.[11 19 20]

Most of hospitals without PCI facility in China are located in rural area, where pre-hospital emergency system is either not existing or pretty weak. The ambulances serve only as a transportation vehicle but no ECG equipped or the results not able to be transmitted back to the hospital. Thrombolytic therapy remains an in-hospital practice throughout the whole country up to now. Thus, the first ECG delay was defined as the time from patient's arrival at hospital to the time the patient had the first ECG done (hospital arrival-to-ECG time) > 10 minutes. [21 22] The working diagnosis of STEMI should had been made by then. The thrombolytic therapy delay was defined as the time from patient had the first ECG done to the time the thrombolytic therapy initiated (ECG-to-thrombolytic therapy time) > 10 minutes.[21] In-hospital delay was defined as the time from hospital arrival to the time the thrombolytic therapy initiated (hospital arrival-to-thrombolytic therapy time) > 30 minutes.[23]

Statistical analysis

The baseline characteristics of our study patients were described as percentages for categorical variables and means with standard deviations (SDs) for continuous variables. The Wilcoxon tests were adopted for the comparison of time durations and Pearson chi-square tests for the comparisons of proportions between thrombolytic therapy patients and non-thrombolytic therapy patients. The logistic regressions with generalized estimating equations (GEE) were used to explore the associates of the time delays (pre-hospital delay, first ECG delay, thrombolytic therapy delay, in-hospital delay), with an exchangeable correlation structure to account for clustering effect within hospitals[24]. Covariates in multivariate analyses were selected based on clinical and sociodemographic interests and

the results of univariate analyses. Missing data of covariates (all categorical variables) were handled as separated groups in multivariate analyses. We used SAS 9.4 (SAS Institute Inc., Cary, NC, USA) to perform data analyses. The significant level α was set at 0.05.

Patient and Public Involvement

No patients but government officers who were responsible for hospital management were involved in the study design of CPACS-3.

RESULTS

The characteristics of our included patients were summarized in Table 1. Their ages ranged from 19 to 102 years old and had a mean age of 63.4 years old. Most patients were males (71.2%), more than half were famers (67.2%), and almost all covered by medical insurances (94.1%). Almost a third of them were illiterate. The vital signs, cardiovascular risk factors and history of cardiovascular diseases were shown in Table 1.

Table 1. Characteristics of included patients

Characteristics	All STEMI patients (N=7312)*
Male, No. (%)	5205 (71.2)
Age, Mean (SD), year	63.37 (12.42)
Farmer, No. (%)	4715 (67.2) (n=7013)
Illiteracy, No. (%)	1604 (27.7) (n=5799)
Medical insurance, No. (%)	5140 (94.1) (n=5462)

Cardiovascular risk factors	
Current smoking, No. (%)	2488 (34.7) (n=7170)
Hypertension, No. (%)	4588 (62.8)
Dyslipidemia, No. (%)	279 (3.8)
Diabetes, No. (%)	851 (11.6)
Cardiovascular disease history	
Myocardial infarction, No. (%)	460 (6.3)
Angina, No. (%)	805 (11.0)
Stroke, No. (%)	635 (8.7)
TIA, No. (%)	111 (1.5)
Heart failure, No. (%)	160 (2.2)
Symptom onset time	
00:00-05:59, No. (%)	1315 (18.0)
06:00-11:59, No. (%)	2681 (36.7)
12:00-17:59, No. (%)	1896 (25.9)
18:00-23:59, No. (%)	1420 (19.4)
Vital signs at admission	
SBP < 90mmHg, No. (%)	407 (5.6) (n=7252)
Heart rates ≥ 100 beats/min, No. (%)	832 (11.6) (n=7192)

STEMI, ST-segment elevation myocardial infarction; SD, standard deviation; TIA, transient ischemic attack; SBP, systolic blood pressure.

* Total number are shown for variable for which data were not completely reported.

The delays to care

For all STEMI patients, 67% had experienced the pre-hospital delay and 31% experienced the first ECG delay. The patients receiving thrombolytic therapy had significantly less pre-hospital and first ECG delays, comparing with patients not receiving the therapy. Among the patients receiving thrombolytic therapy, 86% initiated the treatment after 10 minutes of the first ECG done and 68% after 30 minutes of arrival at hospital.

No matter patients received or not thrombolytic therapy, symptoms onset-to-arrival time was the dominant time segment, accounting for two thirds of the total ischemic time among those who received thrombolytic therapy. Patients who did not received thrombolytic therapy suffered more than twice longer symptoms onset-to-arrival time as their counterparts who received thrombolytic therapy. (See Table 2)

Table 2. Time duration and delay in different segments from onset to care among STEMI patients (min)

	All STEMI patients	Thrombolytic therapy patients	Non-thrombolytic therapy patients	*P* value*
Symptoms onset-to-arrival time				
Time duration, median (IQR)	210 (110-660)	140 (70-240)	360 (130-1364)	<0.01
Delay, % (No. of Participants/Total)	67.1 (4903/7312)	54.6 (1669/3057)	76.0 (3234/4255)	<0.01
Arrival-to-ECG time				
Time duration, median (IQR)	5 (0-17)	4 (0-10)	6 (0-24)	<0.01
Delay, % (No. of Participants/Total)	31.4 (2299/7312)	23.6 (722/3057)	37.1 (1577/4255)	<0.01
ECG-to-thrombolytic therapy time				
Time duration, median (IQR)	-	38 (20-65)	-	-
Delay, % (No. of Participants/Total)	-	85.8 (2623/3057)	-	-
Arrival-to-thrombolytic therapy time				

Time duration, median (IQR)	-	47 (27-80)	-	-
Delay, % (No. of Participants/Total)	-	67.8 (2072/3057)	-	-
Total time				
Time duration, median (IQR)	260 (145-710)†	210 (135-320)	395 (157-1419)‡	-

STEMI, ST-segment elevation myocardial infarction; ECG, Electrocardiograph; IQR, inter quartile range.

