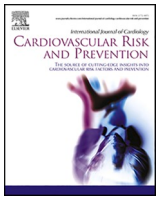
International Journal of Cardiology Cardiovascular Risk and Prevention 21 (2024) 200286

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



Symptom-to-balloon time and risk of ventricular arrhythmias in patients with STEMI undergoing percutaneous coronary intervention: The VERY-STEMI study

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ARTICLE INFO

Handling editor: D Levy

Keywords:
Ventricular arrhythmia
Major adverse cardiovascular event
ST-Segment elevation myocardial infarction
Symptom-to-balloon time
Real-world study

ABSTRACT

Background: Ventricular arrhythmias (VAs) mainly occur in the early post-myocardial infarction (MI) period. However, studies examining the association between total myocardial ischemia time interval and the risk of new-onset VAs during a long-term follow-up are scarce.

Methods: This study (symptom-to-balloon time and **VE**ntricular a**R**rh**Y**thmias in patients with **STEMI**, VERY-STEMI study) was a multicenter, observational cohort and real-world study, which included patients with ST-segment elevation MI (STEMI) undergoing percutaneous coronary intervention (PCI). The primary endpoint was cumulative new-onset VAs during follow-up. The secondary endpoints were the major adverse cardiovascular events (MACE) and changes in left ventricular ejection fraction (ΔLVEF, %).

Results: A total of 517 patients with STEMI were included and 236 primary endpoint events occurred. After multivariable adjustments, compared to patients with S2BT of 24 h-7d, those with S2BT $\leq$ 24 h and S2BT $>$ 7d had a lower risk of primary endpoint. RCS showed an inverted U-shaped relationship between S2BT and the primary endpoint, with an S2BT of 68.4 h at the inflection point. Patients with S2BT $\leq$ 24 h were associated with a lower risk of MACE and a 4.44 increase in LVEF, while there was no significant difference in MACE and LVEF change between the S2BT $>$ 7d group and S2BT of 24 h-7d group.

Conclusions: S2BT of 24 h-7d in STEMI patients was associated with a higher risk of VAs during follow-up. There was an inverted U-shaped relationship between S2BT and VAs, with the highest risk at an S2BT of 68.4 h.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and health loss worldwide [1]. According to the Report on Cardiovascular Health and Diseases in China, the prevalence of CVD in China continues to rise, and CVD still ranked first in the proportion of disease deaths among urban and rural residents in 2019 [2]. Acute myocardial infarction (AMI), a severe manifestation of CVD, is the leading cause of sudden death worldwide [3]. Therefore, early identification of high-risk patients and the formulation of individualized prevention and treatment for specific groups are essential to improve patient prognosis.

With advances in pharmacology, reperfusion, and prevention strategies, AMI mortality has initially decreased globally over the past 20 years, with in-hospital and 1-year mortality for ST-elevation myocardial infarction (STEMI) decreasing by 5–6% and 7–18%, respectively [4]. However, the mortality rate of AMI in China has shown a rapid rising trend over the past 20 years [2]. The China-PEACE study showed that during the decade 2001–2011, the number of hospital admissions due to STEMI in China increased significantly, but the in-hospital mortality did

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https://doi.org/10.1016/j.ijcrp.2024.200286
Received 27 February 2024; Received in revised form 9 May 2024; Accepted 12 May 2024
Available online 16 May 2024

Abbreviations

BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
LDL-C	low-density lipoprotein cholesterol
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MI	myocardial infarction
NT-proBNP	NT-pro-brain natriuretic peptide
PCI	percutaneous coronary intervention
RCS	restricted cubic spline
S2BT	symptom-to-balloon time
STEMI	ST-segment elevation myocardial infarction
TG	triglyceride
VA	ventricular arrhythmia

not decrease [5], and the quality and outcome of medical care still needed to be improved [6]. In addition, sex differences are still significant, and women are less likely to receive evidence-based medical treatment, especially reperfusion therapy [7]. This suggests that there is still much space for improvement in the medical quality of STEMI care in China.

Currently, clinical guidelines recommend that primary percutaneous coronary intervention (pPCI) should be performed for STEMI within 12 h of onset and at an early stage (guidelines suggest within 24 h) for STEMI more than 12 h of onset but with ongoing symptoms suggestive of ischemia [3,8]. However, it has been reported that only about 30% of STEMI patients who undergo PCI receive pPCI in China. Besides, many patients in grass-roots areas miss the best PCI opportunity after being transferred to the chest pain center in a PCI qualified hospital due to pre-hospital delay and inter-hospital referral or even refuse PCI [9]. Considering the large number of MI that occurs in China every year, this percentage is relatively low [10]. For STEMI patients who have missed the optimal pPCI treatment window, current research results are mixed and clinical guidelines fail to provide clear recommendations on when to initiate PCI [3,8].

