Factors Associated with Symptom-to-Door Delay in Patients with ST-Segment Myocardial Infarction: A Systematic Review

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Abbreviations:
D2B: door-to-balloon
PICO: population-intervention-comparison group-outcome strategy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
S2D: symptom-to-door
STEMI: ST-segment elevation myocardial infarction

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Abstract

Background: Decreasing symptom-to-door (S2D) delay is of vital importance for reducing morbidity and mortality in patients with ST-segment elevation myocardial infarction (STEMI). The factors associated with S2D delay in STEMI patients have not been well-characterized.

Objectives: The aim of this study was to identify factors associated with S2D delay in patients with STEMI.

Methods: The PubMed, CINAHL, and Embase databases were searched for data. References from the selected articles and relevant background papers were also manually searched to identify additional eligible studies. The included articles were reviewed and assessed for risk of bias. The level of evidence for each identified factor was evaluated using a semiquantitative synthesis.

Results: Twelve (12) papers were included in the review. Factors associated with S2D delay were complex and could be divided into sociodemographic, clinical history, and onset characteristics. The level of evidence regarding female sex and diabetes was strong, and the evidence was moderate regarding older age, smoking, history of hypertension, self-transport, or referral.

Conclusions: Female sex, older age, previous diabetes, previous hypertension, smoking, and self-transport are all strong or moderate risk factors for S2D time delay in patients with ST-segment myocardial infarction. More efforts should be made to educate at-risk populations concerning symptoms of STEMI and the importance of seeking early medical assistance.

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Introduction

A longer total ischemic time, measured from symptom onset to reperfusion, in patients with ST-segment elevation myocardial infarction (STEMI) results in more severe myocardial infarction size and a poorer clinical prognosis. Every 30 minutes of treatment delay increases the death risk by 7.5%.[1] Reducing the total tissue ischemic time remains an important focus of health care systems world-wide to reduce morbidity and mortality.[2] The American College of Cardiology (ACC; Washington, DC USA) and American Heart Association (AHA; Dallas, Texas USA) guidelines suggest a total ischemic time of 120 minutes or less, consisting of symptom-to-door (S2D) time and door-to-balloon (D2B) time.[3] Many effective strategies have been developed to reduce the D2B time; more efforts should be made to reduce the S2D delay.[1,4]

Several studies have explored factors related to S2D delay, but the results from these studies are inconclusive. Some studies have identified female sex,[5–9] diabetes,[5,7,8,10] and weekday[6] as potential risk factors for a prolonged delay in STEMI patients. In contrast, other studies did not indicate that female sex,[10,11] diabetes,[11,12] or weekday[5,10,12] were associated with S2D delay. The identification of factors related to S2D delay is important. To the authors' knowledge, no attempts have been made to systematically review these factors.

The aim of this review was to identify prehospital factors associated with S2D delay in patients with STEMI.

Methods

Prespecified Systematic Review

A systematic review protocol was completed in PROSPERO (CRD42020159207) before beginning the review process. The review process was organized in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

Search Method and Selection Criteria

The CINAHL (EBSCO Information Services; Ipswich, Massachusetts USA), PubMed (National Center for Biotechnology Information, National Institutes of Health; Bethesda, Maryland USA), and Embase (Elsevier; Amsterdam, Netherlands) databases were systematically searched to identify studies examining the relationship between prehospital factors and S2D time in patients with acute ST-segment myocardial infarction. The inclusion criteria were as follows, using the PICO (population-intervention-comparison group-outcome) strategy:

P	Patients presented to the emergency department confirmed with STEMI
I	Factors reported associated with S2D time
C	Shorter S2D time
O	Longer S2D time

The following search strategy was constructed with the assistance of qualified librarians: search (((((((prehospital[Title/Abstract]) OR pre hospital[Title/Abstract]) OR time to treatment [Title/Abstract]) OR delayed treatment[Title/Abstract]) OR treatment delay[Title/Abstract]) OR therapy delay[Title/Abstract])) AND ((((ST segment elevation[Title/Abstract]) OR ST elevation [Title/Abstract])) AND Myocardial Infarction [Mesh]).

