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ORIGINAL RESEARCH

Inpatient-Onset Versus Outpatient-Onset ST-Segment–Elevation Myocardial Infarction in Patients With Percutaneous Coronary Intervention: A National Registry Study

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BACKGROUND: Compared with patients who develop ST-segment–elevation myocardial infarction (STEMI) outside the hospital and present at the emergency department (outpatient-onset), patients with inpatient-onset STEMI may paradoxically experience a poorer prognosis due to underlying disease, despite the apparent immediate access to acute health care services.

METHODS: Patients with first-onset STEMI who underwent percutaneous coronary intervention (PCI) in the Singapore Myocardial Infarction Registry (2007–2020) were included. For patients with inpatient-onset STEMI, the recognition-to-balloon time was measured from symptom onset to PCI. For outpatient-onset STEMI, the recognition-to-balloon time was defined as the sum of the symptom-to-door and door-to-balloon time. Logistic regression was used to identify factors associated with delayed PCI after inpatient-onset STEMI. Cox regression was used to assess 30-day, 1-year, 5-year, and 10-year all-cause and cardiovascular mortality.

RESULTS: A total of 19 149 patients, 17 659 (92.2%) outpatient-onset and 1595 (7.8%) inpatient-onset, were included. The median follow-up duration was 6.91 years. Patients with inpatient-onset STEMI were older, more frequently women, nonsmokers, more likely to have comorbidities, less likely to present with typical STEMI symptoms, and more likely to experience delays in PCI than patients with outpatient-onset STEMI within the hospital setting. The independent predictors of delayed PCI for inpatient-onset STEMI were age ≥65 years, diabetes, breathlessness at presentation, and Killip class III. After adjustment for differences in baseline and clinical characteristics, inpatient-onset STEMI was associated with significantly greater 1-year, 5-year, and 10-year all-cause mortality (1-year hazard ratio [HR], 1.27 [95% CI, 1.13–1.43]; 5-year HR, 1.27 [95% CI, 1.13–1.43]). There was no difference in 30-day all-cause or short-/long-term cardiovascular mortality.

CONCLUSIONS: Inpatient-onset STEMI was linked to an increased long-term risk of all-cause mortality compared with outpatient-onset STEMI despite a shorter recognition-to-balloon time.

Key Words: all-cause mortality ■ cardiovascular mortality ■ inpatient ■ myocardial infarction ■ percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- This study accounts for the major differences in recognition-to-balloon time between patients with inpatient-onset and patients with outpatient-onset ST-segment–elevation myocardial infarction, a potentially major confounder not adjusted for in prior studies.
- Inpatient-onset ST-segment–elevation myocardial infarction was associated with a greater risk of all-cause mortality in the long term versus outpatient-onset ST-segment–elevation myocardial infarction, despite a shorter recognition-to-balloon time.

What Are the Clinical Implications?

- Implementing protocols tailored to inpatient-onset ST-segment–elevation myocardial infarction, including optimizing ECG interpretation within inpatient settings, may facilitate more rapid recognition and thus, timely initiation of treatment.

Nonstandard Abbreviations and Acronyms

GDMT	guideline-directed medical therapy
SMIR	Singapore Myocardial Infarction Registry

The primary treatment method of eligible patients presenting with ST-segment–elevation myocardial infarction (STEMI) is prompt reperfusion with percutaneous coronary intervention (PCI).[1] Substantial evidence supporting this strategy has led to the development of initiatives to facilitate and enhance the relevant systems of care.[2] The primary objective is to minimize total ischemic time,[3] defined as the interval from initial symptom recognition by the patient to reperfusion at a PCI-capable hospital.[4,5] Reducing delays at each step of care and expediting PCI are keys to shortening total ischemic time, which has been consistently associated with improved survival outcomes.[4,5] However, present initiatives primarily focus on STEMI pathways for patients presenting at the emergency department after developing STEMI outside of the hospital (outpatient-onset). There are limited frameworks in place to facilitate the identification, triage, and treatment of hospitalized patients who develop STEMI (inpatient-onset).[6] In addition, research specific to inpatient-onset STEMI is comparatively sparse.[2,7]

For patients with outpatient-onset STEMI, the sequence of care begins with seeking medical attention at the hospital either via emergency medical services or personal transport after patient recognition of symptom onset. This introduces a time interval that can be referred to as the symptom-to-door time.[4,5] Patients with inpatient-onset STEMI, in contrast, do not have a similar time component, because they are already in the hospital. For patients with outpatient-onset STEMI, the subsequent time interval is the door-to-balloon time, which is the time from arrival at the emergency department regardless of mode of transport until PCI is performed.[4,5] The total time from symptom recognition to PCI is called the recognition-to-balloon time and is relevant to patients with inpatient-onset STEMI and patients with outpatient-onset STEMI. Given that a shorter time between symptom onset and PCI is linked to better survival rates,[8] one might hypothesize that patients with inpatient-onset STEMI have an advantage over patients with outpatient-onset STEMI, because immediate access to health care could lead to faster intervention. Alternatively, it is also possible that patients with inpatient-onset STEMI fare worse, because their hospitalization for an existing disease condition suggests they are already in poorer health, which could then predispose poorer outcomes.

Some studies have shown increased mortality risk with inpatient-onset STEMI.[2,7,9,10] However, many of these studies included a large proportion of patients who did not undergo PCI,[2,7] which significantly reduces mortality risk and could have skewed results.[11] Stehli et al[9] were the first study to include only patients who underwent PCI. Moreover, most studies did not explicitly state whether only patients with first acute myocardial infarction (AMI) were analyzed[2,7,10]; the presence of recurrent STEMIs, which carry higher mortality risk, could have confounded results.[12] Our study aimed to not only address these potential confounders, but also examine whether differences in recognition-to-balloon time would influence short- and long-term mortality outcomes between inpatient-onset and outpatient-onset STEMI. This important aspect has not been adjusted for in previous studies, highlighting a notable gap in existing literature. We also sought to compare differences in demographics and management between inpatient-onset and outpatient-onset STEMI using a national AMI registry. Moreover, we investigated factors associated with delayed PCI for inpatient-onset STEMI, referencing the recommended recognition-to-balloon times from the European Society of Cardiology[4] and the American College of Cardiology/American Heart Association.[5] This aimed to support the development of future pathways/guidelines specifically tailored for inpatient-onset STEMI.