*, comparison between thrombolytic therapy patients and non-thrombolytic therapy patients ; †, representing symptoms onset-to-thrombolytic therapy time among those received thrombolytic therapy but symptoms onset-to-ECG time among those not; ‡, representing onset-to-ECG time.

Factors associated with the delays

A number of patient-level factors were associated with pre-hospital delay. The patients who were female, order than 65 years, illiterate, farmers, symptom onset during 00:00-05:59 and 06:00-11:59, with a faster heart rate were more likely to experience a pre-hospital delay. While, patients who had a history of myocardial infarction or hypertension, with a cardiac shock at presentation were less likely to experience a pre-hospital delay. (See Table 3)

Few patient level factors were found associated with the first ECG delay, thrombolytic therapy delay and in-hospital delay. Only patients who arrived on regular hours independently associated with higher first ECG delay rate. The first ECG delay was decreasing during the study period. (See Table 3)

Thrombolytic therapy delay was less likely to take place among patients who experienced

pre-hospital delay or first ECG delay. Patients who presented with faster heart rate were more likely to experience a delay in thrombolytic therapy. (See Table 3)

Patients arrived on regular hours and with history of dyslipidemia were less likely to have in-hospital delay. (See Table 3)

Table 3. Multivariate analyses of factors associated with pre-hospital delay, first ECG delay, thrombolytic therapy delay and in-hospital delay, using logistic regression with generalized estimating equations.

	Pre-hospital delay (N=7312)	First ECG delay (N=7312)	Thrombolytic therapy delay (N=3057)	In-hospital delay (N=3057)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female	1.20(1.05-1.38)	1.03(0.90-1.18)	1.07(0.80-1.43)	0.97(0.80-1.16)
≥ 65 years old	1.54(1.37-1.73)	1.04(0.92-1.18)	0.97(0.77-1.23)	1.11(0.94-1.31)
Illiteracy	1.44(1.17-1.77)	1.12(0.92-1.35)	0.86(0.59-1.25)	1.03(0.78-1.35)
Farmer	1.61(1.36-1.90)	1.02(0.85-1.23)	1.21(0.90-1.63)	1.03(0.80-1.34)
Medical insurance	1.14(0.73-1.79)	1.21(0.88-1.67)	0.69(0.32-1.45)	0.82(0.49-1.38)
Current smoking	1.00(0.86-1.15)	0.90(0.74-1.09)	1.07(0.81-1.42)	1.08(0.84-1.39)
History of disease, %				
Myocardial infarction	0.67(0.52-0.87)	1.20(0.94-1.53)	1.16(0.70-1.92)	1.19(0.80-1.78)
Angina	0.91(0.78-1.06)	0.82(0.67-1.00)	0.84(0.60-1.17)	0.82(0.59-1.14)
Stroke	1.19(0.99-1.42)	0.92(0.74-1.14)	1.30(0.83-2.03)	1.32(0.92-1.88)
Heart failure	1.25(0.84-1.88)	0.95(0.64-1.41)	0.74(0.24-2.25)	1.09(0.37-3.22)
TIA	0.68(0.45-1.05)	1.01(0.56-1.82)	1.06(0.46-2.42)	0.63(0.31-1.28)
Diabetes	0.98(0.85-1.13)	1.00(0.84-1.18)	1.19(0.86-1.64)	1.26(0.94-1.68)
Hypertension	0.89(0.79-0.99)	1.01(0.90-1.14)	1.03(0.83-1.29)	1.04(0.89-1.22)
Dyslipidemia	1.04(0.80-1.35)	1.03(0.74-1.43)	0.68(0.40-1.15)	0.62(0.40-0.97)
Time cycles (every 6 months)	0.97(0.91-1.05)	0.87(0.76-0.99)	1.01(0.87-1.17)	0.99(0.84-1.15)
Symptom onset time				
00:00-05:59	2.04(1.80-2.32)	-	-	-
06:00-11:59	1.47(1.28-1.68)	-	-	-

12:00-17:59	ref	-	-	-
18:00-23:59	1.00(0.89-1.13)	-	-	-
Vital signs at admission				
SBP < 90 mmHg	0.57(0.46-0.71)	0.78(0.59-1.04)	0.85(0.56-1.28)	0.86(0.60-1.24)
Heart rates ≥ 100 beats/min	1.71(1.48-1.99)	1.05(0.90-1.23)	1.61(1.04-2.50)	1.35(0.94-1.96)
Arrived on regular hours	-	1.12(1.00-1.25)	0.94(0.77-1.15)	0.81(0.68-0.96)
Pre-hospital delay	-	1.14(0.99-1.32)	0.78(0.64-0.95)	0.86(0.73-1.02)
First ECG delay	-	-	0.56(0.41-0.78)	
CPACS-3 intervention*	1.08(0.86-1.36)	0.78(0.51-1.18)	1.03(0.65-1.63)	0.73(0.47-1.13)

ECG, electrocardiograph; OR, odds ratio; TIA, transient ischemic attack; SBP, systolic blood pressure.

*, the intervention of the third phase of the Clinical Pathways for Acute Coronary Syndromes study.