Ventricular arrhythmia (VA) is a common complication of AMI. Sustained ventricular tachycardia (VT), ventricular flutter, and ventricular fibrillation (VF) can lead to sudden cardiac death (SCD) [11]. VA usually occurs in the early post-MI period, and about 5–10% of patients with AMI have sustained VT/VF [12]. Perioperative VAs in STEMI patients undergoing pPCI were significantly associated with increased 90-day mortality [13]. Therefore, prevention or early identification and management of post-STEMI VAs is critical to improving patient outcomes.

Collectively, for STEMI patients who miss the opportunity of pPCI treatment, when to initiate PCI after symptom onset can benefit patients the most, that is, the determination of the optimal threshold of S2BT remains elusive. Besides, the risk of VAs was higher in acute ischemic phase after MI, while limited studies have focused on S2BT (reflecting total myocardial ischemia time) and the long-term risk of VAs in STEMI patients.

Therefore, we designed a multicenter and prospective cohort to explore the association between S2BT and VA risk during follow-up in STEMI patients, so as to provide real-world evidence for clinical decision-making in STEMI in China.

2. Methods

2.1. Study design and population

The VERY-STEMI (Symptom-to-balloon time and **VE**ntricular a**R**-rh**Y**thmias in patients with **STEMI**) study is a multicenter, observational cohort and real-world study. A total of 652 STEMI patients hospitalized in the Department of Cardiology from July 1, 2019 to June 30, 2021 were selected from 6 tertiary medical centers in East China. All patients were older than 18 years and were diagnosed with STEMI according to the 4th Universal Definition of Myocardial Infarction [14]. Patients were excluded if they received thrombolysis therapy before PCI or had other organic heart diseases, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy or congenital heart disease, severe hepatic insufficiency (alanine aminotransferase>3 times the upper limit of reference value) or uremia requiring dialysis, malignant tumors and serious mental diseases. Supplementary Fig. 1 presents the details of the inclusions and exclusions. Five hundred and seventeen patients were included in the final analysis. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and registered on the *ClinicalTrials.gov* website (identifier, NCT04660474). All patients signed informed consent.

2.2. Data collection and grouping

Data were collected through face-to-face communication, hospital information systems, and telephone inquiries, and included: (1) patients' age, sex, type of myocardial infarction, history of hypertension, history of diabetes, history of prior coronary artery disease, family history of CVD, smoking status, drinking status, body mass index (BMI, defined as the weight divided by the square of height (kg/m^2)), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) at admission; (2) patients' symptom-balloon time (S2BT), defined as the interval between symptom onset and the first balloon dilation during PCI; (3) first post-admission laboratory parameters, including fasting blood glucose (FPG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), white blood cell count (WBC), neutrophil count, NT-pro-brain natriuretic peptide (NT-proBNP), and hypersensitive C-reactive protein (hsCRP) level; (3) coronary angiography results, the number of stents implanted and medications during hospitalization; (4) left ventricular ejection fraction (LVEF) measured using the modified Simpson method.

Based on the collected S2BT values, referring to clinical guidelines [3,8,15] and combining the characteristics of the data, the study population was divided into three groups: (1) early revascularization group: S2BT $\leq$ 24 h; (2) late revascularization group: S2BT within 24 h to 7d; (3) very-late revascularization group: S2BT $>$ 7d. In this study, the definition of early revascularization as S2BT $\leq$ 24 h was based on several STEMI management guidelines, which defined "early angiography" as $\leq$24 h after the onset of symptoms of ischemia [3,8]. However, there is no standard criteria for dividing the timing of late and very-late revascularization. This study used 7d as the dividing point of late and very-late revascularization based on several clinical studies [9,16,17], which also used 7d as the dividing point and suggested that the clinical outcomes of patients with STEMI undergoing PCI within 7d and after 7d of onset might be different.

2.3. Endpoint events and follow-up

The primary endpoint event of the VERY-STEMI study was the cumulative risk of ventricular arrhythmias (VAs) during follow-up, including frequent premature ventricular contractions (defined as PVCs >5/min or >500/24 h), sustained or non-sustained ventricular tachycardia, ventricular flutter and ventricular fibrillation [11]. The

primary endpoint events were determined by 24-h Holter electrocardiogram during follow-up. The secondary endpoint consisted of two components: (1) major adverse cardiovascular event (MACE), defined as a composite event of cardiovascular death, fatal or nonfatal stroke, chest pain requiring rehospitalization, or revascularization; (2) changes in LVEF from baseline during follow-up (ΔLVEF). All enrolled patients were followed up at 1, 3, 6, and 12 months after discharge and every 6 months thereafter. It was recommended that Holter electrocardiography be performed at each follow-up visit. Patients with cardiac discomfort were required to undergo Holter electrocardiography and echocardiography. Follow-up time was calculated from the day of PCI to the occurrence of the endpoint event or the end of follow-up (December 31, 2022), whichever came first.

2.4. Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and the one-way ANOVA was used for comparison among the three S2BT groups. Continuous variables with non-normal distribution were represented by median (interquartile range), and comparison among the groups was performed using Kruskal-Wallis test. Categorical data were expressed as frequencies (percentage) and Chi-square test was used for comparison.

