Analysis of potential factors contributing to refusal of invasive strategy after ST-segment elevation myocardial infarction in China

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Abstract

Background: Reduced application of percutaneous coronary intervention (PCI) is associated with higher mortality rates after ST-segment elevation myocardial infarction (STEMI). We aimed to evaluate potential factors contributing to the refusal of PCI in STEMI patients in China.

Methods: We studied 957 patients diagnosed with STEMI in the emergency departments (EDs) of six public hospitals in China. The differences in baseline characteristics and 30-day outcome were investigated between patients who refused PCI and those who underwent PCI. Multivariable logistic regression was used to evaluate the potential factors associated with refusing PCI.

Results: The potential factors contributing to refusing PCI were older than 65 years (odds ratio [OR] 2.66, 95% confidence interval [CI] 1.56–4.52, $P < 0.001$), low body mass index (BMI) (OR 0.91, 95% CI 0.84–0.98, $P = 0.013$), not being married (OR 0.29, 95% CI 0.17–0.49, $P < 0.001$), history of myocardial infarction (MI) (OR 2.59, 95% CI 1.33–5.04, $P = 0.005$), higher heart rate (HR) (OR 1.02, 95% CI 1.01–1.03, $P = 0.002$), cardiac shock in the ED (OR 5.03, 95% CI 1.48–17.08, $P = 0.010$), pre-hospital delay (>12 h) (OR 3.31, 95% CI 1.83–6.02, $P < 0.001$) and not being hospitalized in a tertiary hospital (OR 0.45, 95% CI 0.27–0.75, $P = 0.002$). Compared to men, women were older, were less often married, had a lower BMI and were less often hospitalized in tertiary hospitals.

Conclusions: Patients who were older, had lower economic or social status, and had poorer health status were more likely to refuse PCI after STEMI. There was a sex difference in the potential predictors of refusing PCI. Targeted efforts should be made to improve the acceptance of PCI among patients with STEMI in China.

Keywords: ST-segment elevation myocardial infarction; Emergency department; PCI; Invasive strategy; Percutaneous coronary intervention

Introduction

Positive reperfusion of the infarct-related artery is the major determinant of long- and short-term prognosis of ST-elevation myocardial infarction (STEMI).[1,2] However, even in the current era, many eligible patients do not receive timely reperfusion therapy despite having no absolute contraindications.[3,4] In China, the proportion of patients who did not receive reperfusion has not significantly changed.[5] Recently, the proportion of STEMI patients not undergoing percutaneous coronary intervention (PCI) remains high in China, and the possible related factors are still unknown, hindering our ability to improve medical treatment for this condition. Therefore, we explored the related factors.

Additionally, significantly higher rates of early death among women with STEMI than among men still persist across developed and developing countries.[6-9] Women had a lower probability of being given guideline-based management and acute reperfusion therapy after STEMI.[10-12] Women are less invasively examined and

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001171

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Chinese Medical Journal 2021;134(5)
Received: 22-09-2020 **Edited by:** Yan-Jie Yin and Xiu-Yuan Hao

subsequently less treated than men, even after adjusting for differences in comorbidity and number of significant stenoses.[13,14]

The objective of this study was to evaluate potential factors contributing to the refusal to perform PCI among patients with STEMI in the Chinese emergency department (ED). Sex subgroups were also investigated. The findings of this study will help identify the factors that potentially affect patients' decisions regarding PCI and stimulate quality improvement efforts to improve outcomes for STEMI patients.

Methods

Ethical approval

The study was approved by the Central Ethics Committee at the Qilu Hospital of Shandong University and was subsequently approved by all collaborating hospitals (No. [2015]058). Written informed consent was obtained from all participants.

Study design and patient enrollment

This study was a retrospective analysis of data from a prospective cohort study. The primary data were collected through a prospective, multicenter registry study of patients with STEMI presenting to the ED from August 24th, 2015, to September 30th, 2017, in China. All six of the public hospitals in the study were equipped with catheter centers capable of 24-h interventional therapy, including four tertiary and two secondary grade hospitals.