The search was limited to studies in the English language. No date restrictions were imposed, and the search was completed on May 4, 2022. In addition, references from the selected reports and reference papers were manually searched to identify additional eligible studies.

Duplicate studies were removed. Then, the titles of the retrieved studies were screened to identify potentially relevant studies; if there were any doubts, the abstract was also screened against the inclusion criteria. Studies that appeared to meet the inclusion criteria were then subjected to full-text screening, and their reference lists were checked for additional studies. The reference lists of relevant reviews identified through the search were also searched for additional studies.

Study Quality Assessment

All remaining studies fulfilling the inclusion criteria were evaluated by the Joanna Briggs Institute (JBI; University of Adelaide; Adelaide, South Australia) checklists for cohort studies to assess the risk of bias.[13]

Data Extraction

Two reviewers independently extracted and collected data from the included studies using a standardized data extraction protocol. Data were extracted regarding the type of association that was identified for each examined factor. An association was deemed to exist when the threshold for significance given in each study had been reached. In cases where no threshold for significance was given, $P < .05$ was specified. Semiquantitative synthesis of the data obtained was conducted based on the procedure described by Wibring, et al.[14] Three criteria were used to determine the level of evidence for each reported factor: (1) number of studies evaluating the factor, (2) scored quality of each study evaluating the factor, and (3) the consistency between studies regarding reported association between factor and outcome. If a factor fulfilled the criteria for multiple levels of evidence, the highest level was chosen. The definition of each level of evidence is shown in Table 1. The recommendations of the Cochrane and PRISMA guidelines were followed.

Level of Evidence	Criteria
Strong Evidence	Association found in ≥75% studies evaluating the variable, at least one high quality
Moderate Evidence	Association found in >50% of the studies evaluating the variable
Inconclusive Evidence	Association found in ≤50% of the studies evaluating the variable
No Evidence	No association found in >75% studies evaluating the variable

Table 1. Criteria for Each Level of Evidence

Results

Study Identification

The search of the databases yielded 1,831 unique references; 1,770 studies were excluded after title and abstract screening. Two studies were added by cross-reference checking, and thus, 63 studies remained for full-text screening. After full-text screening, 12 studies were found to meet all the inclusion criteria. In those cases, the articles judged to be the most relevant to the objective of this review were included (Figure 1).

Study Characteristics

In total, 12 studies were included; 61 factors were examined within those articles, (Table 2[5–12,15–18]), and 28 of those factors were assessed in two or more studies (Table 3).

Level of Evidence

The results of the semiquantitative synthesis are presented in Table 3. There was strong evidence for the presence of S2D delay in patients with STEMI who were also diabetes patients or of female sex. The level of evidence in regard to factors including older age, smoking, history of hypertension, self-transport, or referral was moderate. The evidence was inconclusive regarding the distance from the emergency room, body mass index, living alone, alcohol use, lack of medical insurance, education time < nine years, symptom onset weekday, typical chest pain, symptom onset time, awareness of acute myocardial infarction, previous coronary artery bypass grafting, myocardial infarction, percutaneous coronary intervention, stroke, dyslipidemia, and family history of coronary artery disease. There was no evidence to support the effects of income, history of chronic kidney disease, symptom-onset-situation, symptom-onset-location, localization of myocardial infarction, or responses to symptoms of myocardial infarction on S2D delay.

Some factors showed an association with S2D delay but were only evaluated in one study; those factors were beyond the scope of this research. Those factors included the following: absence of previous coronary artery disease, number of children < three,