The Schoenfeld's residuals method confirmed that there was no evidence of a violation of the proportional hazard assumption for S2BT and the primary endpoint. The log-rank test was used to compare the differences in primary endpoint event among the different S2BT groups, and Kaplan-Meier curves were plotted. Univariable and multivariable Cox regression models were used to assess the hazard ratio (HR) and 95% confidence interval (CI). Furthermore, to clarify the dose-response relationship between S2BT and the primary endpoint, restricted cubic spline (RCS) regression was performed, with the default knots at the 5th, 35th, 65th, and 95th percentiles of S2BT [18]. In addition, subgroup analysis was conducted with age (≥60 or <60 years), sex (male or

Table 1
Baseline characteristics of the study population, according to the S2BT groups.

Characteristic	Overall (n = 517)	S2BT ≤ 24 h (n = 197)	24 h < S2BT ≤ 7 days (n = 180)	S2BT > 7 days (n = 140)	*P* value
Age, years	64 ± 12	60 ± 12	65 ± 12	67 ± 11	<0.001
Sex , N (%)					<0.001
Male	332 (64.2)	145 (73.6)	113 (62.8)	74 (52.9)	
Female	185 (35.8)	52 (26.4)	67 (37.2)	66 (47.1)	
Type of MI , N (%)					<0.001
Inferior and lateral MI	282 (54.5)	99 (50.3)	87 (48.3)	96 (68.6)	
Anterior, anterior interwall or extensive anterior wall MI	235 (45.5)	98 (49.7)	93 (51.7)	44 (31.4)	
Hypertension , N (%)					0.001
Yes	295 (57.1)	100 (50.8)	97 (53.9)	98 (70.0)	
No	222 (42.9)	97 (49.2)	83 (46.1)	42 (30.0)	
Diabetes , N (%)					0.258
Yes	236 (45.6)	81 (41.1)	86 (47.8)	69 (49.3)	
No	281 (54.4)	116 (58.9)	94 (52.2)	71 (50.7)	
Prior CAD history, N (%)					0.937
Yes	66 (12.8)	25 (12.7)	22 (12.2)	19 (13.6)	
No	451 (87.2)	172 (87.3)	158 (87.8)	121 (86.4)	
Family history of CVD , N (%)					0.038
Yes	165 (31.9)	53 (26.9)	56 (31.1)	56 (40.0)	
No	352 (68.1)	144 (73.1)	124 (68.9)	84 (60.0)	
Smoking status , N (%)					0.825
Yes	246 (47.6)	97 (49.2)	83 (46.1)	66 (47.1)	
Never	271 (52.4)	100 (50.8)	97 (53.9)	74 (52.9)	
Drinking status , N (%)					<0.001
Yes	157 (30.4)	88 (44.7)	46 (25.6)	23 (16.4)	
Never	360 (69.6)	109 (55.3)	134 (74.4)	117 (83.6)	
SBP (mmHg)	130.0 ± 19.7	126.2 ± 19.2	128.8 ± 19.6	136.8 ± 19.0	<0.001
DBP (mmHg)	76.6 ± 12.2	78.1 ± 13.0	75.0 ± 11.4	76.5 ± 11.9	0.051
BMI (kg/m^2)	24.7 ± 3.8	24.5 ± 3.8	25.0 ± 4.0	24.5 ± 3.5	0.357
Fasting glucose (mmol/L)	6.7 ± 3.1	6.4 ± 3.1	6.8 ± 2.9	7.1 ± 3.4	0.107
HbA1c, %	6.7 ± 1.6	6.6 ± 1.6	6.7 ± 1.5	6.9 ± 1.8	0.566
Total cholesterol (mmol/L)	4.2 ± 1.2	4.2 ± 1.2	4.1 ± 1.1	4.3 ± 1.2	0.319
Triglyceride (mmol/L)	1.53 (1.17–2.11)	1.59 (1.14–2.06)	1.48 (1.14–2.10)	1.52 (1.21–2.25)	0.516
LDL (mmol/L)	2.6 ± 0.9	2.6 ± 0.9	2.5 ± 0.8	2.7 ± 0.9	0.429
HDL (mmol/L)	1.0 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	0.025
WBC ($10^9/L$)	9.1 ± 3.6	8.8 ± 3.7	9.1 ± 3.6	9.6 ± 3.4	0.143
Neutrophil ($10^9/L$)	6.5 ± 3.1	6.6 ± 3.2	6.4 ± 3.1	6.3 ± 2.8	0.520
Neutrophil (%)	69.4 ± 13.7	75.2 ± 12.0	69.4 ± 13.2	61.0 ± 12.3	<0.001
NT-proBNP (ng/L)	1017 (316–2686)	842.5 (210.7–2239.0)	1318.5 (423.5–3752.0)	666.5 (303.6–2499.2)	0.001
hsCRP (mg/L)	5.1 (3.5–19.1)	5.0 (2.8–8.1)	8.4 (5.0–46.6)	6.1 (4.4–17.6)	<0.001
LVEF (%)	53.2 ± 10.3	51.7 ± 10.5	53.2 ± 10.4	55.3 ± 9.5	0.007
Number of lesion vessels	2.1 ± 0.9	2.0 ± 0.9	2.1 ± 0.9	2.2 ± 0.9	0.219
Number of stents	1.2 ± 0.8	1.1 ± 0.8	1.2 ± 0.8	1.5 ± 0.9	<0.001
Medications during hospitalization, N (%)					
Aspirin	463 (89.6)	178 (90.4)	156 (86.7)	129 (92.1)	0.254
Clopidogrel	215 (41.6)	76 (38.6)	85 (47.2)	54 (38.6)	0.164
Ticagrelor	256 (49.5)	102 (51.8)	82 (45.6)	72 (51.4)	0.420
Statins	494 (95.6)	191 (97.0)	167 (92.8)	136 (97.1)	0.082
Beta-blocker	328 (63.4)	123 (62.4)	107 (59.4)	98 (70.0)	0.141
Other Antiarrhythmic	24 (4.6)	4 (2.0)	13 (7.2)	7 (5.0)	0.055