We consecutively included patients with a definite diagnosis of index STEMI before discharge from the ED. The diagnosis of STEMI was defined as new left bundle branch block or persistent ST-segment elevation (new ST elevation at the J point in two contiguous leads with the cut points: ≥0.1 mV in all leads other than leads V2–V3 where the following cut points were applied: ≥0.2 mV in men ≥40 years old; ≥0.25 mV in men <40 years, or ≥0.15 mV in women).[15] The electrocardiogram results were validated by a cardiologist not involved in data abstraction. Patients were excluded if they were unable or unwilling to provide informed consent. Some patients were excluded because they did not have opportunity to make a decision on receiving or refusing the PCI therapy, including patients died in the ED, died before angiography, or had a critical situation or contraindication for PCI. Patients who were discharged against physicians' advice or transferred to other hospitals were also excluded. Since we did not exclude patients with a pre-hospital delay of more than 12 h, all kinds of PCI rather than only primary PCI were selected as the observational indicator. All enrolled patients were recommended to undergo PCI while in the hospital.

Data collection and measures

Data were collected by trained research assistants using a standardized case report form. Demographic, medical history, and patient behavior data were collected directly from the patient or the family members. Married referred to the state of being married, and single and divorced individuals, widowers, and widows were assigned a value of 0 for this measure. Pre-hospital delay (>12 h) refers to situations in which the time from the onset of symptoms to present at the ED and contact with medical staff was over 12 h. Nocturnal presentation indicated that the patients arrived at the ED during the period from 8 PM to 8 AM. Information about the emergency evaluation and interventional therapeutics was abstracted from medical records. Data quality was controlled by specialized personnel regularly to rectify quality problems and provide feedback to the individual researchers.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation or median (interquartile range), whereas categorical variables are summarized as numbers and percentages. Demographics, risk factors, medical history, patients' behaviors, and clinical status at presentation between patients who refused PCI or not were compared using t test for continuous variables and Chi-square (χ^2) test for categorical variables. The potential factors contributing to refusing to undergo PCI in candidate patients were investigated by multivariable logistic regression. A P value of less than 0.05 (two-sided) was considered statistically significant in the analysis. All statistical analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 1061 patients were diagnosed with STEMI in participating hospitals from August 24th, 2015 to September 30th, 2017. One hundred and four patients were excluded for the following reasons: denial of informed consent ($n = 54$), discharged against physicians' advice ($n = 7$), died in ED ($n = 15$), transferred to other hospitals ($n = 8$), died before angiography ($n = 11$) or were in a critical situation or had a contraindication for PCI ($n = 9$). Finally, 957 patients (260 women and 697 men) remained for analysis, and 98 patients refused PCI therapy. There were no missing data regarding the use of medical treatment or survival status in any patient [Figure 1].

Comparisons of the baseline and clinical characteristics between patients who refused PCI or not are presented in Table 1. The refused PCI group had more female patients (odds ratio [OR] 2.54, 95% confidence interval [CI] 1.66–3.90, $P < 0.001$), was much older (OR 1.09, 95% CI 1.06–1.11, $P < 0.001$). Meanwhile, there were more patients who were older than 65 years (OR 4.63, 95% CI 2.88–7.45, $P < 0.001$) in the refusal group. Patients in the refused PCI group had a lower body mass index (BMI) (OR 0.87, 95% CI 0.81–0.93, $P < 0.001$), was less often married (OR 0.18, 95% CI 0.11–0.29, $P < 0.001$) and had a lower education level (OR 0.59, 95% CI 0.36–0.95, $P = 0.028$) than the not-refused PCI group. The refused PCI group had a lower prevalence of smoking habits (OR 0.41, 95% CI 0.25–0.67, $P < 0.001$) but a greater