METHODS

We conducted a retrospective analysis of patients with STEMI from Singapore's national AMI registry, SMIR (Singapore Myocardial Infarction Registry). The local institutional review board granted an exemption for

written consent from participants for this study (National Healthcare Group Domain Specific Review Board: 2023/00263), as it used deidentified data. Managed by the National Registry of Diseases Office, SMIR collects epidemiological and clinical information on all AMI cases diagnosed in both public and private hospitals, as well as a small number of out-of-hospital AMI deaths certified by physicians. The mandatory reporting of AMI to SMIR was instituted by the National Registry of Diseases Act of 2012, with public hospitals contributing 98% of registered cases. The data used in this study are owned by the National Registry of Diseases Office and are intended primarily for internal use. Access to the deidentified data for public health research is available upon obtaining approval from the Ministry of Health and the institutional review board. Before 2012, AMI cases were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 410. From 2012 onward, *ICD-10* (*Australian Modification*) codes I21 and I22 were used. Data from various sources, including patient medical claim records, hospital inpatient discharge summaries, and cardiac biomarker listings from laboratories were compiled and processed to identify unique cases. These data were subsequently integrated with mortality information from the Registry of Births and Deaths in Singapore, which captures all mortality outcomes through mandatory reporting, including the cause of death.[13] The definition of STEMI involved: (1) typical chest pain of ≥20 minutes, (2) significant ST-segment elevation (0.1 or 0.2 mV on 2 adjacent limb or precordial leads, respectively), and (3) confirmation by elevated troponins. From 2013 onward, left bundle-branch block was no longer considered diagnostic of STEMI in isolation, in accordance with the 2013 American Heart Association/American College of Cardiology guidelines.[14] Nonetheless, all STEMI diagnoses made before 2013 were based on clinical judgment and adjudicated by physicians. To further ensure uniformity, all ECGs were interpreted and diagnoses centrally validated at the National Registry of Diseases Office. Annual audits were performed to ensure accuracy and interrater reliability. Logic checks flagged any illogical or outlier data for review.

This study analyzed STEMI cases reported to SMIR from January 2008 to December 2020, focusing on patients who received PCI. Patients without PCI were excluded to examine the impact of PCI timing on mortality outcomes. Only patients experiencing their first-ever myocardial infarction, specifically first-onset STEMI cases, were included. For patients with outpatient-onset STEMI, the recognition-to-balloon time was defined as the sum of symptom-to-door and door-to-balloon times. For inpatient-onset STEMI, the recognition-to-balloon time was measured from symptom recognition by the hospitalized patient to PCI. Patients with missing data on symptom-to-door, door-to-balloon, and recognition-to-balloon time were excluded. Primary outcomes were all-cause and cardiovascular mortality (Figure S1) at 30 days, 1 year, 5 years, and 10 years.

Statistical Analysis

Categorical variables representing patients' baseline characteristics were expressed as frequencies and percentages, whereas continuous variables were summarized using mean±SD. Differences between patients with outpatient-onset STEMI and patients with inpatient-onset STEMI were analyzed using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. The median follow-up duration was derived using the reverse Kaplan-Meier estimator.[15] Univariate logistic regression identified variables predictive of delayed PCI (recognition-to-balloon time of >60 to ≤90 minutes, or >90 minutes)[4,5] for inpatient-onset STEMI, which were then independently assessed in a multivariate model. Time-to-mortality data were graphically represented using the Kaplan-Meier method and compared using the log-rank test. The relationship between the location of STEMI onset and all-cause mortality was determined via Cox proportional hazards regression. Variables with a P value <0.1 in the univariate Cox model and variables deemed clinically significant based on the opinion of institutional experts were included in the final multivariable Cox model presented.[16,17] Multivariate analyses were adjusted for sex, age, smoking, heart failure status at admission (Killip class I, II, III, and IV respectively), diabetes, hypertension, hyperlipidemia, previous PCI, chest pain at presentation, and recognition-to-balloon time. Sensitivity analyses were conducted among patients who survived to discharge, with additional adjustment in different models for the prescription of guideline-directed medical therapy (GDMT) at discharge, left ventricular ejection fraction, presence of left ventricular systolic dysfunction, and the occurrence of cardiogenic shock during hospitalization. Missing values within categorical variables were encoded as a distinct category labeled missing to preserve sample size within the multivariate model. Such covariates were included only if they had low missingness (<10%).[18] Subgroup analyses were performed to evaluate whether the comparative risks of all-cause mortality and cardiovascular mortality varied according to specific patient groups. The subgroups included patients aged <65 or ≥65 years, male or female sex, history of smoking, chest pain at presentation, diabetes, hypertension, and hyperlipidemia. Statistical analysis was performed using R statistical software version 4.3.1 (R Core Team, 2021), with statistical significance set at P<0.05. The research was conducted with reference to the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) statement[19] and in accordance with the Declaration of Helsinki.[20]

RESULTS

A total of 19 149 patients with first-onset STEMI were included in the analysis, with 17 659 (92.2%) outpatient-onset and 1490 (7.8%) inpatient-onset cases (Figure 1). The median follow-up duration was 6.91 years (interquartile range [IQR], 3.80–10.39). Baseline characteristics are presented in Table 1. Patients with inpatient-onset STEMI were older, more frequently women, and nonsmokers. They were more likely to have hypertension and diabetes, whereas the percentages of patients with hyperlipidemia were similar between groups. Additionally, more patients with inpatient-onset STEMI had a previous PCI. Patients with inpatient-onset STEMI were less likely to present with typical STEMI symptoms such as chest pain, dyspnea, and diaphoresis. Conversely, more patients with outpatient-onset STEMI experienced cardiogenic shock (Killip class IV) on admission.