The results of univariate analyses of four kinds of delays were shown in Supplementary Table 1.

Association of receiving thrombolytic therapy with pre-hospital delay and first ECG delay

Patients who suffered pre-hospital delay or first ECG delay were less likely to receive thrombolytic therapy at hospital. Even further adjusted for potential confounders, pre-hospital delay and first ECG delay separately linked to 32% and 28% reductions of receiving thrombolytic therapy among our patients. (See Table 4)

Table 4. Association of receiving thrombolytic therapy with pre-hospital delay and first ECG delay.

	Thrombolytic therapy rate (%) (No. of Participants/Total)	Crude RR* (95% CI)	Adjusted RR† (95% CI)
Pre-hospital delay			
Yes	34.0 (1669/4903)	0.62(0.58-0.67)	0.68(0.64-0.73)
No	57.6 (1388/2409)		
First ECG delay			
Yes	31.4 (722/2299)	0.71(0.66-0.76)	0.72(0.66-0.78)
No	46.6 (2335/5013)		

ECG, electrocardiograph; RR, risk ratio.

*, crude RR calculated from logistic regression with GEE model only included pre-hospital delay and first ECG delay; †, further adjusted for sex, age, education level, occupation, medical insurance, current smoking, histories of myocardial infarction, angina, stroke, heart failure, transient ischemic attack, diabetes, hypertension, dyslipidemia, time cycles (every 6 months), vital signs at admission, arrived on regular hours, CPACS-3 intervention.

DISCUSSION

Main results

In the present study, we found that two thirds of STEMI patients in non-PCI hospitals in China had the pre-hospital delay after their disease onsets in their seeking for medical care;

and about one third of them had their first ECG delayed after they arrived at hospitals, according to the criteria from ESC and ACC/AHA guidelines or previous researches.[11 19 20] Among patients who received their thrombolytic therapy as high as 86% of them had the treatment delayed according to the new criteria of ESC (time from ECG to thrombolytic therapy >10 min.)[21] and 68% had the treatment delayed according to the old criteria,[23] i.e after 30 minutes of hospital arrival.

Compared with STEMI patients from large medical centers in metropolitan areas of China[11] and other developed countries[12 25], where the median symptoms onset-to-arrival time was about 113 to 150 minutes, the median time found in our study was much longer, about 210 minutes. But our results were similar to that was reported in the Middle East[9] and shorter than that in India[26]. The first ECG delay in our study was much better than that in Brazil (67%)[7] and India (55%)[6] but worse than that in developed countries like Japan (18.4%)[27] and Germany (28.7%)[8]. As previous studies including ours have demonstrated the significant association of ischemic time with the short and long term mortality among patients with STEMI, our findings in this study highlighted the urgent needs to reduce the delays to care for STEMI patients in the similar settings in China and other developing countries.

Our further analyses showed that the pre-hospital and first ECG delays were significantly associated with the risk of not receiving thrombolytic therapy. In fact, only 43% of our study patients received thrombolytic therapy. Since these patients admitted to non-PCI hospitals of China often lived far away from large tertiary medical centers equipped with PCI facilities, thrombolytic therapy was the only revascularization treatment they could

have in the first line. Reducing the pre-hospital and first ECG delays should have great potential to permit more patients with thrombolytic therapy, which in turn will save many more lives in these remote areas. In our study, half of the patients not receiving thrombolytic therapy arrived at hospital beyond 6 hours after their disease onsets and hence lost the best opportunity to receive the treatment. If the median time could be reduced to 3 hours, probably the most of these patients would still have chance for the thrombolytic therapy.

The study on the factors associated with the delays to care could help to find solutions to reduce the delays. Like previous studies, the symptoms onset-to-door time took the most part of the total ischemic time, and we should pay more attention to reduce the pre-hospital delay. In our study, patients who were older than 75 years old, illiterate, and farmer were found more likely to have the pre-hospital delay. This implies that efforts should be made to improve the medical access for the vulnerable patients with low social economic status. A recent study among Indian STEMI patients supports our findings and found that the difficulty of arranging money was an important factor leading to the pre-hospital delay.[6] Furthermore, the elderly and illiterate patients might misinterpret the symptoms of STEMI with symptoms of ageing, aggravating their pre-hospital delays.[20]

Our findings that women patients were more likely to have pre-hospital delay among STEMI patients have been reported in previous studies.[9 11 20 28 29] The possible explanations include women suffering more atypical symptoms,[30 31] women discriminating culture and lower social economic status,[32] greater sympathy that prevent women to trouble anyone[33] etc..

Patients with history of myocardial infarction, hypertension, or presented with shock at admission were found less likely to have the pre-hospital delay. We believe this is because these patients had more knowledge of myocardial infarction and realized the importance of in-time medical rescue. We believe the reason for patients who presented with shock at admission were found less likely to have pre-hospital delay was due to the severity of the symptom, which alarmed the patient itself, family members or a companion person that helped to access medical care in time. In contrast, we believe the reason for patients who presented with tachycardia at admission more likely to have pre-hospital delay was probably an inverse causal relationship, i.e. the tachycardia was a result of pre-hospital delay.

Similar to previous studies,[6 11 12] we also found patients suffered pre-hospital delay had their symptom onset most during 00:00 to 05:59. Most people are in sleep during this time, and most patients would not want to bother others at this time if they believe the disease was not severe. Those patients might be prone to going to the hospital the next day avoiding troublesome visits at late night. The phenomenon might be exaggerated by the fact that the most of our study patients were living in rural areas. The barriers for patients living in rural areas seeking for medical service include long distance, poor transport facilities and costs concerns. The evidence that patients who had shorter symptoms onset-to-door time were with less stroke or heart failure history supported this explanation to some extent.

