PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pre- and in-hospital delays to care and associated factors in STEMI patients: an observational study in 101 non-PCI hospitals in China
AUTHORS	Feng, Lin; Li, Min; Xie, Wuxiang; Zhang, Aihua; Lei, Licheng; Li, Xian; Gao, R; Wu, Yangfeng

VERSION 1 – REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna
REVIEW RETURNED	05-Jul-2019

GENERAL COMMENTS	Generally, a good paper to raise issues of care seeking delay and reason for delay in China. The paper provides an analysis of data from the CPACS-3large observational registry related to treatment delay in patients with STEMI. Overall the design is dictated by the registry. Here are suggestions to help with clarity for the reader: 1. Abstract: Change term "time from onset to door" to " time from symptom onset to hospital admission ". 2. Abstract: initially this was confusing for how " pre-hospital delay " was operationalized. 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. In addition, as mentioned, time from onset to door is not typically used. It would be good to refer to 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 (at: http://www.heart.org/idc/groups/heartpublic/@wcm/@mwa/documents/downloadable/ucm_455976.pdf) Results: a. Were women more likely to have 'atypical chest pain' symptoms? b. Important to note that 34.0% of the patients received thrombolytic therapy despite “Pre-hospital delay” and 57.6% of the patients received thrombolytic therapy with NO-Pre-hospital delay”. However, in table 4 it does not specify if those who did not receive thrombolytic therapy were in part represented by ineligible patients for reperfusion based on delay timing of more than 12 hours. Yet it is unclear why only 57.6% of the patients who sought medical attention within 2 hours after symptom onset received thrombolytic therapy.

	Discussion: a. Top of page 16 (line 20): are you referring to "total ischemic time" (time of symptom onset to time of lytic therapy)? Recommend revising that terminology b. Need to include in the discussion (or results) why women may have longer delays. c. Limitations. You state that you did not collect the onset symptoms and hence could hardly study on the possible associations between the symptoms and the delays to care. Again, this is confusing. Recommend revising that terminology Reference: Some are very old. You have more recent references that could replace them. Search in pub-med and try to collect all the new studies on delay in STEMI

REVIEWER	Peter Bogaty Quebec Heart Institute Quebec City, Quebec, Canada
REVIEW RETURNED	21-Jul-2019

GENERAL COMMENTS	This is an observational study from China describing pre-hospital and in-hospital delays to thrombolysis and factors associated with these delays in 7312 patients with ST-elevation myocardial infarction (STEMI) in 101 hospitals without facilities to perform percutaneous coronary intervention (PCI) in the period 2011-2014. Three timeframes were examined: symptoms to treatment (norm: less than 120 min); arrival (door) to performing diagnostic ECG (norm: less than 10 min); ECG to thrombolytic treatment (less than 10 min). Delay was defined as any time exceeding these norms and the percentages of delay occurrence for these time frames were: 67.1%, 31.4% and 85.8%, respectively. A number of clinical factors were associated with delays (female sex, older age, illiteracy, farmer status, tachycardia, night hour symptoms) and non-delays (hypotension, previous myocardial infarction, hypertension). The authors conclude that delays are frequent and efforts should be deployed to decrease them in ‘a vulnerable population with low social economic status’. This well written descriptive study invites a few comments. 1. Introduction. Authors affirm that the effectiveness of thrombolysis is more time dependent than PCI. Although widely believed, this is questionable. As if the myocardium that knows it is going to receive PCI, in up to or more than the 2-hour additional delay compared with thrombolysis, will withstand ischemic time better. 2. This data comes from an acute coronary syndrome (ACS) registry. How did the authors determine that their patients specifically had STEMI? It is not that simple to ensure a validated STEMI diagnosis and no details are provided. What was the larger ACS numerator from which the STEMI sub-population was selected? 3. The authors employ a binary delay criteria. But does it really matter if an ECG delay exceeds 10 min to 11 or 12 min and the same for ECG to treatment time. A few minutes’ delay is unlikely to have a major impact on outcome while larger delays will. It would be informative to have more granular data on the delay spread for

