

Clinical characteristics and influencing factors of pre-hospital delay of the second acute myocardial infarction

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Abstract

Background: Knowledge is limited concerning the clinical characteristics and the influencing factors of pre-hospital delay at the second myocardial infarction in China.

Object: This study was designed to investigate the factors associated with interval of <12 months between the first and second acute myocardial infarction (AMI), the type of symptoms of the first and second AMI and their gender differences, and the factors associated with pre-hospital delay of ≥ 1 hour at the second AMI.

Methods: A retrospective cohort study of 98 patients with a first and a second AMI from Affiliated Hospital of Jiaying University between January 2014 and January 2020 was conducted. All data of this study were extracted from medical records.

Results: Patients who recurred within one year after the first AMI accounted for 43.9% of all recurrent patients. Without percutaneous coronary intervention (PCI) at the first AMI was an independent risk factor for interval of <12 months between the first and second AMI. Atypical symptoms of the second AMI were less than that of the first AMI, which was significant for males but not for females when comparing men and women separately. Atypical symptoms were independent risk factors for pre-hospital delay of ≥ 1 hour at the second AMI.

Conclusions: Patients, with two or more AMI, who did not undergo PCI at the first AMI were more likely to recur within one year. Patients (males) with atypical symptoms at the second AMI decreased compared with that of the first AMI. Patients with atypical symptoms had a longer pre-hospital delay at the second AMI.

Keywords: acute myocardial infarction, pre-hospital delay, atypical symptoms, percutaneous coronary intervention

Introduction

Acute myocardial infarction (AMI) is caused by acute occlusion of the coronary arteries, which leads to partial myocardial necrosis due to severe and persistent ischemia (Anderson, J. L., & Morrow, D. A., 2017). The complications of AMI include arrhythmia, shock or heart failure (Anderson, J. L., & Morrow, D. A., 2017; Sulo et al., 2020; Rubini et al., 2020). The typical clinical symptom of AMI is severe and long-lasting post-sternal pain. According to typical clinical manifestations, characteristic electrocardiographic changes and laboratory

examinations, it is not difficult to diagnose AMI. However, the diagnosis of patients without clinical symptoms is relatively difficult, and the prognosis of these patients is poor (Amier et al., 2018). The general principle of the treatment of AMI is to restore coronary perfusion as soon as possible, including percutaneous coronary intervention (PCI) and intravenous thrombolysis (Kumar & Cannon, 2009). Some patients with the first AMI will recur after treatment, and the peak period of recurrence is the first year after treatment (McConnell, Olson, Delate, & Merenich, 2009; Stromback, Vikman, Lundblad, Lundqvist, & Engstrom, 2017). Delays in the treatment of AMI are mainly caused by uncertain pre-hospital delays, and there are many factors that affect pre-hospital delays (Moser et al., 2006; Angerud et al., 2013). This study was designed to investigate the factors associated with interval of <12 months between the first and

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second AMI, the type of symptoms of the first and second AMI and their gender differences, and the factors associated with pre-hospital delay of ≥ 1 hour at the second AMI.

Literature reviews

With the gradual changes in lifestyle and the continuous improvement of treatment methods, the incidence (Mefford et al., 2020) and mortality (Anderson, J. L., & Morrow, D. A., 2017) of AMI have decreased, and the incidence of male patients has decreased significantly. However, the hospitalization rate of young women with AMI has increased (Arora et al., 2019). In the special period of the new coronary pneumonia epidemic, the number of hospital admissions for AMI has been significantly reduced, but the mortality and complication rate have increased at the same time (De Rosa et al., 2020). So far, a large number of people die every year due to AMI, and some of them are patients with recurrent AMI. Studies have shown that the one-year recurrence rates of AMI in men and women are 5.6% and 7.2% (Smolina, Wright, Rayner, & Goldacre, 2012), respectively, and the 5-year cumulative recurrence rate is 12.7% (Fox et al., 2010). AMI has the highest recurrence rate within one year of treatment (McConnell, Olson, Delate, & Merenich, 2009; Stromback, Vikman, Lundblad, Lundqvist, & Engstrom, 2017), and most of the recurrent patients who have undergone stent implantation are caused by very late stent thrombosis (Li et al., 2020).