As the first ECG delay reflects more medical staff's rather than patients' responses to the disease, no patient side factor was found associated with the first ECG delay in our study. But first ECG delay was found more likely to take place in patients arriving on regular

hours. The same results were also found among NSTE-ACS patients in CRUSADE Quality Improvement Initiative study.[34] Although the reasons are still unknown, this relationship may reflect the medical resources competition by routine clinical patients who rash into hospitals for care. In China, making appointment for care is not a common practice.

Recent STREAM trial demonstrated that thrombolytic therapy (median time from randomization to bolus recorded was 9 min) was as effective as primary PCI beyond 1 hour among STEMI patients who presented within 3 hours after symptom onset.[35] Based on the results from the STREAM trial, European Society of Cardiology recommended time from STEMI diagnosis to the start of fibrinolysis to be within 10 min.[21] According to the new ESC guidelines, only 14% of patients who received fibrinolysis achieved the 10 min target in our study. Even use the old criteria (in-hospital time > 30 min.), there were only 32% of patients received thrombolytic therapy without delay. We consider this new ESC target time may be ideal but quite unrealistic in rural China now, considering there are many barriers that prevent from initiating the thrombolytic therapy in such a short time. Particularly, the new type of fibrinolytic agents (Tenecteplase), which was used in the STREAM trial, is not available yet in China. Hopefully, the ECG-to- thrombolytic therapy time can be shortened as the recombinant human TNK tissue-type plasminogen activator (rhTNKtPA) has been approved by China FDA recently, which is applied in bolus at once and easy for administration. Meanwhile, due to the possible severe bleedings, the patient inform consent often takes a long time, particularly when the doctor-patient relationship is not good and the medical insurance could not cover the entire costs.

One of the interesting findings from our study was that among patients receiving thrombolytic therapy, the treatment delay was lower in patients who had pre-hospital delay or first ECG delay, reflecting medical team's "time catch-up" effort after the patient was confirmed STEMI diagnosis by ECG examination. Physicians were apt to react more rapidly to make up previous delays, as the effects of the treatment are time-dependent. Nevertheless, we should understand that physicians' "catch-up effect" only had limited value for shortening total ischemic time (see Supplementary Tables 2-4), as the major segment was the symptoms onset-to-hospital arrival time. More emphases should be put onto reducing the pre-hospital delay.

Our analysis on factors associated with in-hospital delay showed that arrival on regular hour was negatively associated with the risk of in-hospital delay. We believe that the results indicated physicians at regular hours had more capability to 'catch up' the preceding delays once the diagnosis of STEMI was made.

Another finding was that even no access to PCI, only half eligible patients (51%) received thrombolytic therapy. Previous study also reported low thrombolytic therapy rate (56.1%, 2011) among eligible STEMI patients in non-PCI centers in China.[36] That implies there were other hurdles for patients to receive thrombolytic treatment besides pre-hospital delay. The possible explaining reasons include doctors' concerns/worries on patient safety/adverse events, inadequate or no healthcare insurance to cover the cost, and time waiting for the direct family members to agree and sign the inform consent for initiating thrombolytic therapy.

Strengths and limitations

The strengths of our study include: 1) A large sample from non-PCI hospitals across China. The results could be extended to other places of China and the world with the similar settings. 2) The data were collected prospectively, under strict supervision by an experienced project management team and a steering committee composed of international expertise in cardiology, epidemiology and biostatistics.

The present study also has several limitations. First, we could not exclude the influence of patient's recall bias for symptom onset time. However, data were collected during patient's admission within a very narrow time after their symptom onset. Secondly, we are not 100% sure about the accuracy of the diagnosis of STEMI in our study. We did not collect patient's original ECG file for further independent validation of the diagnoses. Since CPACS-3 study had professional project management with both on-line and on-site data monitoring we believe incorrect diagnosis for STEMI should be minimum. Another limitation is that survivor bias might exist as patients who were dead on arrival or within 10 min of hospital arrival were excluded. Additionally, we did not collect the onset symptoms and hence could hardly study on the possible associations between the onset symptoms and the pre-hospital delay to care.

CONCLUSIONS

In conclusion, the present study demonstrated that STEMI patients in non-PCI hospitals in China suffered severe time delays to care. Among the four types of delay, pre-hospital delay should be emphasized although the other three still have rooms for improvement. Future efforts should be made to improve the pre-hospital delay among vulnerable populations with low social economic status.

Implication

Establishment of pre-hospital rescue system facilitated with ECG examination and results transmission equipment as well as population-wide health education of in-time seeking medical care and chest pain might offer solutions to improve the current clinical practice and enhance the quality of care among STEMI patients.

Author contributions

LF, ML and YW conceived this study. YW obtained research funding. LF conceived and conducted statistical analyses. WX and XL provided statistical advice and statistical validation. AZ supervised the conduct of the study and data collection. LF, ML, LL, WX, YW and RG interpreted the results. LF drafted the manuscript and all authors contributed substantially to its revision. YW takes responsibility for the paper as a whole.