Clinical Management

The recognition-to-balloon time was shorter for inpatient-onset STEMI (Table 2). The median recognition-to-balloon time for inpatient-onset STEMI was 71 minutes (IQR, 52–102), and 210 minutes (IQR, 13–413) for outpatient-onset STEMI.

Patients with inpatient-onset STEMI were less likely to receive dual antiplatelet therapy during the acute phase compared with patients with outpatient-onset STEMI. During hospitalization, patients with inpatient-onset STEM were more often treated with single antiplatelet therapy instead of dual antiplatelet therapy. They also received fewer GDMTs, including fewer β-blockers, fewer angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and fewer lipid-lowering drugs. Among those who survived to discharge, patients with inpatient-onset STEMI were similarly less likely to receive GDMT, except for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (Table 2). Although these differences were significant, the absolute differences in percentages between groups were minimal.

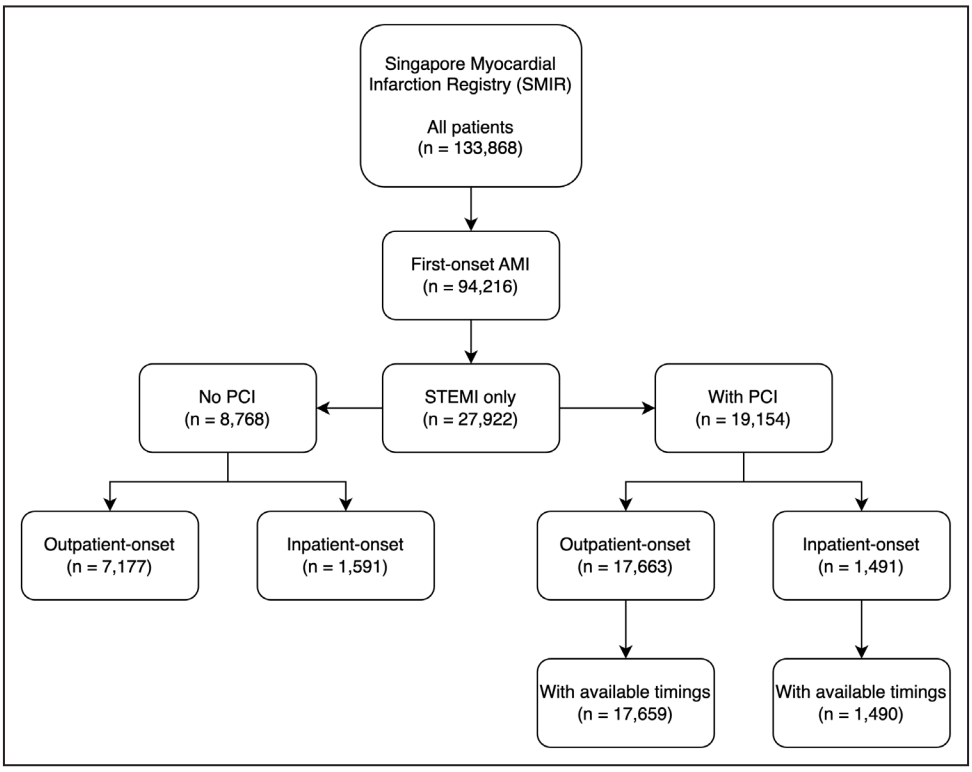

Figure 1. Flowchart for data inclusion.
A total of 133 868 patients were registered in the SMIR from 2008 to 2020. Only those with first-onset STEMI who underwent PCI with valid symptom-to-door, door-to-balloon, and recognition-to-balloon times were included in the analysis. The patients were then divided into outpatient-onset and inpatient-onset STEMI. A total of 7177 patients with outpatient-onset and 1591 with inpatient-onset STEMI did not undergo PCI. AMI indicates acute myocardial infarction; PCI, percutaneous coronary intervention; SMIR, Singapore Myocardial Infarction Registry; and STEMI, ST-segment–elevation myocardial infarction.

Table 1. Baseline Characteristics of Patients With STEMI Categorized According to Outpatient-Onset or Inpatient-Onset

	Overall (n=19149)	Outpatient-onset STEMI (n=17659, 92.2%)	Inpatient-onset STEMI (n=1490, 7.8%)	*P* value
Age, y, median (IQR)	58 (51–66)	58 (51–66)	61 (53–70)	<0.001
Sex, n (%)				<0.001
Men	16187 (85)	15057 (85)	1130 (76)	
Women	2962 (15)	2602 (15)	360 (24)	
Ancestry, n (%)				<0.001
Chinese	12151 (63)	11176 (63)	975 (65)	
Malay	3759 (20)	3527 (20)	232 (16)	
Indian	2929 (15)	2667 (15)	262 (18)	
Others	310 (1.6)	289 (1.6)	21 (1.4)	
Medical history, n (%)				
Hypertension	9926 (52)	9029 (51)	897 (60)	<0.001
Diabetes	6630 (35)	6009 (34)	621 (42)	<0.001
Hyperlipidemia	11822 (62)	10865 (62)	957 (64)	0.10
Previous PCI	484 (2.5)	405 (2.3)	79 (5.3)	<0.001
Smoking status, n (%)				<0.001
Current	8947 (47)	8442 (48)	505 (34)	
Former	2465 (13)	2244 (13)	221 (15)	
Never	7534 (39)	6787 (38)	747 (50)	
Missing	203 (1.1)	186 (1.1)	17 (1.1)	
BMI, kg/m^2, median (IQR)	24.7 (22.5–27.4)	24.7 (22.5–27.4)	24.5 (22.1–27.5)	0.039
Glucose, mmol/L, median (IQR)	8.5 (6.9–12.3)	8.6 (6.9–12.3)	8.2 (6.5–12.2)	<0.001
Total cholesterol*, mmol/L, median (IQR)	5.09 (4.30–5.93)	5.10 (4.30–5.94)	4.92 (4.00–5.80)	<0.001
LDL cholesterol*, mmol/L, median (IQR)	3.35 (2.62–4.12)	3.36 (2.65–4.12)	3.16 (2.34–4.08)	<0.001
HDL cholesterol*, mmol/L, median (IQR)	1.06 (0.90–1.25)	1.06 (0.90–1.25)	1.09 (0.90–1.26)	0.14
Triglycerides†, mmol/L, median (IQR)	1.39 (1.00–1.98)	1.39 (1.00–1.99)	1.33 (0.96–1.90)	0.013
Hemoglobin, g/dL, median (IQR)	14.60 (13.40–15.60)	14.70 (13.50–15.70)	14.10 (12.50–15.20)	<0.001
Presenting symptoms, n (%)				
Dyspnea	10167 (53)	9728 (55)	439 (29)	<0.001
Chest pain	17437 (91)	16350 (93)	1087 (73)	<0.001
Diaphoresis	12287 (64)	11883 (67)	404 (27)	<0.001
Back pain	1671 (8.7)	1568 (8.9)	103 (6.9)	0.010
Shoulder pain	1256 (6.6)	1181 (6.7)	75 (5.0)	0.013
Jaw pain	1094 (5.7)	1047 (5.9)	47 (3.2)	<0.001
Syncope	487 (2.5)	466 (2.6)	21 (1.4)	0.004
Heart failure status at admission, Killip class, n (%)				0.009
I	16185 (85)	14928 (85)	1257 (84)	
II	730 (3.8)	658 (3.7)	72 (4.8)	
III	710 (3.7)	643 (3.6)	67 (4.5)	
IV	1513 (7.9)	1420 (8.0)	93 (6.2)	