Data were presented as mean (SD), median (25th-75th percentile] or N (%) as appropriate. MI, myocardial infarction; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; WBC, white blood cell; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; LVEF, left ventricular ejection fraction. *Note:* HbA1c available: n = 171.

female), hypertension (yes or no), diabetes (yes or no), family history of CVD (yes or no), smoking (yes or no), and drinking status (yes or no) as the stratified variables.

All data in this study were analyzed using Stata software (version 16.0, StataCorp LLC, College Station, Texas, USA) and R software (version 4.1.3). A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of this study

A total of 517 STEMI patients (332 males, 64.2%) were enrolled in this study. The mean age (SD) of the study participants was 64 (12) years. The detailed baseline information of this study is presented in Table 1. Patients with S2BT ≤ 24 h were younger, more likely to be male, had a lower proportion of hypertension and family history of CVD, and lower systolic blood pressure values at baseline (all $P < 0.05$). Patients with S2BT of 24 h-7d had higher NT-proBNP and hsCRP levels at baseline (both $P < 0.05$). Patients with S2BT > 7d were older, more likely to be female, had a higher proportion of inferior or lateral MI, hypertension and family history of CVD, and higher systolic blood pressure and LVEF values at baseline (all $P < 0.05$). There were no significant differences among the three groups in diabetes, prior coronary artery disease history, smoking, BMI, FPG, HbA1c, TG, LDL-C, WBC, neutrophil count, number of lesion vessels and routine medications use during hospitalization (all $P > 0.05$).

3.2. Primary and secondary endpoint of this study

The primary endpoint, VAs determined by 24-h Holter, occurred in a total of 236 patients (45.6%) during 7290 person-months of follow-up (maximum follow-up: 41 months), including 44 (22.3%) in patients with S2BT ≤ 24 h, 123 (68.3%) in patients with S2BT of 24 h-7d, and 69 (49.3%) in patients with S2BT > 7d. The secondary endpoint, MACE, occurred in a total of 128 patients (24.8%), including 23 (11.7%) in patients with S2BT ≤ 24 h, 58 (32.3%) in patients with S2BT of 24 h-7d, and 47 (33.6%) in patients with S2BT > 7d. Patients with S2BT ≤ 24 h had a lower incidence of the primary endpoint ($P < 0.001$), secondary endpoint ($P < 0.001$), and 30-day mortality ($P = 0.028$), while patients with S2BT of 24 h-7d had a higher incidence of the primary endpoint ($P < 0.001$) during follow-up (Table 2).

3.3. Association between S2BT and the risk of primary endpoint

The Kaplan-Meier curve showed that STEMI patients with S2BT within 24 h-7d had a higher risk of primary endpoint (log-rank $P < 0.001$), compared with patients with S2BT < 24 h and S2BT > 7d (Fig. 1). In addition, the univariable and multivariable Cox regression models were employed and shown in Table 3. Univariable Cox regression demonstrated that variables significantly associated with the primary endpoint included S2BT, sex, diabetes, family history of CVD, BMI, HDL-C, NT-proBNP, hsCRP, and LVEF (all $P < 0.05$). Multivariable Cox regression model including the above 9 variables ($P < 0.05$ in the univariable regression model) indicated that compared with STEMI patients with S2BT within 24 h-7d, patients with S2BT ≤ 24 h and S2BT > 7d were associated with a lower risk of the primary endpoint, with HR (95% CI) of 0.49 (0.34, 0.71) and 0.65 (0.47, 0.90), respectively (Table 3).