	the 3 timeframes studied in this population. If the last 2 timeframe limits accepted 5 min more each, what would be the overall delays (time from symptom onset to treatment and door to treatment) to treatment? Notwithstanding STREAM, the longstanding treatment delay of 30 min (door to thrombolysis) is well established. The authors mention in Discussion that 68% of patients had a door to treatment delay exceeding 30 min. More data on the spread of this delay in their population would be informative. 4. No outcome data is provided. It would have been highly informative to see such data and its associations with the delays. 5. Only 43% of STEMI patients received thrombolytic therapy. This is a very low proportion of potentially eligible patients for life-saving treatment and is likely far more important (on a population basis) than relatively slow delays in terms of a few minutes in the minority of patients who did receive thrombolysis. It is said that half the patients not receiving thrombolytic treatment had a symptom onset to arrival time exceeding 6 hours. Yet thrombolytic treatment is recommended out to 12 hours. How do the authors more fully account for such a large proportion of patients not receiving thrombolysis? 6. The presumption that tachycardia was the consequence of pre-hospital delay seems somewhat speculative. 7. More ECG delay during regular working hours seems counter-intuitive. 8. The authors mention need for informed consent as a contributor to treatment delay. Because thrombolysis has been well established to save STEMI lives despite the bleeding risks, it is not clear that any consent is needed beyond standard consent to offer whatever hospital treatment is needed. Is this not even implicit insofar as patients come to hospital to receive treatment?

REVIEWER	Guido Knapp Department of Statistics TU Dortmund University Germany
REVIEW RETURNED	13-Aug-2019

GENERAL COMMENTS	Comments on statistics: page 9, delays to care, first paragraph, second sentence: "... had significantly ...". How do the authors judge the signifcance here? In the section on statistical analysis, the authors do not describe how they compare two independent samples with non-normally distributed random variables. Please add the information! page 11, Table 3, factors associated with the delays: What does generalized estimating equations (GEE) mean here? I think it is a logistic regression problem with random hospital effects- Maybe the authors could motivate their statistical approach. The authors moreover use a lot of explanatory variables and there is clearly a danger of overfitting and spurious statistical significances. Maybe a variable selection procedure is better or more appropriate.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Generally, a good paper to raise issues of care seeking delay and reason for delay in China. The paper provides an analysis of data from the CPACS-3 large observational registry related to treatment delay in patients with STEMI.

Reply: Thanks for your appreciation of our work.

Overall the design is dictated by the registry. Here are suggestions to help with clarity for the reader:

1. Abstract: Change term "time from onset to door" to " time from symptom onset to hospital admission ".

Reply：Thanks. Since “admission” often refers to the admission into the in-patient wards, which usually not happened until the diagnosis is made and have to be done on the regular hour in China. To better reflect the time delayed due to the patient’s own sake, we use the time that the patient arrived at hospital as the end of the time section of the pre-hospital period.

Manuscript change: We revised the sentence as follow:

“Pre-hospital delay was defined as time from symptom onset to hospital arrival > 120 minutes”.

2. Abstract: initially this was confusing for how " pre-hospital delay " was operationalized. 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. In addition, as mentioned, time from onset to door is not typically used. It would be good to refer to 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 (at: http://www.heart.org/idc/groups/heartpublic/@wcm/@mwa/documents/downloadable/ucm_455976.pdf)

Reply：We are sorry for the confusion. We have made sure in the revised version that all our definitions are the same or equivalent to that defined in the 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. However, the ACCF/AHA Definitions does not provide any cut-offs for the delays. Thus, we defined the three delays in our study according to the previous publications.[1-3]**Manuscript change:** We revised the relevant paragraphs and added in the references the 2013 ACCF/AHA key data elements and definitions document.

“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……”

Results:

a. Were women more likely to have 'atypical chest pain' symptoms?

Reply: We did not collect patients’ onset symptoms information, unfortunately.

Manuscript change: None.

b. Important to note that 34.0% of the patients received thrombolytic therapy despite "Pre-hospital delay" and 57.6% of the patients received thrombolytic therapy with NO-Pre-hospital delay". However, in table 4 it does not specify if those who did not receive thrombolytic therapy were in part represented by ineligible patients for reperfusion based on delay timing of more than 12 hours. Yet it is unclear why only 57.6% of the patients who sought medical attention within 2 hours after symptom onset received thrombolytic therapy.

