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Original Article

Prolonged symptom-to-door time, cardiogenic-shock status and adverse in-hospital outcomes in emergency department patients with ST-segment elevation myocardial infarction: a retrospective cross-sectional study with statistical pathway decomposition

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Abstract: Objectives: To quantify the association between prolonged symptom-to-door (StD) time and adverse in-hospital outcome status in ST-segment elevation myocardial infarction (STEMI), and what share of it is statistically represented by cardiogenic-shock status. Methods: Record-based retrospective cross-sectional study of 760 completed index hospital episodes among adults presenting directly to one emergency department with STEMI (March 2020 to August 2025), each contributing one record built at final in-hospital disposition. The exposure was prolonged StD time (>6 h), the pathway variable cardiogenic-shock status, and the outcome a composite of death, cardiac arrest, sustained ventricular arrhythmia, stroke or mechanical complication, from which shock was excluded. Sequentially adjusted logistic models, standardized decomposition with 500 bootstrap resamples, component-specific decomposition, E-values and sensitivity analyses were applied. Results: Median StD time was 3.34 h (IQR 1.85-5.93); 24.5% exceeded 6 h. Cardiogenic-shock status was present in 10.8% patients and the composite outcome in 15.7%. Prolonged StD time was associated with the outcome in the fully adjusted model (OR 2.28, 95% CI 1.48-3.53, P<0.001) and with cardiogenic-shock status (OR 4.57, 95% CI 2.77-7.53), retaining a residual association after shock was included (OR 1.79, 95% CI 1.13-2.83). Decomposition attributed 30.9% (95% CI 13.0-75.1%) of the log-scale association to shock, concentrated in death and cardiac arrest. The E-value was 3.34. Conclusions: Prolonged StD time was associated with higher odds of adverse in-hospital outcome status, and cardiogenic-shock status statistically represented about one third of this association. Because all variables were summarized at a single record-closure assessment, these are statistical associations, not causal mediation.

Keywords: ST-segment elevation myocardial infarction, symptom-to-door time, cardiogenic shock, adverse in-hospital outcomes, retrospective cross-sectional study, statistical pathway decomposition

Introduction

Ischemic heart disease remains the single largest contributor to the global burden of cardiovascular disease and carries the highest age-standardized disability-adjusted life-year rate of any condition worldwide [1]. Within this spectrum, ST-segment elevation myocardial infarction (STEMI) is the most time-critical presentation, because the extent of irreversible myocardial necrosis is governed largely by the duration of coronary occlusion. Contemporary guidance therefore organizes STEMI care around total ischemic time rather than around any single procedural interval, recommends primary percutaneous coronary intervention (PCI) whenever it can be delivered promptly, and reserves fibrinolysis for settings in which timely PCI is not achievable [2, 3].

Total ischemic time has two structurally different components. System delay reflects the performance of pre-hospital and in-hospital networks and has been substantially compressed by chest pain center accreditation, pre-hospital electrocardiography and direct catheterization

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laboratory activation. Patient delay, by contrast, reflects symptom interpretation and care-seeking behavior, and has proved far more resistant to intervention. A nationwide analysis of 458,260 patients with STEMI treated with primary PCI across 2,529 centers reported a median total ischemic time of 4.1 h, a median patient delay of 2.1 h and a median system delay of 1.5 h; each additional hour of patient delay was associated with a 2.2% relative increase in the adjusted odds of in-hospital death (OR 1.022, 95% CI 1.017-1.027), a magnitude essentially indistinguishable from that of system delay (OR 1.023, 95% CI 1.006-1.040) [4].

Patients who reach the hospital late form a clinically distinct group. Among 5,826 consecutive patients with STEMI presenting within 48 h of symptom onset in a national registry, the 624 who presented between 12 and 48 h had considerably worse long-term outcomes than early presenters [5]. In a registry-based single-center analysis, the 49 patients who presented at or beyond 12 h differed from the 365 who presented earlier in being more often female, more often diabetic and less likely to report chest pain, and they experienced significantly higher long-term mortality [6]. Determinants of patient-related delay have been characterized in dedicated network analyses [7], and a systematic review and meta-analysis of 29 studies covering 127,409 patients with acute myocardial infarction found female sex to be associated with prolonged pre-hospital delay (OR 1.17, 95% CI 1.11-1.23) and, more strongly, with patient delay specifically (OR 1.23, 95% CI 1.10-1.38) [8].