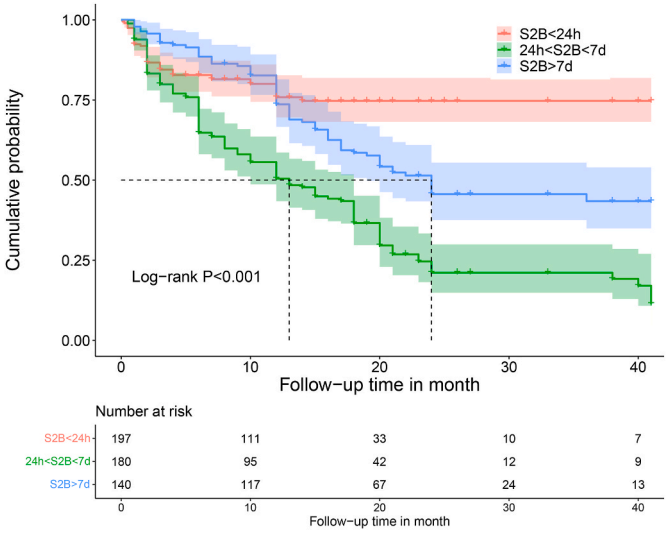

Fig. 1. Kaplan-Meier curves for the primary endpoint. Patients were divided into three groups: (1) early revascularization group: S2BT ≤ 24 h; (2) late revascularization group: S2BT within 24 h to 7d; (3) very-late revascularization group: S2BT > 7d.

Furthermore, the RCS plot showed that after multivariable adjustments, there was an inverted U-shaped non-linear relationship between S2BT and the primary endpoint (P for nonlinearity<0.001), with an S2BT of 68.4 h at the inflection point, suggesting that the risk of primary endpoint was highest at this time point (Fig. 2).

Then we used 2-piecewise Cox regressions with S2BT of 68.4 h as the inflection point (Supplementary Table 1). Consistent with the RCS plot, when S2BT was below 68.4 h, each 1-h delay in S2BT was significantly associated with a 1.4% increase (HR 1.014 [95% CI, 1.003–1.024], $P = 0.011$) in the risk of primary endpoint. However, each 1-h increase in S2BT was associated with a 0.4% decrease (HR 0.996 [95% CI, 0.993–0.999], $P = 0.004$) in the risk of primary endpoint when S2BT was above 68.4 h. In particular, S2BT was not significantly associated with risk of primary endpoint when S2BT > 7d (HR 0.996 [95%CI 0.990–1.001], $P = 0.074$).

Table 2
Primary and secondary endpoint of this study, according to the S2BT groups.

Variable	Overall (n = 517)	S2BT ≤ 24 h (n = 197)	24 h < S2BT ≤ 7 days (n = 180)	S2BT > 7 days (n = 140)	*P* value
Primary endpoint, N (%)	236 (45.6)	44 (22.3)	123 (68.3)	69 (49.3)	<0.001
Secondary endpoint-MACE, N (%)	128 (24.8)	23 (11.7)	58 (32.2)	47 (33.6)	<0.001
30-day mortality, N (%)	28 (5.5)	4 (2.0)	13 (7.2)	11 (7.9)	0.028

Data were presented as frequencies (percentage). S2BT, symptom-to-balloon time; MACE, major adverse cardiovascular event.

3.4. Subgroup analysis

Subgroup analysis for the association of S2BT with the primary endpoint stratified by age, sex, hypertension, diabetes, family history of CVD, smoking, and drinking status at baseline was performed and illustrated in Fig. 3. There was no significant interaction between S2BT and the above stratified variables (all P for interaction >0.05). This suggested that the association between S2BT and the primary endpoint was robust and was not affected by the above variables.

3.5. Association between S2BT and the secondary endpoint

Cox regression model was used to investigate the relationship between S2BT and MACE risk. After multivariable adjustments, patients with S2BT ≤ 24 h were associated with a lower risk of MACE compared with STEMI patients with S2BT within 24 h-7d (HR 0.39 [95%CI,

Table 3
Univariable and multivariable Cox analysis of the primary endpoint in the study.