BMI indicates body mass index; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*To convert total cholesterol, HDL, and LDL from mmol/L to mg/dL, multiply by 38.67.

†To convert triglycerides from mmol/L to mg/dL, multiply by 88.57.

Complications During Hospitalization

Patients with inpatient-onset STEMI more frequently developed complications during hospitalization, including heart failure (Killip class II and III), cardiogenic shock (Killip class IV), reinfarction, and stroke. However, they were less likely to suffer from arrhythmias during hospitalization. The incidence of left ventricular systolic dysfunction and heart block was similar between the 2 groups (Table S1).

Table 2. Clinical Management of Patients With Inpatient-Onset STEMI Versus Patients With Outpatient-Onset STEMI at Admission or Within 24 Hours of Onset, During Hospitalization, and at Discharge (Only for Those Who Survived to Discharge)

	Outpatient-onset STEMI (n=17 659, 92.2%)	Inpatient-onset STEMI (n=1490, 7.8%)	*P* value
Symptom-to-door time, min, median (IQR)	135 (68–330)	NA	NA
Door-to-balloon time, min, median (IQR)	62 (48–85)	NA	
Recognition-to-balloon time, min, median (IQR)	210 (135–413)	71 (52–102)	<0.001
Medications prescribed on admission for outpatient-onset or within 24 h of onset for inpatient-onset, n (%)			
Antiplatelet			<0.001
SAPT	482 (2.7)	88 (5.9)	
DAPT	17 114 (97)	1384 (93)	
Medications prescribed during hospitalization, n (%)			
Antiplatelet			<0.001
SAPT	435 (2.5)	67 (4.5)	
DAPT	16 777 (95)	1368 (92)	
β-Blocker	14 815 (84)	1201 (81)	<0.001
ACEI/ARB	12 817 (73)	1030 (69)	0.004
Lipid-lowering drugs	16 928 (96)	1382 (93)	<0.001
Medications given at discharge*, n/total (%)			
Antiplatelet			<0.001
SAPT	607/16527 (3.7)	89/1329 (6.7)	
DAPT	15 865/16527 (96)	1227/1329 (92)	
β-Blocker	14 240/16527 (86)	1110/1329 (84)	0.008
ACEI/ARB	11 984/16527 (73)	944/1329 (71)	0.2
Lipid-lowering drugs	16 252/16527 (98)	1280/1329 (96)	<0.001

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; DAPT, dual antiplatelet therapy; NA, not applicable; SAPT, single antiplatelet therapy; and STEMI, ST-segment–elevation myocardial infarction.

*For those surviving to discharge.

Predictors of Delayed PCI for Inpatient-Onset STEMI

The findings from the univariate and multivariate logistic regression analyses assessing potential predictors of delayed PCI are detailed in Table 3. Age ≥65 years and diabetes were associated with moderately delayed PCI (recognition-to-balloon time >60 minutes to ≤90 minutes) when compared with timely PCI (recognition-to-balloon time ≤60 minutes). Age ≥65 years, breathlessness at presentation, and heart failure status at admission (Killip class III) were associated with severe delays in PCI (recognition-to-balloon time >90 minutes) relative to timely PCI. The presence of chest pain was associated with timely PCI in both analyses.

All-Cause Mortality

In the overall population, inpatient-onset STEMI was associated with greater 1-year, 5-year, and 10-year all-cause mortality than outpatient-onset STEMI. However, 30-day all-cause mortality was similar (*P*=0.11) between patient groups. These associations persisted even after adjustment for baseline and clinical characteristics such as recognition-to-balloon time (Table 4 and Table S2). The Kaplan-Meier curve (Figure 2A) similarly demonstrated significantly worse survival for inpatient-onset STEMI (*P*<0.001). To further ascertain the correlation between inpatient-onset STEMI and long-term all-cause mortality, we performed secondary analyses on the 17 856 patients who survived to discharge. Significantly greater hazards for 1-year, 5-year, and 10-year all-cause mortality were similarly observed (Table S3). To evaluate the possible influence of postdischarge care on long-term mortality, we additionally adjusted in different models for the prescription of GDMT at discharge, alongside other factors such as left ventricular ejection fraction, presence of left ventricular systolic dysfunction, and cardiogenic shock during hospitalization (n=16 506). The association of inpatient-onset STEMI with higher long-term all-cause mortality remained significant (Table S3).