Patients with AMI mostly present with typical symptom, which characterized by persistent chest pain lasting for 20 min or more, that may radiate to the neck, jaw or back (Roffi et al., 2016), and some with atypical symptoms, such as abdominal pain, unexplained weakness, fatigue and syncope (Steg et al., 2012), and some with a combination of typical and atypical symptoms (Kirchberger et al., 2016). However, a small number of patients are asymptomatic (Amier et al., 2018). With age, the proportion of atypical symptoms of AMI gradually increases (Tisminetzky et al., 2020).

The main treatment principle of AMI is to restore coronary reperfusion as early as possible (Kumar & Cannon, 2009). In non-ST elevation myocardial infarction (NSTEMI), PCI should be accomplished within 24 hours, and it is also advised if it can be completed in 48-72 hours for patients with low risk, although with longer hospital stay, it does not necessarily cause an increase in hospital mortality (Wu et al., 2019; Cannon et al., 2001; Montalescot et al., 2009). However, in ST elevation myocardial infarction (STEMI), PCI should be

considered as priority at PCI-capable hospitals (Vogel et al., 2019; Ghimire, Gupta, & Hage, 2014; O'Gara et al., 2013). When direct transport to a PCI-capable hospital, first medical contact to time of PCI is recommended in 90 minutes or less, which correlates with improved mortality (Cannon et al., 2000; Ibanez et al., 2018b; O'Gara et al., 2013). When initially transport to a non-PCI-capable hospital, an immediate transfer to a PCI-capable hospital is advised if primary PCI can be completed in 120 minutes or less (Ibanez et al., 2018b). Primary PCI is superior to fibrinolysis in improving heart function, reducing bleeding complications, improving quality of life, and reducing mortality in patients with AMI (Thrane et al., 2020; Niccoli et al., 2019; Nichols, Townsend, Scarborough, & Rayner, 2014). However, in areas where PCI performing is impossible within 120 minutes, fibrinolytic therapy within 10 minutes from STEMI diagnosis should be given (Ibanez et al., 2018a).

In patients with AMI, the longer the myocardial ischemia, the worse the prognosis (Guerchicoff et al., 2014; Niccoli et al., 2019). For every 15 minutes delay of effective reperfusion in patients with AMI, the risk of the in-hospital mortality can be increased by 1.6 times; and for every 30 minutes delay, the risk of 1-year mortality can be increased by 1.076 times (Vemulapalli et al., 2013). Studies showed that factors such as gender, age, severity of symptoms, location of symptoms onset, diabetes, and being alone at onset of symptoms may affect pre-hospital delay (Angerud, Brulin, Naslund, & Eliasson, 2013; Jager et al., 2017; Lim, Rahman, & Yaacob, 2019). For patients with a second AMI, some studies concluded that a history of AMI can shorten pre-hospital delay (Ottesen, Dixen, Torp-Pedersen, & Kober, 2004; Perkins-Porras, Whitehead, Strike, & Steptoe, 2009), but some studies reached an opposite conclusion (Henriksson et al., 2011).

Inclusion and exclusion criteria

All data of this study were extracted from medical records. A total of 111 patients, comprising of 89 males (80.2%) and 22 females (19.8%), suffering two or more AMI, were collected from Affiliated Hospital of Jiaxing University between January 2014 and January 2020. Of them, 13 patients were excluded due to insufficient data, and 98 patients, comprising of 79 males (80.6%) and 19 females (19.4%), were included in this retrospective cohort study. The mean age of the patients enrolled in the study at the first AMI was 64.97 ± 1.32 (range, 32-93 years), and the mean age at the second AMI was 67.78 ± 1.29 (range, 33-93 years). Two patients

suffered sudden cardiac death during hospitalization at the second AMI.

Methods

In each case, the diagnosis of AMI relies on biomarker evidence of myocyte necrosis, and either electrocardiographic criteria of ischemia or infarction, or ischemic symptoms, or both (Chapman et al., 2020; Thygesen et al., 2012). The second AMI referred to a new AMI event that occurred at least 28 days after the first AMI (Mendis et al., 2011; Stegmayr, Lundberg, & Asplund, 2003). This study specifically analyzed the second AMI.