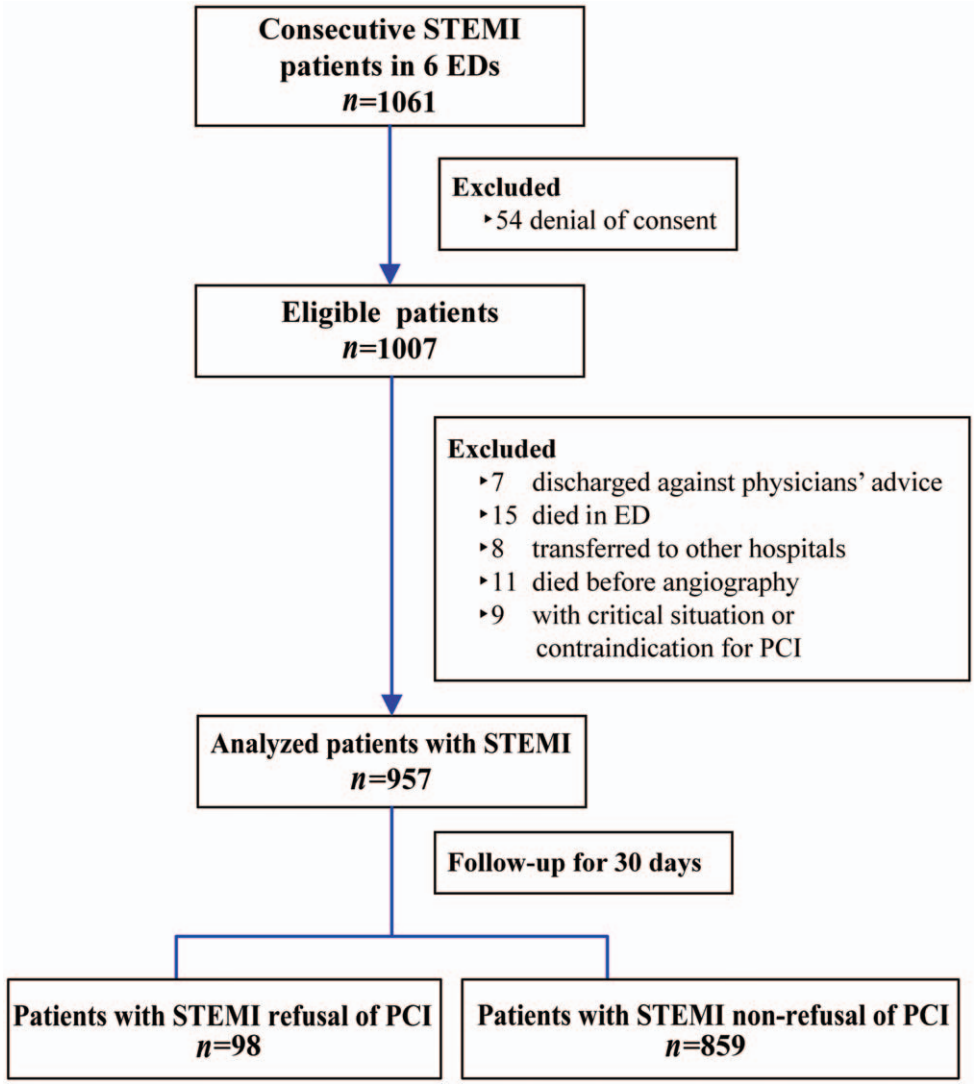

Figure 1: Study flow chart in 1061 patients with STEMI in participating hospitals. ED: Emergency department; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial.

percentage of previous myocardial infarction (MI) (OR 1.92, 95% CI 1.05–3.49, $P = 0.031$), heart failure (OR 5.08, 95% CI 1.67–15.48, $P = 0.010$) and stroke (OR 2.13, 95% CI 1.23–3.69, $P = 0.006$). Furthermore, the refusal group had higher heart rate (HR) (OR 1.02, 95% CI 1.01–1.03, $P = 0.001$), was more likely to present with signs of heart failure, such as pulmonary rales (OR 4.24, 95% CI 1.88–9.60, $P = 0.002$) or lower limb edema (OR 3.55, 95% CI 1.53–8.24, $P = 0.006$), and had more cardiac shock (OR 5.08, 95% CI 1.67–15.48, $P = 0.010$). Pre-hospital delay (>12 h) was much greater in the refused PCI group (OR 3.71, 95% CI 2.20–6.26, $P < 0.001$). Fewer patients in the refused PCI group were treated in the tertiary hospital than the other group (OR 0.46, 95% CI 0.29–0.73, $P = 0.001$).