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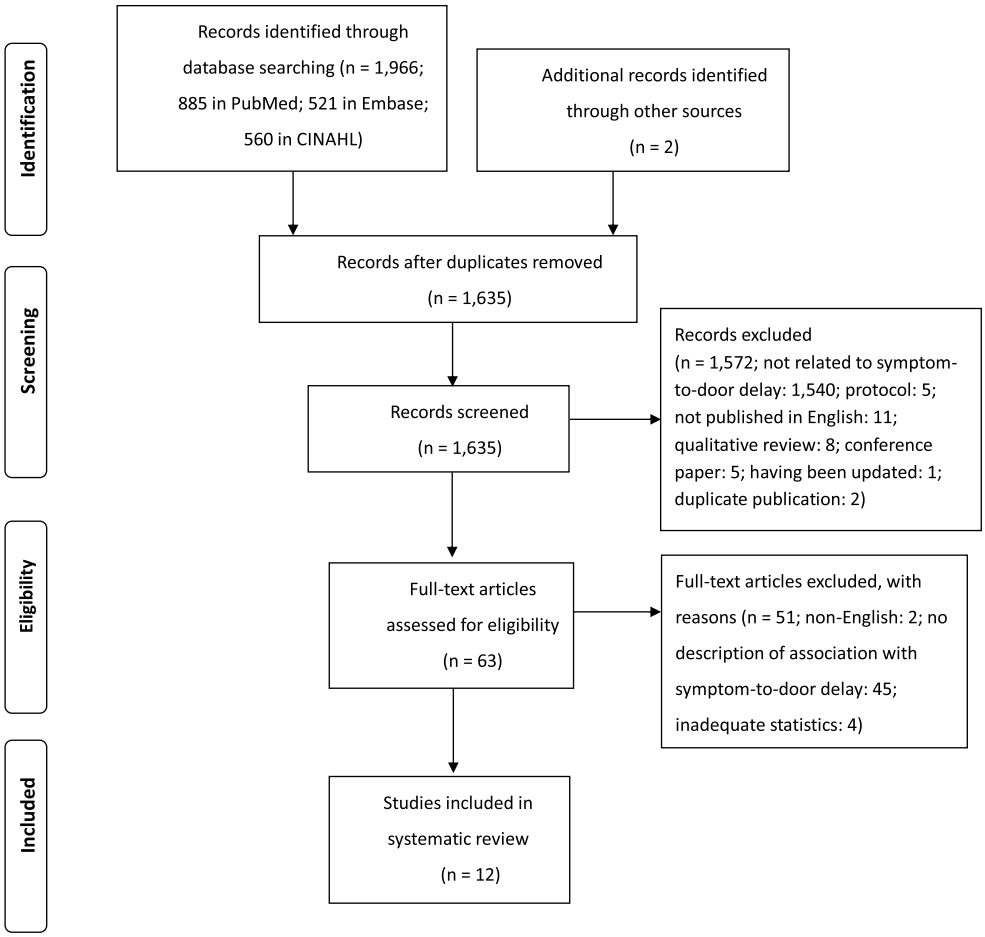

Figure 1. PRISMA Flow Diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

history of aspirin use, beta-blocker use,[5] anxiety concerning symptoms, type of symptom onset, interpretation of symptoms,[6] breathlessness, vomiting, ventricular arrhythmias,[7] presenting shoulder/jaw pain symptoms, diaphoresis,[8] longest linger, pain duration, opium abuse, infarct-related artery,[9] peripheral vascular disease, heart failure, pulmonary embolism, deep venous thrombosis, valvular surgery, chronic obstructive pulmonary disease,[11] and subjective opinion that the event was not an acute myocardial infarction.[18] Moreover, ethnicity was examined in four studies,[8,9,16,18] as there were different races in each study. That factor was also excluded from this study.

Discussion

The major finding from this systematic review was that factors associated with S2D time in STEMI patients were complex and could be divided into sociodemographic, clinical history, and onset characteristics.

According to the included studies, females more often have longer S2D times, which could be explained by women tending to report chest pain less often than men and women having presentation of symptoms that are usually atypical, such as nausea, back pain, and shortness of breath, which they attribute to common health disorders instead of myocardial infarction.[17,18] Prolonged delay in seeking hospital treatment among elderly individuals likely occurs because they misdiagnosed the symptoms of STEMI as symptoms of aging.[8] Furthermore, the relatively diminished sensation, high frequency of cognitive impairment, difficulty moving, and dependence on relatives for transportation further challenge elderly patients' ability to seek care earlier.[7]

Diabetes, hypertension, and dyslipidemia are the main risk factors for STEMI, and patients with those diseases had longer S2D times, which could be explained by the association with silent/painless myocardial infarction.[8] Additionally, some studies have proposed that diabetes may delay S2D time because of poorer sensory feelings caused by diabetic neuropathy.[7] Other medical history variables, such as myocardial infarction history, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous stroke, and family history of coronary artery disease, were found to be related to shorter prehospital delay. Because these patients may be well-aware of the significance of a short delay, they are more easily alarmed, more skilled at recognizing symptoms, and more likely to get to the emergency center quickly.[7,17] However, several other studies reported an inverse relationship between previous angina and S2D delay.[17] This finding can be explained by the fact that patients with previous angina may have a higher threshold of pain because of their chronic condition and assume that the pain will resolve itself as it has in the past. In addition, patients may first attempt to self-treat their symptoms with drugs, particularly nitrates, causing further delay before seeking care.