In this study, the symptoms of the first and second AMI were divided into two types: typical symptoms and atypical symptoms. Typical symptoms refer to chest tightness or chest pain lasting more than 20 minutes. Atypical symptoms include: 1. Chest tightness, chest pain is intermittent, or its duration is less than 20 minutes; 2. The pain is not in the chest, but in the abdomen, arms, chin or neck; 3. Other symptoms, such as dyspnea, vomiting, nausea, unexplained weakness, fatigue and syncope. There were no patients without any symptoms in this study.

The time from symptom onset to first medical contact is called pre-hospital delay. This study follows the definition of first medical contact by the European Society of Cardiology, that is, when paramedics, medical care staff or medical practitioners first become available to the patient, either before the hospital or at a hospital or medical center (Ibanez et al., 2018a). In order to reduce the area of myocardial infarction, the time of myocardial ischemia should be controlled within a relatively short period of time. Especially for STEMI, the total ischemic time should be kept to 120 minutes or less, and ideally 60 minutes or less. In this study, we divided pre-hospital delay into two categories: <1h and ≥1h.

Statistical analysis

SPSS (v19.0; IBM Corp.) was used for all statistical analyses. Comparisons between groups were analyzed using the χ^2 -test for categorical data. Univariate and multivariate logistic regression was used to analyze factors associated with interval of <12 months between first and second AMI, and pre-hospital delay of ≥1 h at the second AMI. All values were expressed as the mean ± standard error of the mean. Differences were considered to be significant if $p < 0.05$.

Ethics

Ethics approval was obtained from the Medical

Ethics Committee of Affiliated Hospital of Jiaxing University (no. LS. Artical-2019-008).

Results

Influencing factors of recurrence within one year after the first acute myocardial infarction (AMI)

The mean interval between the first and second AMI was 34.47 ± 4.01 months. Half of the patients recurred within 15 months after the first AMI, women within 9 months and men within 21 months. Patients who recurred within one year after the first AMI accounted for 43.9% (43/98) of all recurred patients, and men and women accounted for 41.2% (33/79) and 52.6% (10/19), respectively. Among patients who recurred within one year after the first AMI, 28.3% (15/53) of patients underwent percutaneous coronary intervention (PCI) at the first AMI, and 84.4% (38/45) of patients did not. Univariate logistic regression analysis showed that age, smoking, and PCI at the first AMI were associated with recurrence within one year after the first AMI; Multivariate logistic regression analysis showed that no PCI at the first AMI was an independent risk factor for interval of <12 months between the first and second AMI (OR=3.257, 95% IC 1.252-8.476, $P = 0.016$) (Table 1), that is, patients without PCI at the first AMI were more likely to have a new AMI within one year.

Type of symptoms and gender differences at the first and second AMI

The most common symptoms among patients suffered two or more AMI are typical symptoms at the first and second AMI [60.2 (59/98), 74.5% (73/98)]. There were 46.9% (46/98) of patients with inconsistent symptoms when comparing the first and second AMI. Atypical symptoms at the second AMI were reduced compared with those of the first AMI [39.8(39/98) vs 25.5 (25/98), $P=0.033$], which was significant for males [41.8% (33/79) vs 22.8% (18/79), $P=0.011$] but not for females [36.8% (7/19) vs 31.6% (6/19), $P=1.000$] (Table 2), when comparing men and women separately.

Influencing factors of pre-hospital delay of ≥1h at the second AMI

A pre-hospital delay of <1 hour accounted for 16.3% (16/98) of patients and a pre-hospital delay of ≥1 hour accounted for 41.8% (41/98) of patients at both the first and second AMI (Table 3). At the second AMI, 92.0% (23/25) of patients with atypical symptoms and 53.4% (39/73) of patients with typical symptoms had a pre-hospital delay of ≥1 hour, and the difference was statistically significant ($P=0.001$), and when comparing males and females separately, the difference was significant for males

[88.9% (16/18) vs 52.5% (32/61), $P = 0.006$] but not for females [100.0% (7/7) vs 58.3% (7/12), $P=0.106$]. Univariate logistic regression analysis showed that atypical symptoms were associated with pre-hospital delay of ≥ 1 hour at the second AMI (OR=10.026, 95% IC 2.201-45.671, $P=0.003$); Multivariate logistic regression analysis showed that atypical symptoms were independent risk factors for pre-hospital delay of ≥ 1 hour at the second AMI (OR=10.808, 95% IC 2.262-51.651, $P=0.003$).