Potential factors contributing to the refusal of PCI

After multivariable logistic regression analysis in the total candidate cohort, it was shown that older than 65 years (OR 2.66, 95% CI 1.56–4.52, $P < 0.001$), lower BMI (OR 0.91, 95% CI 0.84–0.98, $P = 0.013$), unmarried status (OR 0.29, 95% CI 0.17–0.49, $P < 0.001$), history of MI (OR 2.59, 95% CI 1.33–5.04, $P = 0.005$), higher HR (OR 1.02, 95% CI 1.01–1.03, $P = 0.002$), cardiac shock in the ED (OR 5.03, 95% CI 1.48–17.08, $P = 0.010$), pre-hospital delay (>12 h) (OR 3.31, 95% CI 1.83–6.02, $P < 0.001$) and treatment at a non-tertiary hospital (OR 0.45, 95% CI 0.27–0.75, $P = 0.002$) may contribute to PCI refusal [Table 2].

Sex difference in the potential factors contributing to the refusal

Further analysis by sex illustrated sex disparities in the following factors in regard to the refusal of PCI. Female patients were older (69.5 ± 11.1 *vs.* 60.4 ± 11.9 years, $P < 0.001$), had a larger portion of patients who older than 65 years (66.2% *vs.* 33.4%, $P < 0.001$), had a lower BMI (24.7 ± 3.6 *vs.* 25.3 ± 3.3 kg/m^2, $P = 0.017$), were less

Table 1: Baseline characteristics of the analyzed patients with STEMI.

Variables	Refusal ($n = 98$)	Non-refusal ($n = 859$)	OR (95% CI)	*P* value
Demographics				
Female	45	215	2.54 (1.66–3.90)	<0.001
Age (years)	72.6 ± 13.6	61.8 ± 11.7	1.09 (1.06–1.11)	<0.001
Age >65 years	73	332	4.63 (2.88–7.45)	<0.001
BMI (kg/m^2)	23.9 ± 3.2	25.3 ± 3.4	0.87 (0.81–0.93)	<0.001
Married	64	784	0.18 (0.11–0.29)	<0.001
Employed	43	386	0.96 (0.63–1.46)	0.842
Education (≥high school)	24	306	0.59 (0.36–0.95)	0.028
Risk factors				
Current smoker	23	367	0.41 (0.25–0.67)	<0.001
Diabetes	29	184	1.54 (0.97–2.45)	0.065
Hypertension	54	423	1.26 (0.83–1.93)	0.272
Hyperlipidemia	9	69	1.16 (0.56–2.40)	0.693
Family history of premature CAD	8	87	0.79 (0.37–1.68)	0.538
Medical history				
MI	15	74	1.92 (1.05–3.49)	0.031
Catheterization with stenosis ≥50%	5	77	0.55 (0.22–1.38)	0.196
PCI	4	67	0.50 (0.18–1.41)	0.183
Heart failure	5	9	5.08 (1.67–15.48)	0.010
Stroke	19	87	2.13 (1.23–3.69)	0.006
Vital signs				
SBP (mmHg)	138.3 ± 30.1	136.5 ± 28.9	1.00 (0.99–1.01)	0.579
HR (bpm)	82.5 ± 21.5	75.2 ± 19.6	1.02 (1.01–1.03)	0.001
SpO_2 (%)	96.2 ± 8.9	97.8 ± 5.8	0.98 (0.95–1.00)	0.166
Physical examination				
Abnormal cardiac auscultation	10	60	1.51 (0.75–3.06)	0.246
Pulmonary rales	9	20	4.24 (1.88–9.60)	0.002
Lower limb edema	8	21	3.55 (1.53–8.24)	0.006
Killip class (II–IV)	7	45	1.39 (0.61–3.18)	0.431
Cardiac shock in ED	5	9	5.08 (1.67–15.48)	0.010
Patients' behaviors				
Nocturnal presentation	43	338	1.21 (0.79–1.84)	0.385
Pre-hospital delay (>12 h)	24	69	3.71 (2.20–6.26)	<0.001
Home medication	35	304	1.01 (0.66–1.57)	0.949
Ambulance use	36	246	1.45 (0.94–2.24)	0.096
Tertiary hospital	66	701	0.46 (0.29–0.73)	0.001
Death	17	26	6.72 (3.50–12.91)	<0.001

Values are presented as mean ± standard deviation or *n*. STEMI: ST-segment elevation myocardial; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; SBP: Systolic blood pressure; HR: Heart rate; bpm: Beats per minute; SpO_2: Oxygen saturation; ED: Emergency department.