Cardiogenic shock is the principal mechanism through which a large infarct becomes a lethal one. It remains the leading cause of in-hospital death after acute myocardial infarction, affects an estimated 40,000 to 50,000 people each year in the United States, and carries a 30-day mortality of approximately 40% with 1-year mortality approaching 50% [9]. A systematic review and meta-analysis of 25 studies noted that its reported incidence after myocardial infarction ranged from 2.7% to 10% and identified female sex, advanced age, smoking, diabetes and ST-segment elevation presentation as correlates of its development [10]. Nationwide mortality data covering 187,838 deaths showed that the age-adjusted mortality rate attributable to shock complicating myocardial infarction fell from 5.4 to 3.3 per 100,000 between 1999 and 2023, yet rose again between 2011 and 2021 [11]. Therapeutic progress has been real but incremental: routine use of a microaxial flow pump reduced 180-day all-cause death compared with standard care alone (45.8% versus 58.5%) among 355 patients with STEMI-related shock [12], and standardized severity staging is now embedded in routine practice [13].

Prolonged delay and cardiogenic shock are thus each firmly associated with poor in-hospital outcomes, and the two are widely assumed to be linked. What has not been quantified is how much of the observed association between prolonged symptom-to-door time and adverse in-hospital outcome status is statistically represented by cardiogenic-shock status. Answering that question carries a specific methodological constraint. When symptom-to-door time, shock status and outcome status are all abstracted from one completed hospital record at a single record-closure assessment, no temporal ordering is measured within the episode, and a longitudinal or causal mediation framing would overstate what the data can support. A strictly cross-sectional framing, in which shock is handled as a statistical pathway variable rather than as a causal mediator, is the appropriate alternative. We therefore conducted a record-based retrospective cross-sectional study of completed index hospital episodes with three aims: to quantify the cross-sectional association between prolonged symptom-to-door time and adverse in-hospital outcome status under sequential adjustment; to decompose that association into a component statistically represented by cardiogenic-shock status and a residual component; and to test the robustness of both under prespecified alternative exposure definitions, restricted populations and subgroups.

Materials and methods

Study design and setting

We conducted a single-center, record-based retrospective cross-sectional observational study in the Emergency Department (ED) of Handan First Hospital, Handan, Hebei, China, a tertiary referral hospital operating a 24-hour

primary PCI service within an accredited chest pain pathway. The study window ran from 12 March 2020 to 31 August 2025. The study protocol was reviewed and approved by the Medical Ethics Committee of Handan First Hospital through expedited review on 20 August 2026 (approval No. HDYY-LW-26100). The requirement for individual informed consent was waived by the same committee, which approved the submitted application for waiver of informed consent, because the dataset was de-identified before analysis and the study involved no intervention. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology recommendations for cross-sectional studies.

Cross-sectional index assessment

The analytic unit was one completed index hospital episode. For every patient, a single eligible hospitalization was retained, and all study variables were abstracted on one occasion after that record was complete. The fixed cross-sectional index assessment was defined as the point of final in-hospital disposition, that is, discharge alive or in-hospital death, at which the hospital record had closed. At this single assessment we abstracted the interval from recorded symptom onset to arrival at the study ED, whether cardiogenic shock had been documented at any point during the completed index hospitalization, whether any prespecified adverse in-hospital outcome had been documented, and the prespecified covariates. Each patient therefore contributes exactly one row to the analysis file. No observation was made after the record-closure assessment, no follow-up interval was constructed, and no incidence rate, time-to-event endpoint or hazard ratio was estimated. All estimates reported below are cross-sectional associations between status variables summarized from the same episode.

Participants and eligibility

Eligible patients were adults aged 18 years or older who presented directly to the study ED during the study window and whose completed hospital record supported STEMI as the index episode diagnosis, for whom an interpretable symptom-onset time and ED arrival time permitted calculation of symptom-to-door time, for whom the record had closed at a final in-hospital disposition, for whom cardiogenic-shock status could be classified from the completed record, for whom every component of the prespecified adverse outcome could be adjudicated, and for whom the prespecified core covariates were recorded.