Discussion

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide, especially for patients with recurrent AMI (Reed, Rossi, & Cannon, 2017). The recurrence time of AMI varies. In this retrospective cohort study, half of the patients recurred within 15 months after the first AMI, women within 9 months and men within 21 months, respectively. Patients who recurred within one year after the first AMI accounted for 43.9% of all recurred patients. These indicate that the recurrence rate is highest within one year after the first AMI, and female patients are more likely to recur in a shorter period of time than male patients. The results are similar to the previous studies. According to a study in Northern Sweden (Stromback, Vikman, Lundblad, Lundqvist, & Engstrom, 2017), women suffered their second AMI within a shorter time interval than men do. Within 16 months of their first AMI, 50% of women had a second AMI. While the corresponding time interval for men was 33 months. According to a study in England (Smolina, Wright, Rayner, & Goldacre, 2012), for all survivors of the first AMI, the risk of a second AMI was highest during the first year and the cumulative risk increased gradually thereafter. For men, 1- and 7-year cumulative risks were 5.6% and 13.9%; for women, they were 7.2% and 16.2%.

Factors, such as age, PCI and comorbidity, affecting the recurrence of AMI have been reported (Smolina et al., 2012). Considering the patient's recurrence rate being highest within one year after the first AMI, we further investigated which factors affected the patient's recurrence within one year after the first AMI. Multivariate logistic regression analysis showed that patients who did not undergo PCI during the first AMI were more likely to recur within one year. Among patients who recurred within one year after the first AMI, 28.3% of patients underwent PCI at the first AMI, and 84.4% patients did not. Therefore, patients who have not undergone PCI during the first AMI should be alert

to the possibility of recurrence if they develop symptoms associated with AMI within one year.

Consistent with previous studies (Kirchberger et al., 2016), patients at the first and second AMI presented with typical symptoms (persistent chest tightness or chest pain for more than 20 minutes) mostly in this study. Nearly half of the patients had inconsistent symptoms when comparing the first and second AMI. Patients with atypical symptoms of the second AMI decreased compared with those of the first AMI, especially in men. Previous studies have shown that the prevalence of diabetes in women is higher than that of men (Stromback et al., 2017) and patients with diabetes have more atypical symptoms (Canto et al., 2012), which result in more women with atypical symptoms than men in patients with AMI (Canto et al., 2012; Coventry, Finn, & Bremner, 2011). When presented with atypical symptoms in patients with AMI, pre-hospital delay will be prolonged, which has been confirmed in some previous studies (Canto et al., 2012; Stegmayr et al., 2003). However, these studies are completed without a clear distinction between the first and second AMI. Considering that the second AMI has a higher mortality rate than that of the first AMI, and when the patient has a history of AMI and treatment, the factors affecting pre-hospital delay may change, we specifically target the influencing factors of pre-hospital delay of the second AMI. In this study, univariate and multivariate logistic regression analysis showed that atypical symptoms prolonged the pre-hospital delay of the second AMI, which is consistent with previous studies. In addition, factors such as gender, age, and diabetes were not significantly associated with pre-hospital delay at the second AMI. However, previous studies, without a clear distinction between the first and second AMI, have shown that women (Jager et al., 2017; Meyer et al., 2019; Stehli et al., 2019), advanced age (Mohan et al., 2018; Wechkunanukul, Grantham, & Clark, 2017), diabetes (Jager et al., 2017) lead to prolonged pre-hospital delay. Considering that patients with cardiopulmonary diseases (arrhythmia, heart valve diseases, congenital heart diseases, or chronic bronchitis et al.) may have attribution error in the symptoms associated with AMI, and that patients with pre-hospital delay at the first AMI may influence the decision at the second AMI, and that the interval between the first and second AMI may also affect the judgment of the second AMI, we included these factors in multivariate logistic regression analysis. However, the results showed that these factors had no significant association with pre-hospital delay at the

second AMI.