Table 2: Multivariable logistic regression analysis of factors related to refusal patients with STEMI.

Variables	β	SE	OR (95% CI)	*P* value
Intercept	–0.49	1.04	0.86 (0.11, 6.81)	0.635
Female	0.35	0.25	1.42 (0.86, 2.33)	0.172
Age >65 years	0.98	0.27	2.66 (1.56, 4.52)	<0.001
BMI	–0.10	0.04	0.91 (0.84, 0.98)	0.013
Married	–1.25	0.28	0.29 (0.17, 0.49)	<0.001
History of MI	0.95	0.34	2.59 (1.33, 5.04)	0.005
HR	0.02	0.01	1.02 (1.01, 1.03)	0.002
Cardiac shock in ED	1.62	0.62	5.03 (1.48, 17.08)	0.010
Pre-hospital delay (>12 h)	1.20	0.30	3.31 (1.83, 6.02)	<0.001
Tertiary hospital	–0.81	0.27	0.45 (0.27, 0.75)	0.002

STEMI: ST-segment elevation myocardial infarction; β: Partial regression coefficient; SE: Standard error; OR: Odds ratio; BMI: Body mass index; MI: Myocardial infarction; HR: Heart rate; ED: Emergency department.

Table 3: Multivariable logistic regression analysis for factors related to refusal in female and male patients with STEMI.

Variables	Female				Male			
	β	SE	OR (95% CI)	*P* value	β	SE	OR (95% CI)	*P* value
Intercept	0.66	1.69	1.93 (0.07, 52.52)	0.697	–0.90	1.36	0.51 (0.03, 5.86)	0.509
Age >65 years	0.69	0.56	1.99 (0.66, 5.96)	0.220	1.06	0.31	2.9 (1.58, 5.32)	0.001
BMI	–0.16	0.06	0.86 (0.76, 0.97)	0.011	–0.06	0.05	0.94 (0.85, 1.04)	0.228
Married	–1.39	0.43	0.25 (0.11, 0.57)	0.001	–1.21	0.38	0.3 (0.14, 0.63)	0.002
History of MI	1.45	0.61	4.27 (1.28, 14.24)	0.018	0.78	0.42	2.17 (0.96, 4.91)	0.062
HR	0.03	0.01	1.03 (1.01, 1.05)	0.001	0.01	0.01	1.01 (1.00, 1.02)	0.203
Cardiac shock in ED	2.20	1.09	9.04 (1.06, 77.22)	0.044	1.40	0.77	4.06 (0.90, 18.39)	0.069
Pre-hospital delay (>12 h)	1.65	0.48	5.22 (2.02, 13.46)	0.001	0.98	0.42	2.66 (1.16, 6.12)	0.021
Tertiary hospital	–1.02	0.43	0.36 (0.16, 0.84)	0.018	–0.68	0.36	0.51 (0.25, 1.03)	0.060

STEMI: ST-segment elevation myocardial infarction; β: Partial regression coefficient; SE: Standard error; OR: Odds ratio; BMI: Body mass index; MI: Myocardial infarction; HR: Heart rate; ED: Emergency department.

often married (80.0% *vs.* 91.8%, $P < 0.001$), and had a greater prevalence of pre-hospital delay (>12 h) (12.3% *vs.* 8.8%, $P = 0.099$) than men. Only 76.5% of female patients were treated in tertiary hospitals, compared with 81.5% of male patients ($P = 0.087$).

Multivariable analyses indicated that the significance of these contributing factors was diverse in patients of different sexes [Table 3]. BMI, marital status, history of MI, HR, cardiac shock in ED, pre-hospital delay (>12 h), and tertiary hospital status were shown to be potential factors contributing to PCI treatment in women ($P < 0.05$). Only age, marital status, and pre-hospital delay (>12 h) were significant in men ($P < 0.05$).