Acknowledgements

The CPACS-3 Study Steering Committee (sorted by the first letter of the family name): Kalipso Chalkidou (National Institute for Health and Clinical Excellence), Runlin Gao* (Cardiovascular Institute and Fuwai Hospital), Dayi Hu (Peking University People's Hospital), Yong Huo (Peking University First Hospital), Yahui Jiao (NHFPC of China), Lingzhi Kong (NHFPC of China), Anushka Patel (The George Institute for Global Health), Eric Peterson (Duke Clinical Research Institute), Fiona Turnbull (The George Institute for Global Health), Mark Woodward (The George Institute for Global Health), Yangfeng Wu* (The George Institute for Global Health at PUHSC).

*Co-principal investigators.

Funding

CPACS-3 study is an investigator sponsored study supported by Sanofi. The George Institute for Global Health at PUHSC sponsored the study and owns the data. However, the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Conflict of interest

None declared.

Data availability statement

The George Institute for Global Health at PUHSC owns the de-identified participant data of CPACS3 study. The data are available after a formal application and the approval by The CPACS-3 Study Steering Committee.

REFERENCES

1. Solhpour A, Chang KW, Arain SA, et al. Ischemic time is a better predictor than door-to-balloon time for mortality and infarct size in ST-elevation myocardial infarction. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions* 2016;87(7):1194-200. doi: 10.1002/ccd.26230 [published Online First: 2015/09/04]
2. Chughtai H, Ratner D, Pozo M, et al. Prehospital delay and its impact on time to treatment in ST-elevation myocardial infarction. *The American journal of emergency medicine* 2011;29(4):396-400. doi: 10.1016/j.ajem.2009.11.006 [published Online First: 2010/09/10]
3. Berger PB, Ellis SG, Holmes DR, Jr., et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation* 1999;100(1):14-20. [published Online First: 1999/07/07]
4. Foo CY, Bonsu KO, Nallamothu BK, et al. Coronary intervention door-to-balloon time and outcomes in ST-elevation myocardial infarction: a meta-analysis. *Heart (British Cardiac Society)*

2018;104(16):1362-69. doi: 10.1136/heartjnl-2017-312517 [published Online First: 2018/02/14]

5. Benamer H, Bataille S, Tafflet M, et al. Longer pre-hospital delays and higher mortality in women with STEMI: the e-MUST Registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2016;12(5):e542-9. doi: 10.4244/eijv12i5a93 [published Online First: 2016/08/09]

6. George L, Ramamoorthy L, Satheesh S, et al. Prehospital delay and time to reperfusion therapy in ST elevation myocardial infarction. *Journal of emergencies, trauma, and shock* 2017;10(2):64-69. doi: 10.4103/0974-2700.201580 [published Online First: 2017/04/04]

7. Duraes AR, Bitar YS, Freitas ACT, et al. Gender differences in ST-elevation myocardial infarction (STEMI) time delays: experience of a public health service in Salvador-Brazil. *American journal of cardiovascular disease* 2017;7(5):102-07. [published Online First: 2017/11/29]

8. Post F, Giannitsis E, Riemer T, et al. Pre- and early in-hospital procedures in patients with acute coronary syndromes: first results of the "German chest pain unit registry". *Clinical research in cardiology : official journal of the German Cardiac Society* 2012;101(12):983-91. doi: 10.1007/s00392-012-0487-4 [published Online First: 2012/07/26]

9. Shehab A, AlHabib KF, Bhagavathula AS, et al. Clinical presentation, Quality of care, Risk factors and Outcomes in Women with Acute ST-Elevation Myocardial Infarction (STEMI): An Observational Report from Six Middle Eastern Countries. *Current vascular pharmacology* 2018;16:000-00. doi: 10.2174/1570161116666180315104820 [published Online First: 2018/03/16]

10. Sullivan AL, Beshansky JR, Ruthazer R, et al. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. *Circulation Cardiovascular*

quality and outcomes 2014;7(1):86-94. doi: 10.1161/circoutcomes.113.000396 [published Online First: 2014/01/16]

11. Peng YG, Feng JJ, Guo LF, et al. Factors associated with prehospital delay in patients with ST-segment elevation acute myocardial infarction in China. *The American journal of emergency medicine* 2014;32(4):349-55. doi: 10.1016/j.ajem.2013.12.053 [published Online First: 2014/02/12]
12. Park YH, Kang GH, Song BG, et al. Factors related to prehospital time delay in acute ST-segment elevation myocardial infarction. *Journal of Korean medical science* 2012;27(8):864-9. doi: 10.3346/jkms.2012.27.8.864 [published Online First: 2012/08/10]
13. Naegeli B, Radovanovic D, Rickli H, et al. Impact of a nationwide public campaign on delays and outcome in Swiss patients with acute coronary syndrome. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2011;18(2):297-304. doi: 10.1177/1741826710389386 [published Online First: 2011/04/01]
14. Quinn T, Johnsen S, Gale CP, et al. Effects of prehospital 12-lead ECG on processes of care and mortality in acute coronary syndrome: a linked cohort study from the Myocardial Ischaemia National Audit Project. *Heart (British Cardiac Society)* 2014;100(12):944-50. doi: 10.1136/heartjnl-2013-304599 [published Online First: 2014/04/16]
15. Mooney M, McKee G, Fealy G, et al. A review of interventions aimed at reducing pre-hospital delay time in acute coronary syndrome: what has worked and why? *Eur J Cardiovasc Nurs* 2012;11(4):445-53. doi: 10.1016/j.ejcnurse.2011.04.003 [published Online First: 2011/05/14]
16. Duan T, Xiang D, Qin W, et al. [Impact of establishing regional collaborative network on reperfusion

time and prognosis of patients with ST-segment elevated myocardial infarction admitting to community hospitals without percutaneous coronary intervention capacity]. *Zhonghua xin xue guan bing za zhi* 2014;42(8):641-5. [published Online First: 2014/11/13]