Record selection

An initial electronic search identified 1,286 ED records carrying STEMI diagnostic coding or a qualifying electrocardiographic flag. Records were then excluded in eight prespecified steps. We removed 81 duplicate extractions or repeat eligible admissions so that one index hospital episode was retained per patient (n=1,205), 102 records in which final chart review did not support STEMI as the index diagnosis (n= 1,103), and 89 patients transferred from another acute hospital or given initial reperfusion treatment before arrival at the study ED, whose symptom-to-door interval is not directly comparable with that of direct presenters (n=1,014). We further excluded 76 patients with out-of-hospital cardiac arrest before ED arrival or without a sufficiently reliable symptom-onset time (n=938), 58 patients whose symptom onset preceded arrival by more than 48 h or whose recurrent or stuttering symptoms precluded assignment of a single onset point (n=880), 51 patients whose completed record was insufficient to classify cardiogenic-shock status (n=829), and 69 patients with missing adverse-outcome status or missing prespecified core covariates. The final analytic sample comprised 760 patients.

Exposure

The primary exposure was symptom-to-door time, defined as the elapsed interval in hours between recorded symptom onset and arrival at the study ED. The prespecified primary exposure status variable was prolonged symptom-to-door time, coded 1 for intervals longer than 6 h and 0 otherwise. The 6-hour threshold is a prespecified analytic cut-point chosen for this study and is not a guideline-defined diagnostic boundary. Symptom-to-door time was additionally retained as a continuous variable and as an alternative binary indicator of very late presentation beyond 12 h.

Statistical pathway variable

The statistical pathway variable was cardiogenic-shock status, coded 1 if cardiogenic shock was documented at any point within the completed index hospitalization and 0 otherwise. A separate indicator recorded whether cardiogenic shock was already documented at the initial ED assessment, and this was used only for a timing-oriented sensitivity analysis. Throughout, cardiogenic shock is described as a status variable and as a statistical pathway variable. It is not interpreted as a causal mediator, because the assessment design provides no measured temporal separation between exposure, pathway and outcome within the episode.

Outcome

The primary outcome was composite adverse in-hospital outcome status, coded 1 if at least one of the following was documented during the completed index hospitalization: in-hospital death, resuscitated cardiac arrest, sustained ventricular tachycardia or ventricular fibrillation requiring treatment, in-hospital ischemic or hemorrhagic stroke, or an acute mechanical complication such as ventricular septal rupture, papillary muscle rupture with acute severe mitral regurgitation, or ventricular free-wall rupture. Cardiogenic shock was deliberately excluded from this composite so that the pathway variable and the outcome share no definitional overlap, which would otherwise render the decomposition mathematically circular. The number of documented outcome components was retained as a secondary count outcome.

Covariates

Covariates were prespecified and grouped into three blocks. The demographic block comprised age, sex and body mass index. The comorbidity block comprised hypertension, diabetes mellitus, chronic kidney disease, current smoking and prior myocardial infarction. The clinical and presentation block comprised anterior STEMI, atypical presenting symptoms, arrival by emergency medical services (EMS), weekend arrival and night-time symptom onset. Variables recorded after ED arrival, including first ED vital signs, admission laboratory values, left ventricular ejection fraction, reperfusion strategy, primary PCI and door-to-wire time, were treated as descriptive or as sensitivity variables and were not entered into the primary confounder set, because adjustment for post-arrival treatment characteristics would condition on consequences of the exposure.

Statistical analysis

Continuous variables are summarized as mean with standard deviation or as median with interquartile range according to distribution, and categorical variables as counts with percentages. Between-group comparisons used the independent-samples t test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher exact test for categorical variables [14, 15]. Four sequential binary logistic regression models estimated the association between prolonged symptom-to-door time and adverse in-hospital outcome status: Model I was unadjusted; Model II added age, sex and body mass index; Model III added the comorbidity block; and Model IV, the prespecified primary model, added the clinical and presentation block. Results are reported as odds ratios with 95% confidence intervals. Symptom-to-door time was additionally modelled continuously after base-2 logarithmic transformation, so that the coefficient represents the association per doubling of the interval, and as a four-level categorical variable with a test for linear trend. Test statistics are reported in the tables alongside every *P* value: t for the independent-samples t test, Z for the Mann-Whitney U test and the chi-square statistic for categorical comparisons, the last computed with the Yates continuity correction for 2×2 tables.