Previous studies defined pre-hospital delay differently as more than 2 hours (Angerud et al., 2013), 3 hours (Perkins-Porrás et al., 2009), 5 hours (Farshidi, Rahimi, Abdi, Salehi, & Madani, 2013), or 6 hours (Mohan et al., 2018) from the onset of symptoms of AMI to the first medical contact. In order to reduce the area of myocardial infarction, the time of myocardial ischemia should be controlled within a relatively short period of time. Especially for STEMI, the total ischemic time should be controlled within 120 minutes, preferably within 60 minutes. Therefore, this study defined pre-hospital delay as ≥ 1 hour from the onset of AMI to the first medical contact. The results of this study showed that 16.3% (16/98) of patients had a pre-hospital delay of <1 hour and 41.8% (41/98) of patients had a pre-hospital delay of ≥ 1 hour in both the first and second AMI, indicating that pre-hospital delay is common phenomenon. Pre-hospital delay is worldwide problem. The delay time varies from country to country. 42% of patients in India delay more than 6h (Mohan et al., 2018). 32.92% of patients in China delay more than 5 hours (Farshidi et al., 2013). 36% of patients in Malaysia delay more than 3 hours (Lim et al., 2019). More than half of patients in Sweden delay more than 2 hours (Angerud et al., 2013). More than half of patients in Andalusian delay more than 1 hour (Daponte-Codina et al., 2016). The average delay time is 3.4 h (Wechkanukul et al., 2017). Pre-hospital delay persist, and a series of improvement measures do not show significant effects (Bett, Tonkin, Thompson, & Aroney, 2005; Mooney et al., 2012). Previously, the researchers conducted a pre-hospital delay trend study (Saczynski et al., 2008) in Massachusetts for more than two decades, and the results showed no substantially changes in pre-hospital delay during the study period 1986-2005.

Conclusions

The results of this study showed that the majority of patients who did not undergo PCI during the first AMI recurred within one year, and nearly half of the patients did not present with the same symptoms between the first and second AMI, and atypical symptoms prolonged pre-hospital delay at the second AMI. Therefore, if atypical symptoms appear within one year after the first AMI for patients who did not undergo PCI, emergency medical services should be sought in time to reduce the pre-hospital delay.

Limitations and future research directions

All data of this study were extracted from

medical records, collected by different physicians, which may bias the data. In addition, 11.7% (13/111) of patients were not included in this study due to insufficient data, which also had an impact on the results of the study. In this study, symptoms of AMI such as pain in upper abdomen, arm, jaw and neck were classified as atypical symptoms, while some studies previously categorized these symptoms as typical symptoms of myocardial ischemia (Roffi et al., 2016; Canto et al., 2012). This means that when comparing with previous research results, we must be aware of the differences. In the future, we will increase the number of cases, collect data from multiple hospitals to take multi-center research, and incorporate more influencing factors to make the research more comprehensive to better guide clinical practice.

Implications

1. The majority of patients who did not undergo PCI during the first AMI recurred within one year. Therefore, patients who did not undergo PCI during the first AMI should be informed that they are relatively easy to recur within one year. If symptoms occur, seek medical attention promptly.
2. Nearly half of the patients did not present with the same symptoms between the first and second AMI. Patients should be informed of this to avoid delaying medical treatment when AMI recurs.
3. Atypical symptoms prolonged pre-hospital delay at the second AMI. Patients should be made aware that even if atypical symptoms appear, it may be recurrence of AMI.

Authors' contributions

Peng Wang participated in study design, data collection, statistical analysis, data interpretation, manuscript preparation and literature search. Yijuan Huang participated in study design, statistical analysis, data interpretation and funds collection.

Conflict of interest

The authors declare that there is no conflict of interest.