Discussion

In this STEMI cohort, 10.2% of the patients declined physician recommendations of PCI and had poor prognosis. Potential influencing factors, such as older age, lower BMI, unmarried status, history of MI, pre-hospital delay, higher HR, cardiac shock in the ED, and treatment at a non-tertiary hospital, may contribute to the refusal of PCI.

A progressive decline in early mortality of STEMI over time has been observed in many national surveys, which is considered to be explained by the more frequent use of invasive revascularization strategies.[16-18] However, many studies have shown that reperfusion therapy in STEMI patients is still grossly inadequate.[3,5] Even if some patients lose the chance to undergo primary PCI due to delay, they still lack treatment for later reperfusion. To assess the overall interventional situation of STEMI patients, we took stock of not only primary PCI but also all kinds of PCI treatment. The refused PCI group had more female patients, were older, were slimmer, were less often married and had a lower education level. We also found that patients who refused PCI had poorer disease status and more negative health management attitudes. Patients in the refused PCI group had more complications and a greater prevalence of pre-hospital delay than those in the non-refused group. Furthermore, they were more likely to present with signs of heart failure when admitted to the ED, such as pulmonary rales and lower limb edema.

Our study found that older STEMI patients were more likely to refuse PCI. Age over 65 years is an independent risk factor for the refusal of PCI treatment in STEMI patients. With the promotion of PCI application, the rates of not undergoing reperfusion over the past decade have remained significantly higher among STEMI patients aged ≥75 years than among the younger patients of both sexes.[7] The increased use of PCI in elderly STEMI patients is associated with decreased mortality, with and without cardiogenic shock.[19] Therefore, it is important to focus on reducing the refusal of PCI therapy in elderly patients. We also find that women were older than men and had a higher proportion of refusing revascularization. Many studies also show that women with AMI undergo PCI at lower rates than men.[8,12,20] However, sex was not a significant predictor for the refusal of PCI after adjusting for age in our study. One of the possible explanations of the sex disparity may be the age gap between women and men.

Interestingly, we found that a lower BMI was a potential predictor of the refusal of PCI. Some studies have shown that the lower BMI population was characterized by the most advanced age, a higher proportion of women, unstable clinical presentation, and the greatest coronary calcification.[21,22] These are known predictors of worse outcomes following PCI. On the other hand, BMI is inversely associated with an increased risk of bleeding and mortality after PCI.[23] The association between a lower BMI and a higher bleeding risk may increase patients' scruple about PCI. We hypothesized that the rejection of PCI in patients with lower BMI might be due to older age, lower economic status or greater complications and bleeding risk.

Our study showed that marriage was a positive factor in patients' decision to undergo PCI. Studies have demonstrated that symptom-to-first-medical contact time is longer among unmarried patients, while marital status may improve outcomes.[24,25] With a complete family, patients may have better spiritual or financial support from family members, which leads to more timely visits and better treatment adherence. We also found a higher proportion of unmarried status among women than among men. Based on the age gap between sexes, a greater proportion of unmarried women may be widowed.

It has been shown that admission tachycardia was a strong independent predictor of mortality.[26] In this study, we found that patients with increased HR when admitted to the ED were more likely to refuse PCI while in the hospital. Moreover, we found that a prior history of MI was a potential predictor of PCI refusal. We are still unsure of the potential association among these factors. However, we should further observe and understand these patients and provide more active treatment suggestions.

We found that patients with cardiogenic shock in the ED tended to refuse PCI during hospitalization. A possible explanation is that in China, a critical condition may cause patients or guardians to adopt a conservative management strategy, considering the higher risk of invasive treatment and the possible poor consequences that correspond to serious illness. However, studies have shown that even in patients with cardiogenic shock, aggressive PCI treatment still makes a significant difference in outcome.[27] In principle, as recommended in the guidelines, the more severe the disease, the more aggressive PCI should be considered, and the significance of the Global Registry of Acute Coronary Events and the Thrombolysis in Myocardial Infarction scores are used to screen out high-risk patients for early intervention.[1,2,28,29]

Many studies have confirmed that pre-hospital delays are related to inappropriate care-seeking, less revascularization, and poor outcomes in patients with STEMI.[30-32] In this study, a pre-hospital delay of more than 12 h was a predictor of a patient's likely rejection of PCI. Patients' negative attitudes were reflected not only in the delayed time of seeking medical service but also in the decision of treatment methods. We should identify these negative patients and provide more positive treatment recommendations and strategies.