17. Wu Y, Li S, Patel A, et al. Effect of a Quality of Care Improvement Initiative in Patients With Acute Coronary Syndrome in Resource-Constrained Hospitals in China: A Randomized Clinical Trial. *JAMA Cardiol* 2019 doi: 10.1001/jamacardio.2019.0897 [published Online First: 2019/04/18]
18. Cannon CP, Brindis RG, Chaitman BR, et al. 2013 ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Acute Coronary Syndromes and Coronary Artery Disease Clinical Data Standards). *Circulation* 2013;127(9):1052-89. doi: 10.1161/CIR.0b013e3182831a11 [published Online First: 2013/01/30]
19. Ladwig KH, Fang X, Wolf K, et al. Comparison of Delay Times Between Symptom Onset of an Acute ST-elevation Myocardial Infarction and Hospital Arrival in Men and Women <65 Years Versus >/=65 Years of Age.: Findings From the Multicenter Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction (MEDEA) Study. *The American journal of cardiology* 2017;120(12):2128-34. doi: 10.1016/j.amjcard.2017.09.005 [published Online First: 2017/11/11]
20. Wah W, Pek PP, Ho AF, et al. Symptom-to-door delay among patients with ST-segment elevation myocardial infarction in Singapore. *Emergency medicine Australasia : EMA* 2017;29(1):24-32. doi: 10.1111/1742-6723.12689 [published Online First: 2016/10/12]

21. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017;00:1-66. doi: 10.1093/eurheartj/ehx393

22. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127(4):e362-425. doi: 10.1161/CIR.0b013e3182742cf6

23. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33(20):2569-619. doi: 10.1093/eurheartj/ehs215 [published Online First: 2012/08/28]

24. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemporary clinical trials* 2007;28(2):182-91. doi: 10.1016/j.cct.2006.05.007 [published Online First: 2006/07/11]

25. Fujii T, Masuda N, Suzuki T, et al. Impact of transport pathways on the time from symptom onset of ST-segment elevation myocardial infarction to door of coronary intervention facility. *Journal of cardiology* 2014;64(1):11-8. doi: 10.1016/j.jjcc.2013.11.008 [published Online First: 2014/01/09]

26. Isezuo S, Subban V, Krishnamoorthy J, et al. Characteristics, treatment and one-year outcomes of patients with acute coronary syndrome in a tertiary hospital in India. *Indian heart journal* 2014;66(2):156-63. doi: 10.1016/j.ihj.2013.12.023 [published Online First: 2014/05/13]

27. Noguchi M, Ako J, Morimoto T, et al. Modifiable factors associated with prolonged door to balloon

time in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Heart and vessels* 2018;33(10):1139-48. doi: 10.1007/s00380-018-1164-y [published Online First: 2018/05/08]

28. Sederholm Lawesson S, Isaksson RM, Ericsson M, et al. Gender disparities in first medical contact and delay in ST-elevation myocardial infarction: a prospective multicentre Swedish survey study. *BMJ open* 2018;8(5):e020211. doi: 10.1136/bmjopen-2017-020211 [published Online First: 2018/05/05]

29. Zhang B, Zhang W, Huang R, et al. Gender and Age Differences Associated With Prehospital Delay in Chinese Patients Presenting With ST-Elevation Myocardial Infarction. *The Journal of cardiovascular nursing* 2016;31(2):142-50. doi: 10.1097/jcn.0000000000000219 [published Online First: 2014/11/25]

30. Allana S, Moser DDK, Ali DTS, et al. Sex differences in symptoms experienced, knowledge about symptoms, symptom attribution, and perceived urgency for treatment seeking among acute coronary syndrome patients in Karachi Pakistan. *Heart Lung* 2018;47(6):584-90. doi: 10.1016/j.hrtlng.2018.06.009 [published Online First: 2018/08/16]

31. Sederholm Lawesson S, Isaksson RM, Thylen I, et al. Gender differences in symptom presentation of ST-elevation myocardial infarction - An observational multicenter survey study. *International journal of cardiology* 2018;264:7-11. doi: 10.1016/j.ijcard.2018.03.084 [published Online First: 2018/04/13]

32. Allana S, Khowaja K, Ali TS, et al. Gender differences in factors associated with prehospital delay among acute coronary syndrome patients in Pakistan. *J Transcult Nurs* 2015;26(5):480-90. doi: 10.1177/1043659614524787 %/ (c) The Author(s) 2014.

33. Moser DK, McKinley S, Dracup K, et al. Gender differences in reasons patients delay in seeking treatment for acute myocardial infarction symptoms. *Patient education and counseling* 2005;56(1):45-54. doi: 10.1016/j.pec.2003.11.011 [published Online First: 2004/12/14]

34. Diercks DB, Peacock WF, Hiestand BC, et al. Frequency and consequences of recording an electrocardiogram >10 minutes after arrival in an emergency room in non-ST-segment elevation acute coronary syndromes (from the CRUSADE Initiative). *The American journal of cardiology* 2006;97(4):437-42. doi: 10.1016/j.amjcard.2005.09.073 [published Online First: 2006/02/08]

35. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *The New England journal of medicine* 2013;368(15):1379-87. doi: 10.1056/NEJMoa1301092 [published Online First: 2013/03/12]