Subgroup Analyses for All-Cause Mortality

There was no difference in 30-day all-cause mortality between inpatient-onset STEMI and outpatient-onset STEMI across all subgroups. In contrast, an elevated 5-year all-cause mortality risk with inpatient-onset

Table 3. Univariate and Independent Predictors of Delayed Recognition-to-Balloon Time in Inpatient-Onset ST-Segment–Elevation Myocardial Infarction

	Moderate delays in PCI, recognition-to-balloon time >60 min to ≤90 min* (n=501)				Severe delays in PCI, recognition-to-balloon time >90 min* (n=452)			
	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Male sex	0.86 (0.64–1.16)	0.3			0.65 (0.48–0.86)	0.003	0.87 (0.62–1.24)	0.4
Ancestry		0.8				0.049		0.3
Chinese	1.00 (reference)				1.00 (reference)		1.00 (reference)	
Malay	0.85 (0.60–1.20)				1.01 (0.71–1.43)		1.06 (0.73–1.55)	
Indian	0.92 (0.67–1.27)				0.64 (0.45–0.91)		0.75 (0.51–1.09)	
Others	1.03 (0.32–3.32)				1.67 (0.60–5.04)		1.81 (0.61–5.69)	
Age ≥65 y	1.64 (1.27–2.12)	<0.001	1.47 (1.13–1.92)	0.005	2.12 (1.63–2.75)	<0.001	1.48 (1.10–2.01)	0.011
Chest pain	0.52 (0.39–0.70)	<0.001	0.58 (0.43–0.79)	<0.001	0.31 (0.23–0.42)	<0.001	0.36 (0.26–0.49)	<0.001
Breathlessness	0.93 (0.71–1.22)	0.6			1.44 (1.10–1.89)	0.008	1.46 (1.09–1.95)	0.012
Back pain	0.74 (0.44–1.21)	0.2			1.04 (0.65–1.67)	0.9		
Diaphoresis	0.93 (0.71–1.22)	0.6			0.81 (0.61–1.08)	0.15		
Jaw pain	0.84 (0.42–1.67)	0.6			0.81 (0.39–1.64)	0.6		
Syncope	0.94 (0.33–2.63)	>0.9			0.89 (0.29–2.58)	0.8		
Shoulder pain	0.59 (0.34–1.01)	0.057			0.53 (0.29–0.94)	0.029	0.68 (0.36–1.24)	0.2
Smoking		>0.9				0.031		0.8
Never	1.00 (reference)				1.00 (reference)		1.00 (reference)	
Former	1.06 (0.74–1.53)				0.90 (0.62–1.31)		0.83 (0.54–1.25)	
Current	0.95 (0.73–1.25)				0.68 (0.51–0.89)		0.87 (0.62–1.21)	
Diabetes	1.45 (1.13–1.86)	0.003	1.35 (1.04–1.75)	0.022	1.34 (1.04–1.74)	0.023	1.16 (0.87–1.54)	0.3
Hypertension	1.36 (1.06–1.74)	0.015	1.14 (0.88–1.48)	0.3	1.66 (1.29–2.16)	<0.001	1.31 (0.98–1.76)	0.070
Hyperlipidemia	1.12 (0.86–1.44)	0.4			0.82 (0.63–1.06)	0.13		
Previous PCI	0.75 (0.42–1.31)	0.3			1.00 (0.58–1.70)	>0.9		
Heart failure at admission, Killip class		0.2				<0.001		0.035
I	1.00 (reference)				1.00 (reference)		1.00 (reference)	
II	1.25 (0.71–2.21)				1.17 (0.63–2.13)		0.75 (0.39–1.43)	
III	2.22 (1.09–4.80)				4.12 (2.12–8.62)		2.63 (1.29–5.71)	
IV	0.99 (0.57–1.73)				1.90 (1.16–3.17)		1.29 (0.76–2.21)	

OR indicates odds ratio; and PCI, percutaneous coronary intervention.
*Relative to a recognition-to-balloon time of ≤60 min (timely PCI, n=537).

STEMI was observed in patients aged ≥65 years, both sexes, nonsmokers, those with chest pain at presentation, and those with diabetes, hypertension, and hyperlipidemia, but not in other subgroups (Figure 3).

Cardiovascular Mortality

In the overall population, the hazards for 30-day, 1-year, 5-year, and 10-year mortality were similar between inpatient-onset STEMI and outpatient-onset STEMI in both univariate and multivariate analyses (Table 4 and Table S4). The Kaplan-Meier curve (Figure 2B) similarly demonstrated significantly worse survival free from cardiovascular mortality for inpatient-onset STEMI (P<0.001). These findings on 1-year, 5-year, and 10-year cardiovascular mortality remained consistent across aforementioned sensitivity analyses in patients who survived to discharge (Table S3), thereby affirming their robustness.

Subgroup Analyses for Cardiovascular Mortality

The risk of 30-day cardiovascular mortality for inpatient-onset STEMI versus outpatient-onset STEMI were comparable across a majority of subgroups, mirroring the overall population. However, significant interaction was observed with hyperlipidemia status ($P_{interaction}$<0.05), where inpatient-onset STEMI was associated with a lower risk of 30-day cardiovascular

Table 4. Risks of 30-Day, 1-Year, 5-Year, and 10-Year All-Cause Mortality and Cardiovascular Mortality for Inpatient-Onset ST-Segment–Elevation Myocardial Infarction Compared With Outpatient-Onset ST-Segment–Elevation Myocardial Infarction

	All-cause mortality				Cardiovascular mortality			
	Unadjusted HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value	Unadjusted HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
30 d	1.65 (1.39–1.93)	<0.001	1.15 (0.97–1.37)	0.11	1.42 (1.19–1.69)	<0.001	1.01 (0.84–1.22)	0.9
1 y	1.86 (1.63–2.13)	<0.001	1.27 (1.10–1.46)	0.001	1.48 (1.26–1.73)	<0.001	1.03 (0.88–1.22)	0.7
5 y	1.88 (1.68–2.10)	<0.001	1.27 (1.13–1.43)	<0.001	1.50 (1.30–1.73)	<0.001	1.04 (0.90–1.21)	0.6
10 y	1.75 (1.58–1.94)	<0.001	1.20 (1.08–1.34)	0.001	1.44 (1.26–1.65)	<0.001	1.01 (0.88–1.16)	0.9

HR indicates hazard ratio.