Reply: Thanks for your comments. The contrast between patients with and without pre-hospital delay in out analyses (34.0% vs 57.6%) implies that the pre-hospital delay should be one of the causes which affected the rate of receiving thrombolytic therapy. However, it was not the only reason for patients not having thrombolytic therapy. Among all 7312 STEMI patients in our study, 5631 (77.0%) arrived at hospital within 12 hours from their symptom onset and out of them 2874 (51.0%) received thrombolytic therapy. That implies there were other hurdles for patients to receive thrombolytic treatment besides pre-hospital delay.

Previous study also reported low thrombolytic therapy rate (56.1%, 2011) among eligible STEMI patients in non-PCI centers in China. [4] The possible explaining reasons include doctors' concerns/worries on patient safety/adverse events (In fact, patients with higher risk of death were less likely to receive thrombolytic therapy), 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. The hurdles to initiating thrombolytic therapy among Chinese STEMI patients are important and have been reported in previous studies but are not the study purposes of the present paper.

Manuscript change: We added explanation to this phenomenon in discussion part as below.

"……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. 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..……"

Discussion:

a. Top of page 16 (line 20): are you referring to "total ischemic time" (time of symptom onset to time of lytic therapy)? Recommend revising that terminology

Reply: Accepted.

Manuscript change: Done.

b. Need to include in the discussion (or results) why women may have longer delays.

Reply: Accepted.

Manuscript change: We add in discussion part the following paragraph.

"……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 27 28] The possible explanations include women suffering more atypical symptoms,[29 30] women discriminating culture and lower social economic status,[31] greater sympathy that prevent women to trouble anyone[32] etc..……"

c. Limitations. You state that you did not collect the onset symptoms and hence could hardly study on the possible associations between the symptoms and the delays to care. Again, this is confusing. Recommend revising that terminology

Reply: Accepted.

Manuscript change: Done. See Page 20, Line 11 to 12.

Reference:

Some are very old. You have more recent references that could replace them. Search in pub-med and try to collect all the new studies on delay in STEMI

Reply: We have updated the references.

Reviewer: 2

This is an observational study from China describing pre-hospital and in-hospital delays to thrombolysis and factors associated with these delays in 7312 patients with ST-elevation myocardial infarction (STEMI) in 101 hospitals without facilities to perform percutaneous coronary intervention (PCI) in the period 2011-2014. Three timeframes were examined: symptoms to treatment (norm: less than 120 min); arrival (door) to performing diagnostic ECG (norm: less than 10 min); ECG to thrombolytic treatment (less than 10 min). Delay was defined as any time exceeding these norms and the percentages of delay occurrence for these time frames were: 67.1%, 31.4% and 85.8%, respectively. A number of clinical factors were associated with delays (female sex, older age, illiteracy, farmer status, tachycardia, night hour symptoms) and non-delays (hypotension, previous myocardial infarction, hypertension). The authors conclude that delays are frequent and efforts should be deployed to decrease them in 'a vulnerable population with low social economic status'.

This well written descriptive study invites a few comments.

1. Introduction. Authors affirm that the effectiveness of thrombolysis is more time dependent than PCI. Although widely believed, this is questionable. As if the myocardium that knows it is going to receive PCI, in up to or more than the 2-hour additional delay compared with thrombolysis, will withstand ischemic time better.

Reply: Accepted.

Manuscript change: We deleted the relevant sentence in introduction part.

2. This data comes from an acute coronary syndrome (ACS) registry. How did the authors determine that their patients specifically had STEMI? It is not that simple to ensure a validated STEMI diagnosis and no details are provided. What was the larger ACS numerator from which the STEMI sub-population was selected?

Reply: We recruited patients according to their final diagnosis at discharge rather than the suspect diagnosis at admission. Although CPACS-3 study was a registry study it had a professional project management team, which did on-line data monitoring as well as the regular site visits to check on the key data elements. However, we did not collect the original ECG for further independent validation of

the diagnosis. Thus, we are not 100% sure about the accuracy of the diagnosis of STEMI in our study but we believe the incorrect diagnosis for STEMI in our study should be minimum.

CPACS-3 study recruited a total of 29,346 patients with ACS from non-PCI hospital. Out of them, 10294 (35.1%) patients were diagnosed with STEMI.[5] The proportion of STEMI was lower than that previously reported in Chinese patients, which partly or mainly from tertiary hospitals with PCI capacity (45%-62.7%).[6,7]

Manuscript change: We add in the limitation section the following paragraph.