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Study	Participants Included	Outcome Measurement Index	Factors Examined	Assessed Quality
Sarı, et al[5] (2008)	439 patients from a local clinic hospital (n = 209, 47.6%) and tertiary fully equipped cardiovascular center (n = 230, 52.4%) between September 2003 and August 2004	S2D Time (minute) (mean ± SD)	Female Age ≥55 Education time <nine years Absence of previous coronary artery disease Diabetes Current smoker Marital status (single/divorced) Household annual income ≥$15,000 Number of children <three Weekday Hypertension Family history of coronary artery disease Alcohol use History of aspirin use Beta-blocker use Localization of myocardial infarction	High Quality
Momeni[6] 2012	162 patients in Dr Heshmat Hospital between August 2010 and May 2011	S2D Time (hours) (mean ± SD)	Female Marriage status single Education level Monthly income Living area: rural Mode of transport: other Type of symptom onset: gradual onset of pain repeating during days Admission day: weekend or holidays Interpretation of symptoms: cardiac in origin versus others Perceiving symptoms: not so serious Anxiety about symptoms: not very	High Quality
Peng, et al[7] (2015)	1,088 patients from the Emergency Center of Anzhen Hospital from March 2004 to March 2007	S2D Time (minute) (median)	Age Male Education (junior high school and below) Diabetes Current smoker Vertigo Onset at day (6:00-18:00) Onset at home Mode of transport Ventricular arrhythmias Vocation Hypertension Myocardial infarction history Stroke Current drinker Chest symptoms Radiating pain Vomiting Shortness of breath Conscious disturbance	High Quality

Table 2. Study Characteristics and Main Results of the Included Studies (*continued*)

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Study	Participants Included	Outcome Measurement Index	Factors Examined	Assessed Quality
Wah, et al[8] (2017)	3,848 patients from the Singapore Myocardial Infarction Registry between 2010 and 2012	S2D Time (cut-off of ≤120 minutes vs >120 minutes)	Age Female Ethnicity Past medical history hypertension Past medical history diabetes mellitus Past medical history acute myocardial infarction Past medical history percutaneous transluminal coronary angioplasty/percutaneous coronary intervention Smoking status: nonsmoker Presenting symptoms chest pain Presenting symptoms back pain Presenting symptoms epigastric pain Presenting symptoms breathlessness Presenting symptoms diaphoresis After office hours presentation Singapore Civil Defense Force ambulance utilization Past medical history hyperlipidemia Past medical history coronary arterial bypass graft Body mass index Presenting symptoms jaw pain Presenting symptoms shoulder pain Presenting symptoms syncope Typical presentation	High Quality
Poorhosseini, et al[9] (2019)	2,103 consecutive STEMI patients at a tertiary cardiac center, Tehran, Iran between January 2016 and December 2018	S2D Time (minute) (median)	Female sex Higher educational level Be transferred to the hospital by Emergency Medical Service Description of symptoms as atypical or typical chest pain Epigastric pain History of diabetes and hypertension Longest linger Pain duration Pain onset time (0 to 6 or 7 to 12) Age Body mass index Marital status Ethnicity Insurance Physical activity status History of coronary stenting History of coronary artery bypass graft Hyperlipidemia Smoking Opium abuse Family history of coronary artery disease Cerebrovascular event Chronic kidney disease History of myocardial infarction Infarct related artery	High Quality

Table 2. Study Characteristics and Main Results of the Included Studies (*continued*)