*Adjusted for sex, age of onset, smoking, heart failure status at admission, diabetes, hypertension, hyperlipidemia, previous percutaneous coronary intervention, chest pain at presentation, and recognition-to-balloon time.

mortality, specifically among patients without hyperlipidemia (Figure 3). There was no significant difference in the risk of 5-year cardiovascular mortality in all subgroups (Figure 3).

DISCUSSION

In this national registry–based study of patients with first-onset STEMI treated with PCI, we found that patients with inpatient-onset STEMI were older, more frequently women, more likely to have comorbidities, and less likely to present with typical symptoms. Inpatient-onset STEMI was associated with a greater risk of 1-year, 5-year, and 10-year all-cause mortality compared with outpatient-onset STEMI, even after adjustment. However, there was no significant difference in 30-day all-cause mortality or in short- and long-term cardiovascular mortality between the 2 groups.

Our results are consistent, even after adjustment for differences in recognition-to-balloon time, with the findings by Stehli et al,[9] who reported similar 30-day but significantly higher 1-year odds of all-cause mortality for inpatient-onset versus outpatient-onset STEMI. However, our short-term outcomes differ from those found by Kaul et al,[2] which showed significantly greater odds of in-hospital mortality for inpatient-onset STEMI. This might be due to the inclusion of patients who did not receive PCI in the study by Kaul et al,[2] suggesting the protective effect of PCI in the short term after STEMI.[21] However, it could also reflect selection bias by treating physicians such that sicker patients with poorer short-term prognosis were treated medically instead of being referred for primary PCI. We further analyzed patients who survived to discharge and accounted for the prescription of discharge GDMT to affirm the long-term influence (even up to 5 years and 10 years) of inpatient-onset versus outpatient-onset STEMI on all-cause and cardiovascular mortality. The overall results remained consistent across these sensitivity analyses, underscoring the robustness of our study in demonstrating that, regardless of differences in baseline and clinical characteristics, patients with inpatient-onset STEMI experience greater long-term all-cause mortality.

The higher long-term (1-year, 5-year, and 10-year) all-cause mortality among patients with inpatient-onset STEMI when compared with patients with outpatient-onset STEMI could be due to several factors. Given insignificant differences in long-term cardiovascular mortality, patients with inpatient-onset STEMI appeared more likely to die from noncardiovascular causes in the long term. Prior studies have demonstrated a reduction in the long-term risk for cardiovascular mortality when compared against mortality from noncardiovascular causes in patients who underwent PCI after STEMI.[22,23] It is likely that PCI conferred a prolonged protective benefit over cardiovascular health/mortality in both patients with inpatient-onset and patients with outpatient-onset STEMI. The prescription of GDMT at discharge may also have contributed to improved long-term cardiovascular outcomes.[24] This could suggest that patients with inpatient-onset STEMI were more likely to die from the underlying noncardiovascular conditions for which they were originally hospitalized after surviving the initial AMI event. They may have been admitted for noncardiac surgeries, which are not only a risk factor for STEMI, but can also increase the long-term mortality attributed to STEMI.[25] On the other hand, Sibila et al[26] found that prior cardiovascular disease increases all-cause long-term mortality in patients with chronic obstructive pulmonary disease with pneumonia. Therefore, we postulate that among patients with inpatient-onset STEMI, the higher incidence of comorbidities, coupled with an advanced age, concurrent illness or surgery, and the inevitable cardiac dysfunction post-STEMI, could have contributed to a disproportionately worse reduction in their overall physiological reserves compared with those with outpatient-onset STEMI, thereby rendering them more susceptible to adverse outcomes including mortality from noncardiovascular causes.[27,28]