The pathway analysis proceeded in two stages. Pathway model A regressed cardiogenic-shock status on prolonged symptom-to-door time with Model IV covariates. Pathway model B regressed adverse in-hospital outcome status on prolonged symptom-to-door time, cardiogenic-shock status and Model IV covariates simultaneously, yielding the shock-outcome association and the residual exposure association. We then performed a standardized decomposition of the cross-sectional association on the odds-ratio scale using a regression-based g-computation approach, in which the fitted pathway and outcome models were used to compute standardized probabilities across

the observed covariate distribution. The overall association was partitioned into an indirect component statistically represented by cardiogenic-shock status and a residual component not represented by it, and the proportion of the log-scale association attributable to the indirect component was calculated. Confidence intervals for all decomposition quantities were obtained from 500 bootstrap resamples of the analytic dataset using the percentile method. These quantities are reported as a statistical decomposition of cross-sectional associations and are not presented as natural direct or natural indirect effects. The same decomposition was then repeated separately for each component of the composite outcome, so that the share of the association represented by cardiogenic shock could be examined event by event rather than only in aggregate. To quantify robustness to unmeasured confounding, E-values were computed for the primary estimate and for the bound of its confidence interval nearest the null, after converting odds ratios to approximate risk ratios using the observed outcome prevalence in the unexposed group.

Eight prespecified sensitivity analyses were performed: continuous modelling of log-transformed symptom-to-door time; redefinition of delay as more than 12 h; exclusion of patients with cardiogenic shock already documented at ED arrival; restriction to patients treated with primary PCI; exclusion of symptom-to-door times exceeding 24 h; additional adjustment for first ED systolic blood pressure, heart rate and admission lactate; additional adjustment for calendar year of admission; and restriction of the outcome to in-hospital death alone. Subgroup analyses were conducted across age, sex, infarct location, diabetes status, mode of arrival, symptom typicality and receipt of primary PCI, each estimated within the subgroup using Model IV covariates other than the stratifying variable, with multiplicative interaction terms used to test for effect modification. Two-sided *P* values below 0.05 were considered statistically significant. Analyses were performed in Python 3.12 using the statsmodels, pandas, numpy and scipy libraries.

Sample size and precision

No a priori sample size or power calculation was performed. The study was record-based and included every episode in the study window that met the eligibility criteria, so the sample size was fixed by the available records rather than chosen to achieve a target power. Precision is therefore reported post hoc. For the primary comparison, with 574 unexposed and 186 exposed patients and an outcome prevalence of 12.5% in the unexposed group, the sample provided 80% power at a two-sided alpha of 0.05 to detect an odds ratio of 1.87 or larger, and 96% power for the odds ratio actually observed. Model IV contained 119 events for 14 estimated parameters, giving 8.5 events per variable, whereas pathway model A contained 82 events for the same number of parameters, giving 5.9 events per variable. Precision for the decomposition proportion is reported as the width of its bootstrap interval and is interpreted accordingly.

Results

Record selection and analytic sample

Of 1,286 initially identified ED records, 760 completed index hospital episodes met all criteria and formed the analytic sample. Mean age was 62.9 (SD 12.4) years, 551 patients (72.5%) were male, 355 (46.7%) had anterior STEMI and 700 (92.1%) underwent primary PCI. Median symptom-to-door time was 3.34 h (IQR 1.85-5.93). Prolonged symptom-to-door time beyond 6 h was recorded in 186 patients (24.5%) and very late presentation beyond 12 h in 62 patients (8.2%). Cardiogenic-shock status was documented in 82 patients (10.8%), of whom 42 (5.5% of the sample) already had shock documented at initial ED assessment. Composite adverse in-hospital outcome status was documented in 119 patients (15.7%) and in-hospital death in 29 patients (3.8%).

Baseline and presentation characteristics

Baseline characteristics by exposure status are shown in **Table 1**. Patients with prolonged symptom-to-door time resembled earlier presenters in age (62.4 versus 63.1 years, P= 0.496), sex distribution (68.3% versus 73.9% male, P=0.165), body mass index and burden of hypertension, chronic kidney disease and prior myocardial infarction. They were, however, more likely to have diabetes mellitus (32.3% versus 22.3%, P=0.008), to present with atypical symptoms (18.8% versus 10.8%, P=0.007)

Table 1. Baseline, presentation and treatment characteristics of 760 patients with STEMI according to symptom-to-door status