Variables	Univariable Cox		Multivariable Cox	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
S2BT groups：				
≤24 h	0.33 (0.24, 0.47)	<0.001	0.49 (0.34, 0.71)	<0.001
24 h-7d	1 (Reference)		1 (Reference)	
>7d	0.50 (0.37, 0.678)	<0.001	0.65 (0.47, 0.90)	0.010
Age, years	1.00 (0.99, 1.01)	0.484		
Sex	0.73 (0.57, 0.95)	0.019	0.93 (0.70, 1.22)	0.589
Hypertension	1.23 (0.95, 1.59)	0.125		
Diabetes	1.40 (1.09, 1.81)	0.009	1.20 (0.91, 1.59)	0.193
Prior CAD history	1.08 (0.55, 2.09)	0.829		
Family history of CVD	2.05 (1.58, 2.65)	<0.001	1.55 (1.18, 2.05)	0.002
Smoking status	0.84 (0.65, 1.09)	0.187		
Drinking status	0.99 (0.74, 1.31)	0.932		
SBP	1.00 (0.99, 1.01)	0.781		
DBP	0.99 (0.98, 1.01)	0.250		
BMI	1.04 (1.01, 1.08)	0.009	0.97 (0.94, 1.01)	0.140
Fasting glucose	1.04 (1.00, 1.08)	0.079		
HbA1c	1.11 (0.96, 1.29)	0.157		
Triglyceride	0.89 (0.77, 1.01)	0.080		
LDL	0.89 (0.77, 1.03)	0.117		
HDL	0.21 (0.11, 0.38)	<0.001	0.47 (0.25, 0.89)	0.020
WBC	0.97 (0.94, 1.01)	0.127		
NT-proBNP (per 1000 ng/L)	1.42 (1.32, 1.52)	<0.001	1.24 (1.13, 1.36)	<0.001
hsCRP (per 10 mg/L)	1.22 (1.17, 1.27)	<0.001	1.09 (1.03, 1.15)	0.002
LVEF	0.98 (0.97, 0.99)	0.005	1.00 (0.98, 1.01)	0.140
Number of lesion vessels	0.98 (0.85, 1.13)	0.783		
Number of stent implants	1.00 (0.86, 1.16)	0.982		
Beta-blocker	0.77 (0.60, 1.01)	0.055		
Other Antiarrhythmic	0.68 (0.27, 1.68)	0.397		

CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; WBC, white blood cell; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

0.20–0.75], $P = 0.005$), while there was no significant difference in MACE risk between patients with S2BT > 7d and S2BT within 24 h-7d (HR 1.39 [95%CI, 0.90–2.14], $P = 0.139$) (Supplementary Table 2). Besides, linear regression was used to analyze the association between S2BT and the improvement in LVEF. Similarly, the multivariable linear regression showed that compared with STEMI patients with S2BT within 24 h-7d, LVEF levels in patients with S2BT ≤ 24 h were significantly increased by 4.44 ($\beta = 4.44$ [95%CI: 1.83–7.04], $P = 0.001$), while LVEF levels in patients with S2BT > 7d decreased by 0.25, but there was no statistically significant difference ($\beta = -0.25$ [95%CI: −3.05-2.55], $P =$

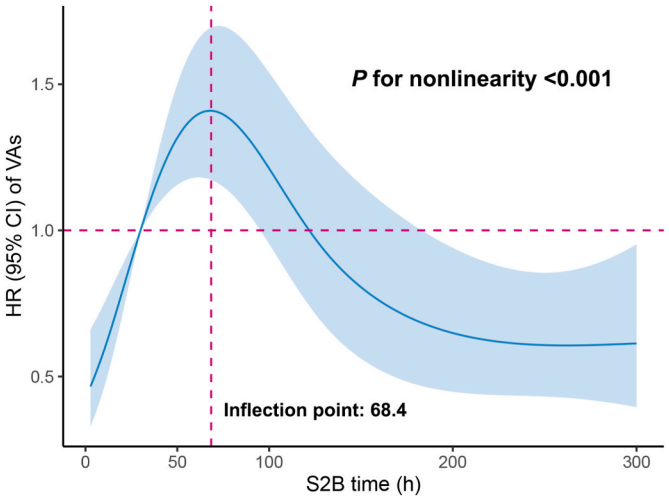

Fig. 2. Restricted cubic spline (RCS) plot of the association of S2BT with the primary endpoint. RCS regression was adjusted for family history of CVD, HDL-C, NT-proBNP and hsCRP. The solid blue line and shadow bands represent the corresponding HR values and 95% confidence intervals. The magenta vertical dashed line indicates the inflection point of the curve (S2BT = 68.4 h). HR, hazard ratio; CI, confidence interval.