"……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. ……"

3. The authors employ a binary delay criteria. But does it really matter if an ECG delay exceeds 10 min to 11 or 12 min and the same for ECG to treatment time. A few minutes' delay is unlikely to have a major impact on outcome while larger delays will. It would be informative to have more granular data on the delay spread for the 3 timeframes studied in this population. If the last 2 timeframe limits accepted 5 min more each, what would be the overall delays (time from symptom onset to treatment and door to treatment) to treatment? Notwithstanding STREAM, the longstanding treatment delay of 30 min (door to thrombolysis) is well established. The authors mention in Discussion that 68% of patients had a door to treatment delay exceeding 30 min. More data on the spread of this delay in their population would be informative.

Reply: Thanks for your valuable comments, which guide us to do the following analyses. The results showed that the change of in-hospital time sections by a few minutes was not associated with the increased change in the total ischemic time, unless the first ECG time prolonged over 30 min. or the time from first ECG to thrombolytic therapy was over 60 in. and the total in-hospital time was over 120 min. (please see the following tables below). In all three tables, we found that with each of the in-hospital time sections increased, the total ischemic time decreased first and then increased, showing an "U" curve. This is well in line with our findings from the multiple variable regression analyses that identified the factors associated with the delays. (see Table 3 in manuscript) We think these following tables are proving useful data and suggest to add in the supplementary file to be published online.

Supplementary Table 1. 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 2. 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

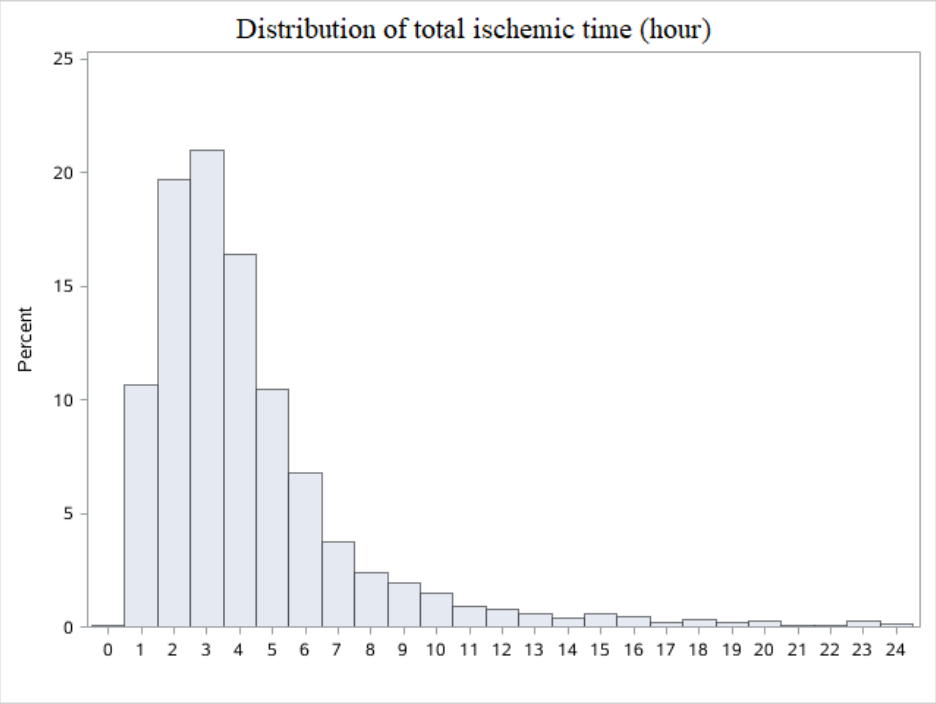
Supplementary Table 3. Total ischemic time by groups of time from arrival to thrombolytic therapy.

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

We take your advices to add in the traditional index – in-hospital delay (defined as the time from arrival at hospital to thrombolytic therapy > 30 min) in our manuscript. See revised Table 2 and Table 3 for corresponding data in details. But we keep the delay in thrombolytic treatment defined as the time from first ECG to thrombolytic therapy > 10 min, because this is the latest recommendation in ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (2017). However, it was selected based on the median time from randomization to bolus use recorded in the STREAM trial, which was 9 min. And we realized that it has a precondition that the new generation of thrombolytics with bonus use could be applied. Unfortunately, r-tPA is still predominant type of thrombolytics in China and new generation thrombolytics such as TNK-tPA is not available yet on the China market. Thus, we agree with the reviewer that the traditional in-hospital delay criteria of =< 30 min should be kept in use.