Characteristic	Total (n=760)	≤6 h (n=574)	>6 h (n=186)	Test statistic	*P* value
Age, years	62.9 ± 12.4	63.1 ± 12.3	62.4 ± 12.8	t=0.68	0.496
Male sex	551 (72.5)	424 (73.9)	127 (68.3)	χ^2=1.93	0.165
Body mass index, kg/m^2	25.0 ± 3.4	25.0 ± 3.5	25.1 ± 3.1	t=0.33	0.741
Current smoking	377 (49.6)	294 (51.2)	83 (44.6)	χ^2=2.19	0.139
Hypertension	328 (43.2)	257 (44.8)	71 (38.2)	χ^2=2.23	0.135
Diabetes mellitus	188 (24.7)	128 (22.3)	60 (32.3)	χ^2=6.96	0.008
Chronic kidney disease	116 (15.3)	83 (14.5)	33 (17.7)	χ^2=0.93	0.335
Prior myocardial infarction	108 (14.2)	80 (13.9)	28 (15.1)	χ^2=0.07	0.796
Prior percutaneous coronary intervention	103 (13.6)	81 (14.1)	22 (11.8)	χ^2=0.45	0.505
Anterior STEMI	355 (46.7)	268 (46.7)	87 (46.8)	χ^2=0.00	1.000
Atypical presenting symptoms	97 (12.8)	62 (10.8)	35 (18.8)	χ^2=7.40	0.007
Night-time symptom onset	306 (40.3)	211 (36.8)	95 (51.1)	χ^2=11.38	<0.001
Weekend arrival	217 (28.6)	167 (29.1)	50 (26.9)	χ^2=0.24	0.626
Arrival by emergency medical services	298 (39.2)	238 (41.5)	60 (32.3)	χ^2=4.62	0.032
Symptom-to-door time, h	3.3 (1.8-5.9)	2.5 (1.5-3.9)	9.4 (7.4-13.6)	Z=20.52	<0.001
First ED systolic blood pressure, mmHg	131.6 ± 19.8	132.7 ± 19.4	128.1 ± 20.6	t=2.71	0.007
First ED heart rate, beats/min	84.7 ± 15.7	84.8 ± 15.1	84.4 ± 17.5	t=0.28	0.783
Admission creatinine, μmol/L	84 (70-98)	84 (70-98)	84 (68-97)	Z=0.40	0.686
Admission glucose, mmol/L	8.1 (6.5-9.6)	7.8 (6.3-9.4)	8.8 (7.5-10.8)	Z=5.68	<0.001
Admission lactate, mmol/L	1.9 (1.5-2.6)	1.9 (1.5-2.5)	2.0 (1.6-3.3)	Z=3.98	<0.001
Left ventricular ejection fraction, %	46.0 ± 9.1	46.8 ± 9.0	43.5 ± 9.2	t=4.30	<0.001
Reperfusion strategy				χ^2=3.17	0.205
Primary percutaneous coronary intervention	700 (92.1)	532 (92.7)	168 (90.3)		
Fibrinolysis	21 (2.8)	17 (3.0)	4 (2.2)		
No acute reperfusion	39 (5.1)	25 (4.4)	14 (7.5)		
Door-to-wire time, min[a]	82 (70-93)	82 (69-93)	82 (72-92)	Z=0.01	0.990
Length of stay, days	8 (6-9)	7 (6-9)	8 (7-10)	Z=3.43	<0.001

Data are mean ± SD, median (interquartile range) or n (%). Between-group comparisons used the independent-samples t test, the Mann-Whitney U test, the chi-square test or the Fisher exact test as appropriate. [a]Restricted to the 700 patients treated with primary percutaneous coronary intervention. ED, emergency department; STEMI, ST-segment elevation myocardial infarction.

and to report night-time symptom onset (51.1% versus 36.8%, P<0.001), and they were less likely to arrive by EMS (32.3% versus 41.5%, P=0.032). Anterior infarct location was almost identically distributed (46.8% versus 46.7%, P=1.000). On arrival, late presenters had modestly lower systolic blood pressure (128.1 versus 132.7 mmHg, P=0.007), higher admission glucose and lactate (both P<0.001) and lower documented left ventricular ejection fraction (43.5% versus 46.8%, P<0.001). Reperfusion strategy did not differ significantly between groups (P=0.205), and among the 700 patients treated with primary PCI the median door-to-wire time was identical at 82 min in both groups (P=0.990), indicating that in-hospital process efficiency was preserved regardless of how late the patient arrived.