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Study	Participants Included	Outcome Measurement Index	Factors Examined	Assessed Quality
Park, et al[10] (2012)	423 patients from Samsung Changwon Hospital in Korea from January 2008 to December 2010	S2D Time (cut-off of ≤180 minutes vs >180 minutes)	Body mass index (≥23.3 kg/m^2) Diabetes Level of education Symptom-onset-time (day [6am-6pm] or night [6pm-6am]) Referral hospital Transport vehicle Age Sex Typical chest pain Hypertension Smoking Dyslipidemia Previous coronary artery bypass graft Previous myocardial infarction Previous percutaneous coronary intervention Previous ischemic heart disease Family history of congenital heart disease History of cerebrovascular accident Residency Living with family Companion Awareness of acute myocardial infarction Responses to symptoms (home or folk remedy, direct contact to hospital) Symptom-onset-day (weekday, weekend) Symptom-onset-situation (rest, physical activities) Symptom-onset-location (home, other)	High Quality
Hafiz, et al[11] (2013)	366 patients at emergency department of tertiary care teaching hospital from 2005 to 2009	S2D Time (minute) (median)	Contacting a physician first Presentation during on-hours Personal mode of transportation Sex: male versus female Diabetes mellitus Hypertension Dyslipidemia Coronary artery disease Cerebrovascular accident Peripheral vascular disease Chronic kidney disease Deep venous thrombosis Valvular surgery Smoker Chronic obstructive pulmonary disease Family history of coronary artery disease Pulmonary embolism Heart failure	High Quality

Table 2. Study Characteristics and Main Results of the Included Studies (*continued*)

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Study	Participants Included	Outcome Measurement Index	Factors Examined	Assessed Quality
Kim, et al[12] (2017)	350 patients at six PCI-capable tertiary hospitals in various regions of Korea from July 2014 to June 2015	S2D Time (cut-off of ≤120 minutes vs >120 minutes)	Sex Age Education level Previous cardiovascular disease Knowledge of disease for acute myocardial infarction Use of Emergency Medical Service Referral hospital Making decision Medical insurance Residency region Living with others Smoking status Alcohol use status Body mass index Family history of cardiovascular disease Hypertension Diabetes mellitus Dyslipidemia Previous percutaneous coronary intervention Previous stroke Symptom-onset-time, weekend and night time Major symptom, chest pain	High Quality
Austin, et al[15] (2014)	1,876 patients at a high-volume UK PPCI center in the north of England from March 2008 to November 2011	S2D Time (cut-off of ≤30 minutes vs >30 minutes)	Unmarried Self-presentation Female Distance from emergency room Age Previous coronary artery bypass grafting Diabetes Ex-smoker Current smoker Infarct location	Acceptable Quality
Brown, et al[16] (2016)	1,020 patients at Sandwell and West Birmingham Hospitals between January 2008 and January 2013	S2D Time (minute) (median)	Sex Ethnicity	Acceptable Quality
Margolis, et al[17] (2018)	2,203 patients at the Tel-Aviv Sourasky Medical Center between January 2008 and December 2016	S2D Time (cut-off of ≤120 minutes vs >120 minutes)	Age Female sex Diabetes mellitus First myocardial infarction Hypertension Negative familial history of coronary artery disease	Acceptable Quality

Table 2. Study Characteristics and Main Results of the Included Studies (*continued*)

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Study	Participants Included	Outcome Measurement Index	Factors Examined	Assessed Quality
Weininger, et al[18] (2021)	218 patients at four New York City Hospitals between January 2009 and August 2012	S2D Time (cut-off of ≤90 minutes vs >90 minutes)	Female sex Education College and above (ref) At least high school diploma Less than high school Subjective opinion event was not an acute myocardial infarction Age White race (versus black/other race) Diabetes mellitus Insured Employment Atypical symptoms	Acceptable Quality

Table 2. *(continued).* Study Characteristics and Main Results of the Included Studies
Abbreviation: S2D, symptom-to-door.