We also took a look at the distribution of the time from symptom onsets to thrombolytic therapy (total ischemic time) in the following.



Manuscript change: We add the results from the additional analyses on the in-hospital delay into Table 2 and Table 3. (See revised Table 2 and Table 3） We also add the following paragraphs in the Method part, Result part and Discussion part.

In the method part:

"……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]……"

In the results part:

"……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.……"

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

In the discussion part:

"……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.……"

1. No outcome data is provided. It would have been highly informative to see such data and its associations with the delays.

Reply: Thanks for your suggestion. A separate article on this particular question has been completed by our group and by a different leading author. In this study, we focused on the status of delays and factors contributing to these delays.

Manuscript change: None.

2. Only 43% of STEMI patients received thrombolytic therapy. This is a very low proportion of potentially eligible patients for life-saving treatment and is likely far more important (on a population basis) than relatively slow delays in terms of a few minutes in the minority of patients who did receive thrombolysis. It is said that half the patients not receiving thrombolytic treatment had a symptom onset to arrival time exceeding 6 hours. Yet thrombolytic treatment is recommended out to 12 hours. How do the authors more fully account for such a large proportion of patients not receiving thrombolysis?

Reply: Thanks for your comments. The contrast between patients with and without pre-hospital delay in out analyses (34.0% vs 57.6%) implies that the pre-hospital delay could be one of the major reason that prevents Chinese patients from receiving thrombolytic therapy. However, it was not the only reason for patients not having thrombolytic therapy. Among all 7312 STEMI patients, 5631 (77.0%) arrived at hospital within 12 hours from their symptom onset and out of them 2874 (51.0%) received thrombolytic therapy. That implies there were other hurdles for patients to receive thrombolytic treatment besides pre-hospital delay. Previous study also reported low thrombolytic therapy rate (56.1%, 2011) among eligible STEMI patients in non-PCI centers in China. [4] The possible explaining reasons include doctors' concerns/worries on patient safety/adverse events (In fact, patients with higher risk of death were less likely to receive thrombolytic therapy), 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. The hurdles to initiating thrombolytic therapy among Chinese STEMI patients are important and have been reported in previous studies but are not the study purposes of the present paper.

Manuscript change: We added explanation to this phenomenon in discussion part as below.

"……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. 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.……"

3. The presumption that tachycardia was the consequence of pre-hospital delay seems somewhat speculative.

Reply: Accepted. We did not have solid evidence to support this assumption. Our presumption mainly based on two reasons below:

1) Pre-hospital delay could lead to increased myocardial ischemia, enlarged area of myocardial necrosis, deterioration of cardiac function, decreased blood pressure and cardiogenic shock, especially in patients with left ventricular anterior wall and right ventricular myocardial infarction. If not treated in time, tachycardia could occur in these patients.
2) Heart attacks can be accompanied by sympathetic excitation, and delays can increase patients' anxiety, which can lead to increased heart rate.
3) The opposite (tachycardia causes the delay for care) should be impossible.

Manuscript change: We have changed the word “actually” to “probably”.

4. More ECG delay during regular working hours seems counter-intuitive.

Reply: Yes, this counter-intuitive phenomenon was also reported among NSTE-ACS patients in CRUSADE Quality Improvement Initiative study. Explanation to this phenomenon is still unclear. In China, making appointment for care is not a common practice. Hence, the diagnosis delay could be caused by more number of patients who rash into hospitals in regular hours and compete for the available medical resources including ECG measurement.

Manuscript change: We revised explanation to this phenomenon in discussion part.

“……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.……”

5. The authors mention need for informed consent as a contributor to treatment delay. Because thrombolysis has been well established to save STEMI lives despite the bleeding risks, it is not clear that any consent is needed beyond standard consent to offer whatever hospital treatment is needed. Is this not even implicit insofar as patients come to hospital to receive treatment?