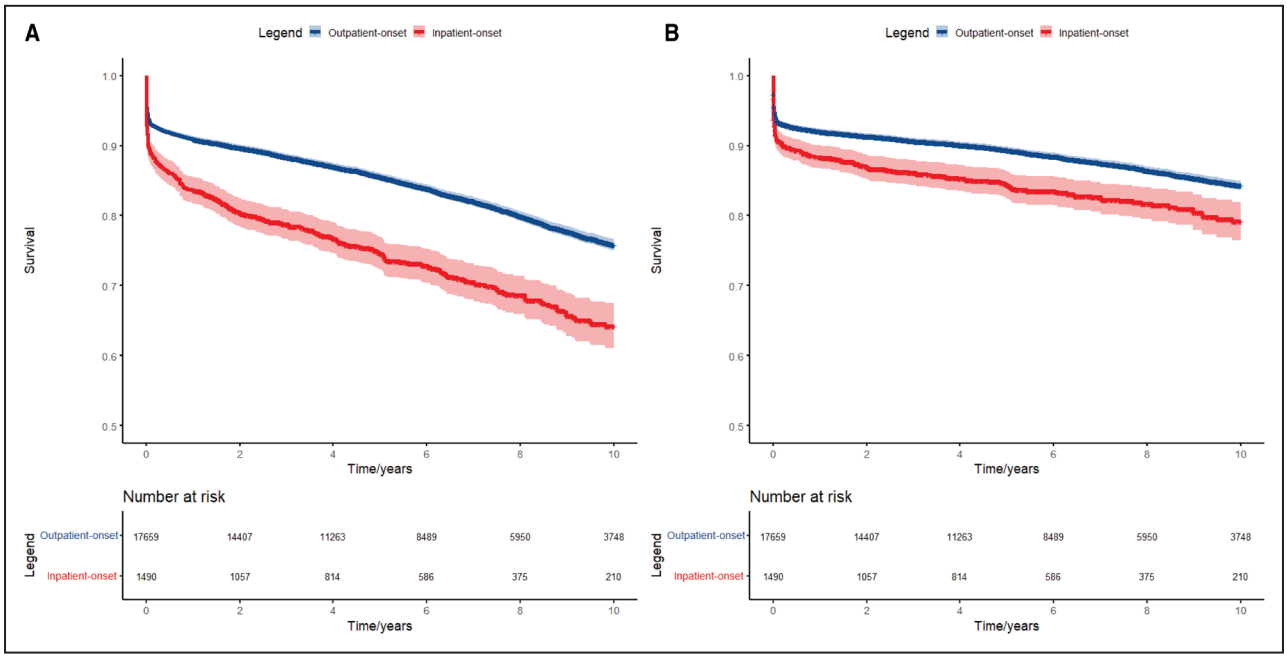

Figure 2. Kaplan-Meier curves for all-cause and cardiovascular mortality.
Kaplan-Meier curves for all-cause mortality (**A**) and cardiovascular mortality (**B**).

Importantly, our study only found a significant association with all-cause mortality among older patients with inpatient-onset STEMI aged ≥65 years, but not in those aged <65 years. Further research is required to elucidate if this is due to the higher physiological reserves in the younger patients, hence reducing the effect of the interplay between cardiac dysfunction and existing disease/comorbidities. Furthermore, some of the inpatient-onset STEMI might be a manifestation of type 2 myocardial infarction with or without significant underlying coronary artery disease, particularly given their higher rate of comorbidities and advanced age.[29,30] It has been shown that patients with type 2 myocardial infarction have higher long-term mortality when compared with patients with type 1 myocardial infarction but die from noncardiovascular causes more frequently than type 1 myocardial infarction.[29,30] This would align with the findings of our study, where the inpatient group experienced higher long-term all-cause mortality but not cardiovascular mortality. However, because all patients underwent PCI, they may be more likely to have had type 1 myocardial infarction, so this hypothesis should be considered with caution.[31]

Patients with inpatient-onset STEMI were less likely to present with typical symptoms. This can result in a major diagnostic challenge to clinicians, attributing the symptoms to their underlying disease, thereby delaying the suspicion of STEMI and subsequent intervention. On the other hand, the symptoms of the underlying disease could have also masked those of STEMI itself (eg, concomitant noncardiac causes of chest pain).[32] The resultant uncertainty of a STEMI would have contributed to delays in PCI. Furthermore, the presence of noncardiac comorbidities necessitates additional evaluation to determine whether the patient is an appropriate candidate for intervention, therefore further prolonging the time to reperfusion. It is also important to consider that the ability of patients with inpatient-onset to communicate symptoms might have been impaired, which is frequent in these patients.[33] Concurrent pharmacological pain management could also have attenuated their perception of pain/discomfort.[34]

We observed that patients with inpatient-onset STEMI had longer intervals from in-hospital diagnosis of STEMI to PCI compared with patients with outpatient-onset STEMI (inpatient-onset recognition-to-balloon time versus outpatient-onset door-to-balloon time: 71 minutes versus 62 minutes). This disparity represents an aspect for potential optimization and further underscores the necessity of efforts targeted at improving recognition and management of patients with inpatient-onset STEMI. Garberich et al[35] reported that a standardized protocol for inpatient-onset STEMI helped reduce in-hospital mortality by 10%. Because the skill of ECG interpretation could also lead to delayed recognition, it is even more crucial for having standardized protocols. Kanaan et al[6] reported improvements in recognition-to-balloon times and administration of GDMT before PCI for patients with inpatient-onset STEMI after protocol implementation but were unable to demonstrate significant changes in in-hospital, 30-day, or 1-year mortality. The protocols