36. Li J, Li X, Ross JS, et al. Fibrinolytic therapy in hospitals without percutaneous coronary intervention capabilities in China from 2001 to 2011: China PEACE-retrospective AMI study. *European heart journal Acute cardiovascular care* 2017;6(3):232-43. doi: 10.1177/2048872615626656 [published Online First: 2016/01/21]

Figure 1. Study flow diagram of included patient

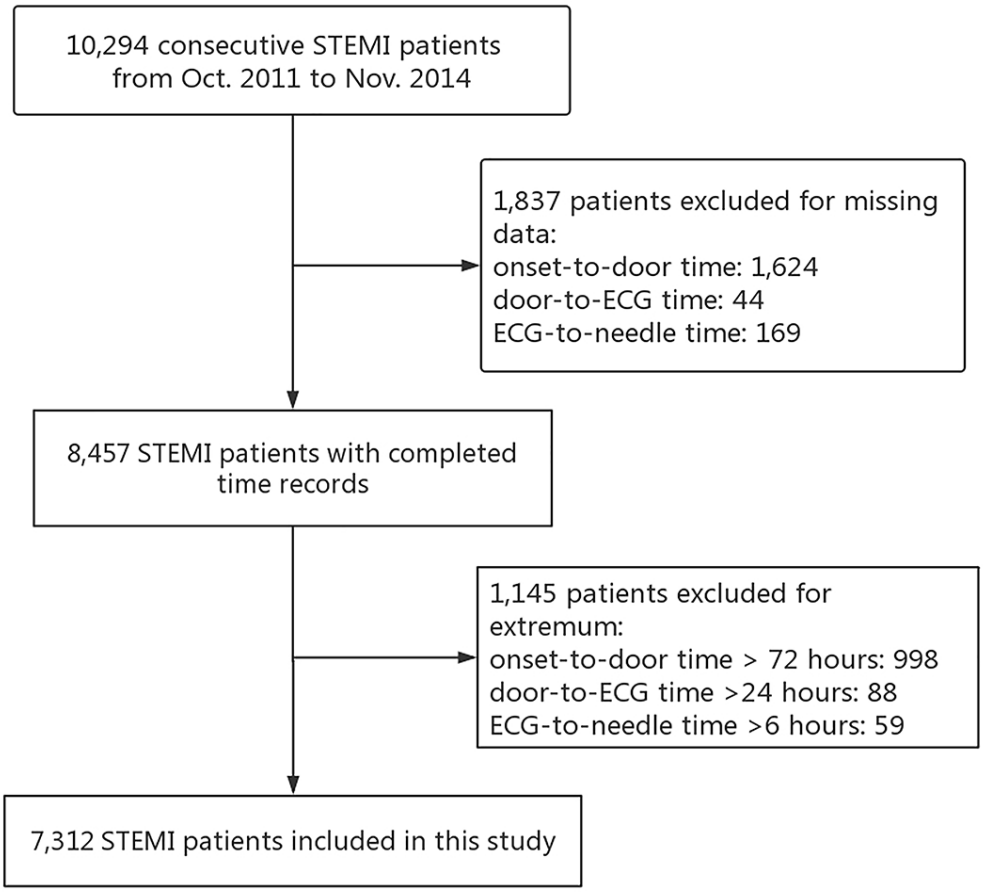

Figure 1. Study flow diagram of included patient

Supplementary Table 1. Univariate analyses of four kinds of delays, using logistic regression with generalized estimating equations.

	Pre-hospital delay (N=7312)		First ECG delay (N=7312)		Thrombolytic therapy delay (N=3057)		In-hospital delay (N=3057)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Gender								
Female	1.56(1.38-1.76)	<0.01	1.13(1.01-1.26)	0.04	0.98(0.76-1.26)	0.86	0.96(0.80-1.13)	0.60
Male	ref		ref		ref		ref	
Age								
≥65 years old	1.75(1.58-1.94)	<0.01	1.13(1.00-1.28)	0.05	0.93(0.74-1.18)	0.56	1.07(0.87-1.30)	0.52
<65 years old	ref		ref		ref		ref	
Education level								
Illiteracy	1.92(1.58-2.34)	<0.01	1.18(0.98-1.43)	0.08	0.87(0.62-1.21)	0.40	1.03(0.79-1.33)	0.83
Others	ref		ref		ref		ref	
Occupation								
Farmer	1.74(1.48-2.06)	<0.01	1.06(0.88-1.28)	0.53	1.13(0.84-1.53)	0.40	1.03(0.79-1.34)	0.80
Others	ref		ref		ref		ref	
Medical insurance								
Yes	1.08(0.72-1.64)	0.70	1.19(0.85-1.68)	0.31	0.69(0.33-1.43)	0.31	0.81(0.49-1.33)	0.41
No	ref		ref		ref		ref	
Smoking status								
Current smoking	0.78(0.68-0.89)	<0.01	0.85(0.72-1.00)	0.05	1.03(0.77-1.38)	0.82	1.06(0.80-1.41)	0.67
Others	ref		ref		ref		ref	
History of disease								
Myocardial infarction								
Yes	0.68(0.54-0.86)	<0.01	1.14(0.90-1.44)	0.28	1.11(0.67-1.81)	0.69	1.23(0.84-1.79)	0.29
No	ref		ref		ref		ref	
Angina								
Yes	0.87(0.74-1.01)	0.07	0.86(0.71-1.06)	0.15	0.87(0.61-1.24)	0.46	0.86(0.61-1.21)	0.38
No	ref		ref		ref		ref	
Stroke								
Yes	1.15(0.97-1.36)	0.11	0.92(0.76-1.13)	0.44	1.28(0.82-1.98)	0.27	1.25(0.88-1.76)	0.21
No	ref		ref		ref		ref	
Heart failure								
Yes	1.30(0.86-1.97)	0.21	0.96(0.63-1.47)	0.86	0.71(0.25-2.02)	0.53	1.05(0.37-2.93)	0.93
No	ref		ref		ref		ref	
Transient ischemic attack								
Yes	0.80(0.53-1.23)	0.32	0.88(0.48-1.61)	0.68	1.19(0.55-2.58)	0.65	0.67(0.34-1.31)	0.24
No	ref		ref		ref		ref	
Diabetes								
Yes	0.97(0.84-1.11)	0.63	1.01(0.86-1.19)	0.92	1.15(0.83-1.59)	0.39	1.24(0.94-1.65)	0.13
No	ref		ref		ref		ref	
Hypertension								
Yes	0.93(0.85-1.03)	0.20	1.02(0.91-1.14)	0.72	1.03(0.82-1.30)	0.78	1.05(0.90-1.23)	0.53