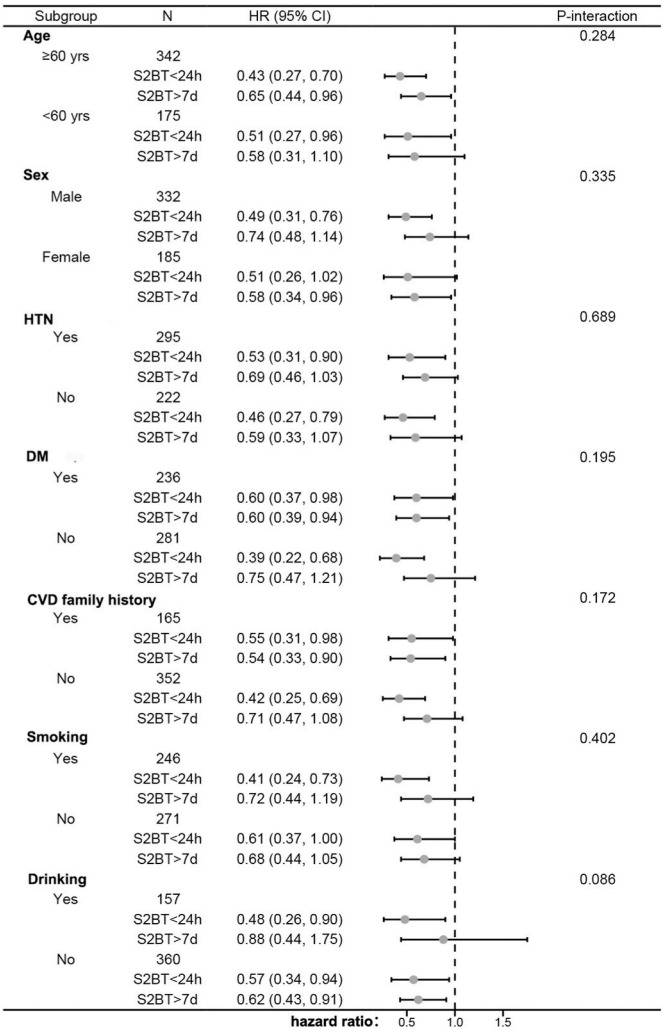

Fig. 3. Subgroup analysis for the association of S2BT with the primary endpoint. HR, hazard ratio; CI, confidence interval.

0.863) (Supplementary Table 3).

4. Discussion

Based on real-world evidence, the VERY-STEMI study showed that STEMI patients with S2BT within 24 h-7d were associated with a higher risk of VAs during follow-up. There was an inverted U-shaped relationship between S2BT and the risk of VAs, with the highest risk when S2BT was 68.4 h. These findings suggest that for STEMI, PCI should be performed urgently in patients within 24 h of symptoms onset. For patients with more than 24 h of symptoms, initiation of PCI after 7d was associated with a lower risk of VAs without an increased risk of MACE and worsening cardiac function compared with initiation of PCI within 7d.

PCI for revascularization is recognized as one of the key steps in the treatment of STEMI. Clinical guidelines recommend that pPCI should be performed for STEMI patients within 12 h of onset and is also recommended at an early stage (within 24 h) when the onset of STEMI is more than 12 h, with ongoing symptoms suggestive of ischemia [3,8]. A Danish study showed that S2BT was significantly associated with an increased risk of mortality and hospitalization for heart failure, highlighting the importance of S2BT for survival outcomes of STEMI [19]. The benefits of the early revascularization group in the primary and secondary endpoints in this study supported the current guidelines recommendations [3,20].

However, with the development of interventional devices such as a new generation of drug-eluting stents and the emergence of new drugs such as ticagrelor, the prognostic impact of S2BT in STEMI, especially in patients with delayed visits, remains controversial, and the results of multiple studies are inconsistent. Wei et al. found that shortening the symptom-to-first medical contact time could improve the prognosis of patients with STEMI [21]. Similarly, a Korean study demonstrated that shortening the door-to-balloon time was significantly associated with survival benefits in patients with STEMI [22]. However, Li et al. found that in patients with STEMI 12–72 h after symptom onset and with spontaneous reperfusion of the infarct-related artery, delayed PCI showed a higher procedural success rate without increasing in-hospital and long-term mortality [23]. A propensity matched study revealed that patients with STEMI who underwent early PCI (defined in the study as 3-14d after onset) had a higher risk of recurrent MI than patients with STEMI who underwent late PCI (defined in the study as more than 14d after onset) [24]. The Occluded Artery Trial (OAT) study also showed that in patients with occlusion of the infarct-related artery 3-28d after MI and high-risk criterion, routine PCI did not reduce the incidence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction compared with optimal medical therapy alone [25], and this result was not affected by patient risk level or extended follow-up [26,27]. In addition, a considerable number of studies showed that the impact of late or delayed PCI revascularization on the prognosis of STEMI was not significantly different from early PCI [28–31]. Among them, China Acute Myocardial Infarction (CAMI) Registry demonstrated that the median S2BT in patients with STEMI undergoing pPCI in China was longer than that in developed countries. Longer S2BT after STEMI was associated with impaired myocardial perfusion but not with in-hospital mortality or MACE [32].

Our study also found that patients with very-late revascularization (S2BT $>$ 7d) had a lower risk of VAs than those with late revascularization and were non-inferior to those with late revascularization in terms of MACE risk and maintenance of cardiac function. The dose-response relationship indicated that the risk of VAs was highest when the S2BT was 68.4 h. Previous studies investigating S2BT and the risk of VA in patients with STEMI are very sparse. A recent clinical study revealed that S2BT was inversely associated with malignant arrhythmic events in patients with STEMI [33], but the study was retrospective and had a small sample size (285 patients). Another clinical study showed that S2BT $>$ 3 h in STEMI was an independent predictor of VT/VF [34], but the outcome of that study only focused on in-hospital VT/VF and did not explore the dose-response relationship. Besides, the OAT-EP substudy suggested that PCI of an occluded infarct-related artery 3-28d (median: 12d) after MI compared with medical therapy alone had no significant effect on markers of vulnerability to VAs, such as heart rate variability, the time-domain signal-averaged ECG and T-wave variability [35]. The differences between OAT-EP and our study might lie in: (1). ten-minute Holter recordings were used in the OAT-EP study, while 24 h Holter was conducted in this study. Longer recordings are inflexible but can provide the opportunity to discover more VAs; (2). the median S2BT of patients in the OAT-EP study was 12 days, suggesting that the majority of patients might fall into the S2BT $>$ 7d group of our study, and only a small number of patients fall into the S2BT of 24 h-7d group; (3). although the three parameters were valuable indicators of VAs vulnerability, the OAT-EP study did not directly document the occurrence of VAs; (4). the differences in study population should be noted. In terms of MACE, the findings of our study were consistent with those of many studies mentioned above, including CAMI registration study [32], suggesting that very-late revascularization, although the specific definition was not recognized, seemed reasonable and desirable compared with late revascularization.