Cardiogenic-shock status and adverse outcome status

Cardiogenic-shock status and adverse outcome status by exposure group are presented in **Table 2**. Cardiogenic shock was documented in 23.7% of patients with prolonged symptom-to-door time compared with 6.6% of earlier presenters (P<0.001; crude OR 4.37, 95% CI 2.73-7.01), and shock already present at ED arrival was likewise more frequent (14.5% versus 2.6%; crude OR 6.33, 95% CI 3.29-12.19). The composite adverse outcome was docu-

Table 2. Cardiogenic-shock status and adverse in-hospital outcome status at the record-closure index assessment according to symptom-to-door status

Status variable	Total (n=760)	≤6 h (n=574)	>6 h (n=186)	Test statistic	*P* value	Crude OR (95% CI)
Cardiogenic shock, any during index episode	82 (10.8)	38 (6.6)	44 (23.7)	χ^2=40.61	<0.001	4.37 (2.73-7.01)
Cardiogenic shock already present at ED arrival	42 (5.5)	15 (2.6)	27 (14.5)	χ^2=35.88	<0.001	6.33 (3.29-12.19)
Composite adverse in-hospital outcome	119 (15.7)	72 (12.5)	47 (25.3)	χ^2=16.28	<0.001	2.36 (1.56-3.56)
In-hospital death	29 (3.8)	18 (3.1)	11 (5.9)	χ^2=2.25	0.134	1.94 (0.90-4.19)
Resuscitated cardiac arrest	42 (5.5)	22 (3.8)	20 (10.8)	χ^2=11.59	<0.001	3.02 (1.61-5.68)
Sustained ventricular tachycardia or fibrillation	34 (4.5)	17 (3.0)	17 (9.1)	χ^2=11.14	<0.001	3.30 (1.65-6.60)
In-hospital stroke	17 (2.2)	9 (1.6)	8 (4.3)	χ^2=3.63	0.057	2.82 (1.07-7.42)
Acute mechanical complication	18 (2.4)	10 (1.7)	8 (4.3)	χ^2=2.95	0.086	2.53 (0.99-6.52)
Number of outcome components, mean	0.18	0.13	0.34	Z=4.37	<0.001	-

Data are n (%) unless otherwise indicated. Cardiogenic shock is deliberately excluded from the composite adverse in-hospital outcome to prevent definitional overlap with the statistical pathway variable. CI, confidence interval; ED, emergency department; OR, odds ratio.

Table 3. Sequentially adjusted associations between prolonged symptom-to-door time and adverse in-hospital outcome status (Models I to IV)

Model	Covariates included	OR (95% CI)	*P* value
Model I	Unadjusted	2.36 (1.56-3.56)	<0.001
Model II	Age, sex, body mass index	2.38 (1.57-3.62)	<0.001
Model III	Model II plus hypertension, diabetes mellitus, chronic kidney disease, current smoking, prior myocardial infarction	2.23 (1.46-3.40)	<0.001
Model IV[a]	Model III plus anterior STEMI, atypical symptoms, arrival by emergency medical services, weekend arrival, night-time symptom onset	2.28 (1.48-3.53)	<0.001
Alternative parameterizations of the exposure (Model IV covariates)			
Continuous	Per doubling of symptom-to-door time ($\log_2$)	1.34 (1.14-1.58)	<0.001
<2 h (n=210)	Reference category	1.00	-
2-6 h (n=364)	Categorical symptom-to-door time	1.17 (0.69-2.00)	0.554
6-12 h (n=124)	Categorical symptom-to-door time	2.08 (1.12-3.89)	0.021
>12 h (n=62)	Categorical symptom-to-door time	3.62 (1.77-7.40)	<0.001
P for trend	Across the four ordered symptom-to-door categories	-	<0.001
Other independent correlates within Model IV			
Anterior STEMI	Model IV	2.21 (1.45-3.34)	<0.001
Age, per year	Model IV	1.02 (1.00-1.04)	0.049

[a]Model IV is the prespecified primary model. All estimates derive from binary logistic regression with adjacent-block sequential adjustment; n=760 for every model. CI, confidence interval; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction.

mented in 25.3% versus 12.5% (P<0.001; crude OR 2.36, 95% CI 1.56-3.56). Among individual components, resuscitated cardiac arrest (10.8% versus 3.8%, P<0.001) and sustained ventricular tachycardia or fibrillation (9.1% versus 3.0%, P<0.001) differed significantly, whereas in-hospital death (5.9% versus 3.1%, P=0.134), in-hospital stroke (4.3% versus 1.6%, P=0.057) and mechanical complication (4.3% versus 1.7%, P=0.086) showed consistent directional differences that did not reach significance in this sample. The mean number of documented outcome components was 0.34 in late presenters and 0.13 in earlier presenters (P<0.001), and median length of stay was 8 versus 7 days (P<0.001).