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Table 1. Univariate and multivariate logistic regression analysis of factors associated with an interval of <12 months between the first and second acute myocardial infarction (AMI).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender						
Male						
Female	1.549	0.567-4.233	0.394	0.803	0.225-2.866	0.736
Age at the first AMI						
<60						
60~	3.628	1.405-9.366	0.008	2.162	0.747-6.257	0.155
Smoking after the first AMI						
No						
Yes	0.616	0.399-0.952	0.029	0.688	0.389-1.216	0.198
Symptoms at the first AMI						
Typical						
Atypical	0.692	0.304-1.576	0.381	0.749	0.301-1.863	0.534
Diabetes at the first AMI						
No						
Yes	0.804	0.351-1.838	0.604	0.764	0.301-1.939	0.571
Cardiopulmonary diseases ^a at the first AMI						
No						
Yes	1.458	0.653-3.253	0.358	0.724	0.269-1.947	0.522
PCI at the first AMI						
Yes						
No	4.173	1.786-9.750	0.001	3.257	1.252-8.476	0.016

OR: odds ratio; CI: confidence interval; Cardiopulmonary disease ^a: refer to a history of arrhythmia, heart valve diseases, congenital heart diseases, or chronic bronchitis in this study.

Table 2. Type of symptoms and gender differences at the first and second acute myocardial infarction (AMI).

Symptoms	First AMI			p-Value	Second AMI			p-Value	p-Value	p-Value	p-Value
	Male n (%)	Female n (%)	Total n (%)		male vs female	Male n (%)	Female n (%)				
Typical	79 (80.6)	19 (19.4)	98 (100)	0.415	79 (80.6)	19 (19.4)	98 (100)	0.207	0.033	0.011	1.000
Atypical	46 (58.2)	13 (68.4)	59 (60.2)		61 (77.2)	12 (63.2)	73 (74.5)				
	33 (41.8)	6 (31.6)	39 (39.8)		18 (22.8)	7 (36.8)	25 (25.5)				

Table 3. Crosstab; pre-hospital delay at the first and second acute myocardial infarction (AMI).

Pre-hospital delay	Second AMI <1 h n (%)	Second AMI 1h~ n (%)	Total n (%)
First AMI <1 h n (%)	16 (43.2)	21 (56.8)	37 (100)
First AMI 1h~ n (%)	20 (32.8)	41 (67.2)	61 (100)

h: hour.

Table 4. Symptom types affect pre-hospital delay at the second acute myocardial infarction (AMI) in men and women.

Pre-hospital delay	Atypical			p-Value	Typical			p-Value	p-Value	p-Value	p-Value
	Male n (%)	Female n (%)	Total n (%)		male vs female	Male n (%)	Female n (%)				
<1 h n (%)	18 (72.0)	7 (28.0)	25 (100.0)	1.000	61 (83.6)	12 (16.4)	73 (100.0)	0.709	0.001	0.006	0.106
1h~ n (%)	2 (11.1)	0 (0.0)	2 (8.0)		29 (47.5)	5 (41.7)	34 (46.6)				
	16 (88.9)	7 (100.0)	23 (92.0)		32 (52.5)	7 (58.3)	39 (53.4)				

h: hour.

Table 5. Univariate and multivariate logistic regression of factors associated with a pre-hospital delay of ≥ 1 hour at the second acute myocardial infarction (AMI).

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender						
Male						
Female	1.808	0.592-5.523	0.298	1.065	0.296-3.835	0.923
Age at the second AMI						
<60						
60~	1.636	0.694-3.856	0.261	2.225	0.761-6.508	0.144
Symptoms at the second AMI						
Typical						
Atypical	10.026	2.201-45.671	0.003	10.808	2.262-51.651	0.003
Diabetes at the second AMI						
No						
Yes	0.64	0.276-1.486	0.299	0.579	0.226-1.484	0.255
Cardiopulmonary diseases ^a at the second AMI						
No						
Yes	0.771	0.338-1.758	0.537	0.505	0.189-1.348	0.172
Pre-hospital delay ≥ 1 h at the first AMI						
No						
Yes	1.562	0.673-3.625	0.299	1.578	0.611-4.075	0.346
Interval <12 M between the first and second AMI						
No						
Yes	1.239	0.542-2.83	0.611	1.304	0.509-3.338	0.58

OR: odds ratio; CI: confidence interval; h: hour; M: months; Cardiopulmonary diseases^a: refer to a history of arrhythmia, heart valve diseases, congenital heart diseases, or chronic bronchitis in this study.