Factor Examined	High Quality Study		Acceptable Quality Study		Number of Studies	Level of Evidence
	Association	No Association	Association	No Association		
Socio-Demographic Characteristics						
Female	5, 6, 7, 8, 9,12	10, 11	17, 18	15, 16	12	Strong
Age	5, 7, 8	10	17	15, 18	7	Moderate
Distance from emergency room	6	10, 12		15	4	Inconclusive
Body mass index	9, 10	8, 12			4	Inconclusive
Living alone	6, 9	5, 10, 12	15		6	Inconclusive
Medical insurance	9	12		18	3	Inconclusive
Income	6	5			2	No Evidence
Education time <nine years	5, 6, 7, 10		18		5	Inconclusive
Awareness of acute myocardial infarction	10, 12	5		15	4	Inconclusive
Clinical History Characteristics						
Chronic kidney disease			9, 11		2	No Evidence
Previous coronary artery bypass grafting		8, 9, 10		15	4	Inconclusive
Previous myocardial infarction	8	7, 9, 10	17		5	Inconclusive
Previous percutaneous coronary intervention	8	9, 10, 12			4	Inconclusive
Previous stroke		7, 9, 10, 11, 12			5	Inconclusive
Diabetes	5, 7, 8, 10	11, 12	17	15, 18	9	Strong
Hypertension	8	5, 7, 10, 11, 12		17	7	Moderate
Dyslipidemia		10, 8, 9, 11, 12			5	Inconclusive
Smoking	5, 8	9, 10, 11, 12	6	15	8	Moderate
Alcohol use		5, 7, 12			3	Inconclusive
Family history of coronary artery disease		5, 9, 10, 11, 12		17	6	Inconclusive
Onset characteristics						
Mode of transfer (ambulance/ self-transport/referral)	6, 7, 8, 10, 11, 12		15		7	Moderate
Weekday	6	5, 10, 12			4	Inconclusive

Table 3. Level of Evidence for Each Factor (*continued*)

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Factor Examined	High Quality Study		Acceptable Quality Study		Number of Studies	Level of Evidence
	Association	No Association	Association	No Association		
Symptom-onset-situation (rest/physical activities)		9, 10			2	No Evidence
Symptom-onset-location (home/others)	7	10			2	No Evidence
Symptom-onset-time (day/night)	7, 8, 10, 11	12			5	Inconclusive
Localization of myocardial		5		15	2	No Evidence
Typical chest pain	6, 8	10, 7, 12		18	6	Inconclusive
Responses to symptoms (home or folk remedy, direct contact to hospital)	11	10			2	No Evidence

Table 3. *(continued).* Level of Evidence for Each Factor

Onset characteristics were also important factors related to S2D delay. Patients who were not transported by ambulance and first contacted a private physician instead of directly presenting to the emergency department tended to have delayed arrival at the emergency department.[6–8,11] These patients were more likely to present during on-hours and have less awareness of STEMI, and they did not believe they were suffering from myocardial infarction. Additionally, onset during the night had longer S2D times, which could be explained by patients being prone to going to the hospital the next day because it is troublesome to travel there at night. Patients with onset at home had a longer prehospital delay as a result of bystander intervention.[7]

Limitations

Initial statistical pooling and meta-analyses were considered for potential factors associated with S2D time in patients with STEMI. However, during the process of screening and quality assessment of potentially relevant studies, there were some difficulties due to methodological heterogeneity regarding statistics and outcome measurement indexes. A semiquantitative synthesis of data was used, obtained based on the procedure described by Wibring, et al.[14]

There may be a risk of bias for systematic reviews due to the inclusion of English-only articles; potential benefits and problems related to language restriction have been reported in other studies.[19,20] In addition, to reduce the heterogeneity of the studies, studies that collected data during the coronavirus disease 2019/COVID-19 peak pandemic were not included.[21] Due to the limited database access, small number of included studies, and limited sample size, the conclusions of this study need to be further studied. Additionally, unpublished results were not reported in this review, since there may be some quality issues in unpublished studies that would be addressed during editorial or peer review.[22]

Conclusions

Female sex, older age, previous diabetes, previous hypertension, smoking, and self-transport are all strong or moderate risk factors for S2D delay in patients with STEMI. Greater efforts are needed to educate high-risk populations regarding the symptoms of STEMI and the importance of seeking medical help as soon as possible to reduce the delay of treatment and reduce morbidity and mortality.

Supplementary Materials

To view supplementary material for this article, please visit https://doi.org/10.1017/S1049023X23006039

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