There are several possible explanations for these findings. First, from a pathophysiological point of view, residual coronary antegrade flow and retrograde collateral circulation after MI ensures the survival of hibernating and stunned myocardium, and rescue of these cardiomyocytes can prevent myocardial remodeling and electrophysiological disorders [9]. Second, it has been proposed that patients with STEMI who present later (S2BT delay) are at a lower risk than those who present earlier because they have passed the initial high-risk period [36]. This could also be suggested in our study that patients with S2BT $>$ 7d were more likely to be female, had a lower proportion of anterior MI, and higher LVEF at baseline. However, when interpreting this, it is also important to keep in mind that only patients who survived prior to treatment were eligible for analysis. Patients who presented early had a high mortality rate without reperfusion therapy and could benefit from pPCI. Conversely, patients who presented late (S2BT delay) were generally low-risk patients who had already survived the prehospital phase and would benefit less from reperfusion therapy [19]. Finally, updated interventional devices and medications, increased adherence to optimal medical therapy, and more careful and comprehensive management may make it difficult to observe the prognosis differences among S2BTs, for example, the ORBITA [37] and ISCEHMIA [38] trials suggest that maintaining high adherence to guideline-directed medical therapy in the contemporary context may make the benefits of invasive treatments such as PCI less obvious.

4.1. Strengths and limitations

The present study has several strengths. First, the study design of VERY-STEMI study was a multicenter, prospective real-world study. The source of cases was diverse, and the study conclusion had strong external extrapolation [39]. Second, our study used RCS to visualize the dose-response relationship between S2BT and VAs risk, providing for the first time the risk inflection point of STEMI from a VA perspective. Nevertheless, several limitations should also be acknowledged. First, although we included a series of confounders, there were still potential confounders such as duration of PCI procedure, other chronic medical history, medication adherence after PCI, sedentary or active lifestyle, dietary patterns, physical stress, mental health and sleep habits that were not included in the regression analysis. In addition, information on ICD implantation was not documented. Second, VAs were diagnosed by 24 h Holter electrocardiography during follow-up, and the exact timing of first VA occurrence might not be accurately recorded owing to personal delay or availability of medical resources. Third, since the timing of symptom onset was self-reported by the patients, recall bias might exist. Besides, the possibility of selection bias and survivor bias could not

be excluded. Fourth, the study enrolled patients with STEMI in China, so the conclusions may not be extended to other populations. Finally, the non-randomized and observational study design limited the causal inferences. Therefore, the association shown in this study needs to be validated in future prospective cohorts with larger sample and diverse races.

5. Conclusions

S2BT within 24 h-7d in patients with STEMI was associated with a higher risk of VAs during follow-up. The relationship between S2BT and VAs was inverted U-shaped, with the highest risk at an S2BT of 68.4 h. Further studies with larger sample and longer follow-up are warranted.

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and registered on the *ClinicalTrials.gov* website (identifier, NCT04660474). All patients signed informed consent.

Funding

This work was supported by grants from the Key Clinical Frontier Technology Project of Department of Science and Technology of Jiangsu Province (NO. BE2022806), China, the National Natural Science Foundation of China (NO. 82070367), China, and a Project Funded by the Major Program of Wuxi Medical Center, Nanjing Medical University (NO. WMCM202304), China.

Consent for publication

Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Tian-Kai Shan: Writing – original draft, Formal analysis, Conceptualization. **Ling-Ling Qian:** Writing – original draft, Formal analysis, Conceptualization. **Xu-Dong Han:** Writing – review & editing, Validation, Data curation. **Bo Deng:** Writing – review & editing, Validation, Data curation. **Ling-Feng Gu:** Writing – review & editing, Validation, Data curation. **Ze-Mu Wang:** Writing – review & editing, Validation, Data curation. **Ye He:** Writing – review & editing, Validation, Data curation. **Ting Zhu:** Writing – review & editing, Data curation. **Peng Jing:** Writing – review & editing, Data curation. **Qi-Ming Wang:** Writing – review & editing, Data curation. **Zi-Dun Wang:** Writing – review & editing, Data curation. **Ru-Xing Wang:** Writing – review & editing, Supervision, Conceptualization. **Si-Bo Wang:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Lian-Sheng Wang:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank for the technical assistance support from Jiangsu Province Collaborative Innovation Center for Cardiovascular Disease Translational Medicine.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200286.

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