We also found that presenting to tertiary hospitals was a positive influencing factor contributing to PCI treatment in STEMI patients. The China PEACE study showed that urban hospitals provide better evidence-based treatment than rural hospitals, which is partly attributed to the higher-level hospitals in cities.[33] We believe that patients' or guardians' decisions about treatment may also be influenced by the strength of the hospital.

In our study, although sex was not an independent potential factor involved in patients' rejection of PCI, female STEMI patients were still more likely to reject revascularization than male STEMI patients. Other studies also showed that women with AMI undergo PCI at lower rates than men.[12,20] We hold the opinion that women have many negative factors associated with the refusal of PCI treatment, such as being older, thinner, and single, which led to a higher rejection rate than that of men.

Older age and pre-hospital delay had negative effects on the decision to undergo PCI, while being married had a positive effect in STEMI patients of both sexes. The previously described effect of BMI on the decision to undergo PCI was observed only in women, not in men. This may be due to a lower social or economic status, and low BMI is more common in female patients.[34] There was no statistically significant sex difference in HR or history of MI. However, their negative effect on PCI intents was observed only in women. Similarly, there was no significant difference in tertiary hospital admission among both sexes, but a favorable influence of tertiary hospitals on PCI decision-making was only shown in women. The underlying causes behind these sex differences in treatment decisions need further research.

It has been suggested that women and men receive equal benefit from early invasive reperfusion after STEMI.[35,36] It is important to fully recognize sex differences in factors involved in refusing PCI for STEMI patients and to develop corresponding improvement plans.

To our knowledge, this is the first attempt to investigate the possible factors influencing the decision to undergo an invasive strategy after STEMI symptom onset. This study included patients consecutively recruited from six public hospitals covering tertiary and secondary grades and urban and rural areas and represented a relatively complete profile of patients with STEMI in China. Efforts have been made to obtain complete information about STEMI, including collecting data prospectively, reviewing readmission medical records, and checking local death registry data. Hence, the findings of our study may help provide valuable targets for public education and emergency care quality improvements with potential impacts on China and other developing countries.

This study also has several limitations. First, we lack the investigation of patients' understanding of the disease and their psychological state at the time of STEMI onset and hospitalization. These factors may also influence patients' or guardians' decision-making. Second, due to the busy work environment and relatively low level of electronic medical records systems in the Chinese ED, the potential for missed identification of eligible patients may persist. To minimize this risk, research assistants screened all the ED visits daily to identify the eligible patients consecutively when possible.

Conclusions

Our study showed that patients who were older than 65 years, unmarried, had a lower BMI, had a history of MI, had higher HR and cardiac shock, had longer pre-hospital delay and were hospitalized in non-tertiary hospitals were more likely to refuse PCI. These contributing factors have diverse effects on patients of different sexes. We should better understand which factors may influence the decision to undergo PCI and take appropriate measures to improve the proportion of patients undergoing recommended treatment and improve the prognosis of patients with STEMI.

Funding

This study was supported by grants from the National Key R&D Program of China (Nos. 2017YFC0908700, 2017YFC0908703), National S&T Fundamental Resources Investigation Project (Nos. 2018FY100600, 2018FY100602), Taishan Pandeng Scholar Program of

Shandong Province (No. tspd20181220), Taishan Young Scholar Program of Shandong Province (Nos. tsqn20161065, tsqn201812129), and Key R&D Program of Shandong Province (Nos. 2016ZDJS07A14, 2018GSF118003).

Conflicts of interest

None.

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How to cite this article: Zhang H, Zheng W, Wu S, Ma JJ, Wang GM, Li Y, Zheng JQ, Lyu Y, Xue MY, Xu F, Wang JL, Chen YG. Analysis of potential factors contributing to refusal of invasive strategy after ST-segment elevation myocardial infarction in China. Chin Med J 2021;134:524–531. doi: 10.1097/CM9.0000000000001171