Reply: Thanks for your comments. In China, thrombolysis treatment belongs to invasive operations that government regulations require doctors / physicians to get consent from the patient or family members before application.

Manuscript change: None.

Reviewer: 3

Reviewer Name: Guido Knapp

Comments on statistics:

page 9, delays to care, first paragraph, second sentence: "... had significantly ...". How do the authors judge the signifcance here? In the section on statistical analysis, the authors do not describe how they compare two independent samples with non-normally distributed random variables. Please add the information!

Reply: Sorry for the confusion. We adopted the non-parametric Wilcoxon tests for non-normally distributed variable: time duration; and use Pearson chi-square test for the proportion of delays between thrombolytic therapy patients and non-thrombolytic therapy patients..

Manuscript change: We added following sentence in method part and added the P values in the revised Table 2.

" … 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.……"

page 11, Table 3, factors associated with the delays: What does generalized estimating equations (GEE) mean here? I think it is a logistic regression problem with random hospital effects- Maybe the authors could motivate their statistical approach. The authors moreover use a lot of explanatory variables and there is clearly a danger of overfitting and spurious statistical significances. Maybe a variable selection procedure is better or more appropriate.

Reply: Sorry for our incorrect descriptions of this statistical method. We noticed that both logistic regression with random hospital effects and logistic regression with GEE could account for the clustering within hospitals from different aspects. To be consistent with the model used in main result publication of CPACS-3 study [5]. We chose logistic regression with generalized estimating equations (GEE) here to account for clustering within each hospital.

Manuscript change: We revised sentence in method- statistical analysis part as below：

"……The logistic regression 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 (the correlation within hospitals).[24]……"

The authors moreover use a lot of explanatory variables and there is clearly a danger of overfitting and spurious statistical significances. Maybe a variable selection procedure is better or more appropriate.

Reply: We had our own variable selection procedure as following.

1) We chose variables based on existing clinical knowledge and factors reported in previous studies.
2) We also performed univariate analyses. The results of univariate analyses were submitted in supplementary file.
3) We used variables not only those significantly associated with the delays in univariate analysis but also those being reported in previous studies as important confounders.

Manuscript change: We added following sentence in method part.

"…… explaining variables in multivariate analyses were selected based on existing knowledge and the results of univariate analyses.……"

FORMATTING AMENDMENTS FROM EDITORIAL OFFICE:

1. Xie, Wuxiang complete affiliation in SC1:

- Please provide complete affiliations (institutions and department) for all the authors both in the manuscript and in the submission system (ScholarOne).

Reply: Accepted

Manuscript changes: Done..

2. No Patient and Public Involvement:

- We have implemented an additional requirement to all articles to include 'Patient and Public Involvement' statement within the main text of your main document. Please refer below for more information regarding this new instruction:

Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'.

This should provide a brief response to the following questions:

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?

How did you involve patients in the design of this study?

Were patients involved in the recruitment to and conduct of the study?

How will the results be disseminated to study participants?

For randomised controlled trials, was the burden of the intervention assessed by patients themselves?

Patient advisers should also be thanked in the contributor ship statement/acknowledgements.

If patients and or public were not involved please state this.

Reply: Thanks and accepted.

Manuscript change: We have added 'Patient and Public Involvement' in method part in revised manuscript.

"……

Patient and Public Involvement

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

……”

3. Figure resolution:

- Please re-upload your figure in 300 dpi and 90mm x 90mm of width. Please see the following link for further details on preparing images for submission:

https://authors.bmj.com/writing-and-formatting/formatting-your-paper/

Reply: Accepted.

Manuscript changes: We have redo and re-upload our figures.

1. 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):2128-2134.
2. 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):349-355.
3. 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.
4. 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):232-243.
5. 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.
6. Zhou M, Liu J, Hao Y, et al. Prevalence and in-hospital outcomes of diabetes among patients with acute coronary syndrome in China: findings from the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome Project. *Cardiovasc Diabetol.* 2018;17(1):147.
7. Bi Y, Gao R, Patel A, et al. Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. *American heart journal.* 2009;157(3):509-516.e501.

VERSION 2 – REVIEW

REVIEWER	Guido Knapp TU Dortmund University Germany
REVIEW RETURNED	25-Sep-2019

GENERAL COMMENTS	No further comments in statistics! Thank you!