No	ref		ref		ref		ref	
Dyslipidemia								
Yes	0.89(0.69-1.14)	0.35	0.99(0.73-1.34)	0.94	0.70(0.41-1.17)	0.17	0.66(0.42-1.03)	0.07
No	ref		ref		ref		ref	
Time trend (every 6 months)	1.02(0.96-1.04)	0.88	0.82(0.76-0.88)	<0.01	1.01(0.91-1.12)	0.80	0.91(0.83-1.00)	0.05
Symptom onset time								
00:00-05:59	1.99(1.74-2.26)	<0.01						
06:00-11:59	1.50(1.32-1.70)	<0.01						
12:00-17:59	ref							
18:00-23:59	1.01(0.89-1.13)	0.93						
Signs at admission								
SBP < 90 mmHg								
Yes	0.66(0.54-0.80)	<0.01	0.79(0.61-1.02)	0.07	0.88(0.59-1.31)	0.53	0.88(0.62-1.26)	0.50
No	ref		ref		ref		ref	
Heart rate≥100 beats/m								
Yes	1.73(1.50-2.00)	<0.01	1.07(0.92-1.24)	0.36	1.52(0.97-2.40)	0.07	1.32(0.92-1.88)	0.13
No	ref		ref		ref		ref	
Arrived on regular hours								
Yes			1.14(1.03-1.26)	<0.01	0.93(0.76-1.14)	0.49	0.80(0.69-0.94)	<0.01
No			ref		ref		ref	
Onset-to-Door time dalay								
Yes			1.19(1.03-1.38)	0.02	0.79(0.66-0.96)	0.02	0.87(0.74-1.03)	0.11
No			ref		ref		ref	
Door-to-ECG time delay								
Yes					0.56(0.40-0.77)	<0.01	3.51(2.59-4.75)	<0.01
No					ref		-	
Intervention group								
Yes	1.02(0.88-1.18)	0.79	0.59(0.45-0.78)	<0.01	1.06(0.76-1.47)	0.73	0.70(0.54-0.91)	<0.01
No	ref		ref		ref		ref	

ECG, electrocardiograph; OR, odds ratio; SBP, systolic blood pressure.

*, the intervention of the third phase of the Clinical Pathways for Acute Coronary Syndromes study.

Supplementary Table 2. Total ischemic time by groups of time from arrival to first ECG.

Time from arrival to first ECG (min.)	No. of patients	Total ischemic time (mean ±SD, min.)
0-4.9	1625	303.8 ±423.4
5.0-9.9	538	278.8 ±354.1
10.0-14.9	269	347.3 ±473.9
15.0-19.9	125	297.4 ±327.6
20.0-24.9	112	321.6 ±427.2
25.0-29.9	48	243.0 ±152.8
≥30.0	340	472.4 ±660.5

Supplementary Table 3. Total ischemic time by groups of time from first ECG to thrombolytic therapy.

Time from first ECG to thrombolytic therapy (min.)	No. of patients	Total ischemic time (mean ±SD, min.)
0-4.9	183	320 ±449.7
5.0-9.9	133	262.5 ±344.1
10.0-14.9	220	247.2 ±257.2
15.0-19.9	184	252.1 ±324.8
20.0-24.9	249	260.4 ±380.5
25.0-29.9	193	234.2 ±284.3
30.0-34.9	235	331.2 ±509.4
35.0-39.9	163	300.5 ±494.4
40.0-49.9	329	329.3 ±544.4
50.0-59.9	256	302.0 ±431.4
60.0-119.9	658	370.4 ±498.3
120.0-179.9	176	426.9 ±415.6
≥180.0	78	603.4 ±510.5

Supplementary Table 4. Total ischemic time by groups of time from arrival to thrombolytic therapy.

Time from arrival to thrombolytic therapy (min.)	No. of patients	Total ischemic time (mean ±SD, min.)
0-9.9	114	298.9 ±467.9
10.0-19.9	311	225.9 ±220.7
20.0-29.9	386	254.5 ±344.3
30.0-59.9	1036	296.4 ±458.2
60.0-119.9	837	332.5 ±421.8
120.0-179.9	240	397.5 ±431.6
180.0-359.9	121	614.5 ±553.8
360.0-719.9	8	1701.5 ±1481.4
≥720.0	4	2861.5 ±1229.1

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	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	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
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	6 and figure 1
		(b) Give reasons for non-participation at each stage	figure 1
		(c) Consider use of a flow diagram	figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	9 table 2
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	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
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	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
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	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.