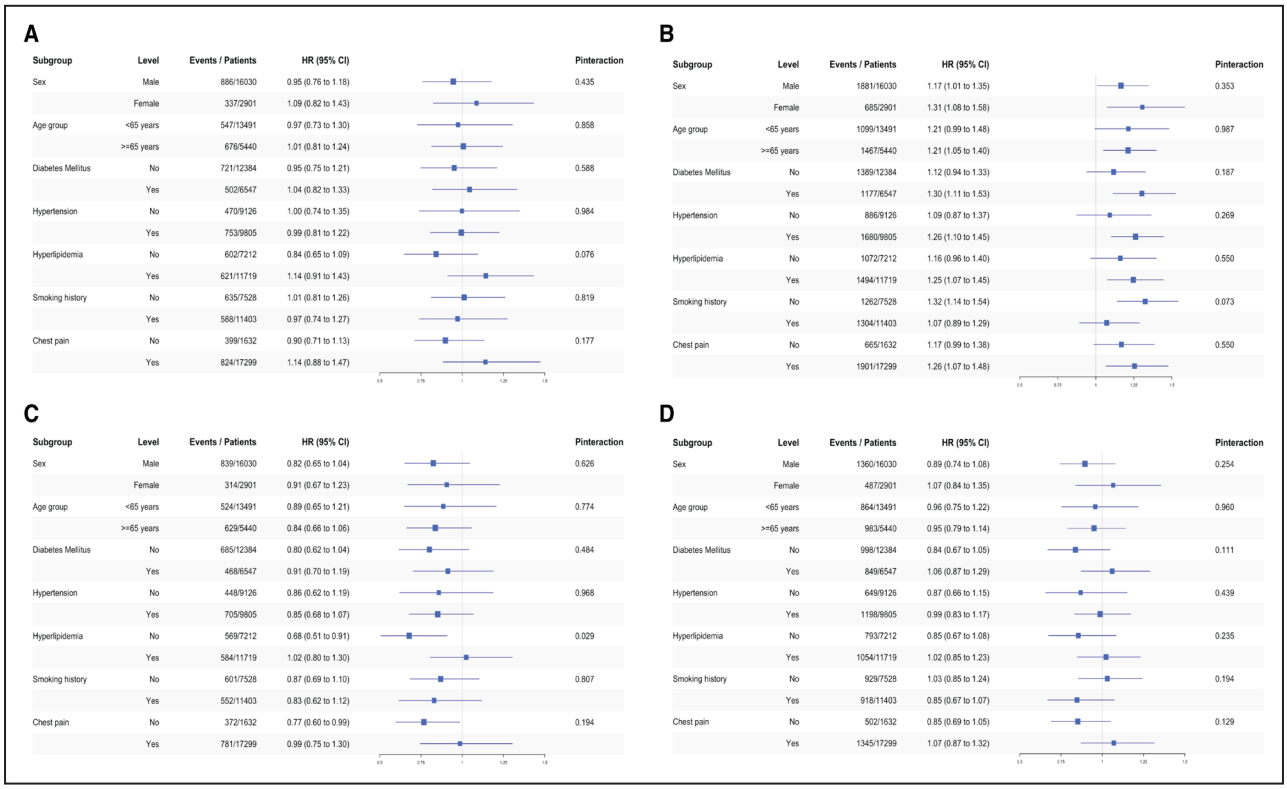

Figure 3. Subgroup analysis for all-cause and cardiovascular mortality at 30 days and 5 years.
A, Subgroup analysis for 30-day all-cause mortality. **B**, Subgroup analysis for 5-year all-cause mortality. **C**, Subgroup analysis for 30-day cardiovascular mortality. **D**, Subgroup analysis for 5-year cardiovascular mortality. HR indicates hazard ratio.

included components such as a protocol for nurses to address chest pain in inpatients, improved ECG access coupled with autointerpretation and notifications, and an inpatient STEMI safe handoff checklist to standardize initial triage and improve antiplatelet administration.[6,35] These components should be considered for adoption in more institutions and evaluated on a larger scale over an extended period to ascertain their efficacy in improving outcomes for inpatient-onset STEMI.

There are several limitations of our study. First, given the retrospective nature of our study, we were unable to demonstrate causation due to the possibility of residual confounding. Second, we were unable to adjust for potentially significant predictors of mortality such as renal failure, the incidence of cardiac arrest, exclusion criteria for typically prescribed medications, ECG-to-balloon time, type 1 myocardial infarction flow during PCI, and information on the time of presentation for inpatient symptoms, because such data were unavailable in the SMIR. Notably, the data lack sufficient granularity, which constrained our ability to investigate (eg, angiographic and other procedural variables that would have enabled a more detailed exploration). Third, SMIR also did not collect information on the cause for hospitalization of inpatients. A thorough investigation of the type of myocardial infarction and causes for hospitalization could have provided greater clarity as to why inpatients suffered from greater mortality than outpatients. Fourth, intercountry and interinstitutional variations in clinical practices, particularly STEMI protocols and the availability of resources crucial for reperfusion, may limit the generalizability of our findings. Nonetheless, our study provides important insights by identifying potentially higher-risk patient groups. Last, to adjust for delays in PCI in our analysis, we primarily used recognition-to-balloon time. This metric captures the total ischemic time from symptom onset to PCI,[3] and not just hospital-related delays, which are measured by door-to-balloon time. However, it is inherently reliant on patient-reported symptom onset, which introduces potential subjectivity.[36] Delays in symptom recognition by the patient may underestimate recognition-to-balloon time, whereas overreporting or exaggerating symptom onset could lead to an overestimation of total ischemic time, of which both scenarios can bias subsequent mortality estimates in either direction. Current international guidelines endorse first medical contact-to-balloon time as the primary metric for evaluating health care system performance in STEMI care, due to greater consistency and applicability in real-world clinical audits.[4,5] However, the time of first medical contact-to-balloon time was not

captured in SMIR. Hence, due to this limitation, we instead used recognition-to-balloon time for our analyses. Recognition-to-balloon time has been used in large cohort studies,[37,38] and longer recognition-to-balloon times have been associated with poorer patient outcomes. The 2025 American College of Cardiology/American Heart Association/American College of Emergency Physicians/National Association of Emergency Medical Services Physicians/Society for Cardiovascular Angiography and Interventions guidelines[5] emphasize minimizing total ischemic time in the management of patients with STEMI, which we aimed to measure via recognition-to-balloon time.

To account for the effect of systolic function on mortality outcomes, we had adjusted for left ventricular ejection fraction, presence of left ventricular systolic dysfunction, and in-hospital cardiogenic shock in patients who survived to discharge as a sensitivity analysis. The association of inpatient-onset STEMI with greater long-term all-cause mortality remained significant in this group of patients. However, we could not adjust for these variables in the overall population (inclusive of patients who did not survive to discharge), because these variables were measured in the course of the patients' stays. There were no data on the time that these measurements were taken during the course of their hospitalization after the initial STEMI. Therefore, these variables may only be measured in patients who have survived for a certain period, possibly incurring a selection bias if adjusted for in the overall population. We attempted to overcome this limitation by adjusting for heart failure status at presentation, which acts as clinical surrogate for systolic function. Future studies should prospectively collect data on left ventricular ejection fraction and the presence of left ventricular systolic dysfunction at discharge to account for the effect of systolic function on mortality outcomes. Subsequent research using large-scale electronic health records or national registries should also aim to capture more detailed information on patients with inpatient-onset STEMI, particularly on the reasons for nonrevascularization. This is especially pertinent given that these patients are generally less likely to undergo PCI.[2,9] A greater understanding of this distinct patient group may enable clinicians and health care systems to better evaluate and address their needs within their own settings.

CONCLUSIONS

Inpatient-onset STEMI was associated with a heightened long-term risk of all-cause mortality compared with outpatient-onset STEMI despite a shorter recognition-to-balloon time. However, short- and long-term cardiovascular mortality risks were similar between both groups. Patients aged ≥65 years, women, patients with comorbidities, patients with no history of smoking, and patients presenting without chest pain were particularly vulnerable. Our findings also emphasize the need for health care professionals and policymakers to enhance the care provided for inpatient-onset STEMI.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figure S1

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