Sequentially adjusted associations

Sequential regression results are shown in **Table 3**. Prolonged symptom-to-door time was positively associated with adverse in-hospital outcome status in every model, and the estimate remained stable across adjustment

Analysis	No. (events)	OR (95% CI)	P value
Sequentially adjusted models			
Model I (unadjusted)	760 (119)	2.36 (1.56–3.56)	<0.001
Model II (+ demographics)	760 (119)	2.38 (1.57–3.62)	<0.001
Model III (+ comorbidity)	760 (119)	2.23 (1.46–3.40)	<0.001
Model IV (primary model)	760 (119)	2.28 (1.48–3.53)	<0.001
Exposure parameterisation			
Per doubling of symptom-to-door time	760 (119)	1.34 (1.14–1.58)	<0.001
< 2 h	210 (24)	1.00 (reference)	—
2–6 h	364 (48)	1.17 (0.69–2.00)	0.554
6–12 h	124 (27)	2.08 (1.12–3.89)	0.021
> 12 h	62 (20)	3.62 (1.77–7.40)	<0.001
Sensitivity analyses			
Delay redefined as > 12 h	760 (119)	2.80 (1.53–5.14)	<0.001
Excluding shock present at ED arrival	718 (100)	2.22 (1.38–3.56)	<0.001
Restricted to primary PCI	700 (110)	2.57 (1.62–4.08)	<0.001
Excluding symptom-to-door time > 24 h	744 (114)	2.19 (1.40–3.43)	<0.001
Adjusted for ED vitals and lactate	760 (119)	2.05 (1.31–3.22)	0.002
Adjusted for calendar year	760 (119)	2.28 (1.47–3.53)	<0.001
Outcome restricted to in-hospital death	760 (29)	1.60 (0.69–3.72)	0.271
Subgroup analyses			
Age < 65 years	419 (60)	3.09 (1.68–5.70)	0.483
Age ≥ 65 years	341 (59)	1.65 (0.85–3.23)	
Male	551 (80)	2.57 (1.51–4.37)	0.369
Female	209 (39)	1.51 (0.64–3.58)	
Anterior STEMI	355 (74)	2.45 (1.38–4.35)	0.587
Non-anterior STEMI	405 (45)	1.89 (0.94–3.81)	
Diabetes mellitus	188 (39)	3.18 (1.44–6.99)	0.191
No diabetes mellitus	572 (80)	1.93 (1.12–3.32)	
Arrival by emergency medical services	298 (43)	2.12 (0.99–4.55)	0.995
Self-transport	462 (76)	2.39 (1.39–4.13)	
Typical presenting symptoms	663 (103)	2.84 (1.78–4.55)	0.015
Atypical presenting symptoms	97 (16)	0.54 (0.13–2.22)	
Treated with primary PCI	700 (110)	2.57 (1.62–4.08)	0.126
Not treated with primary PCI	60 (9)	0.72 (0.11–4.77)	

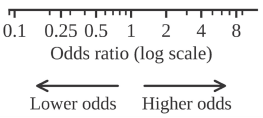


Figure 1. Forest plot of the association between prolonged symptom-to-door time and adverse in-hospital outcome status. Squares denote odds ratios and horizontal lines the 95% confidence intervals on a logarithmic scale; square size is proportional to the precision of the estimate and the dashed line marks the null value. Models I to IV are the sequentially adjusted models defined in **Table 3**. The second panel gives alternative parameterizations of the exposure under the Model IV covariate set, for which the test for linear trend across the four ordered categories gave P<0.001. The third and fourth panels give the prespecified sensitivity analyses and the subgroup analyses, the latter estimated within each stratum using the Model IV covariates excluding the stratifying variable; there the *P* value column reports the *P* value for interaction, shown once per pair of strata. CI, confidence interval; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

blocks: OR 2.36 (95% CI 1.56-3.56) unadjusted, OR 2.38 (95% CI 1.57-3.62) after demographic adjustment, OR 2.23 (95% CI 1.46-3.40) after comorbidity adjustment, and OR 2.28 (95% CI 1.48-3.53, P<0.001) in the fully adjusted primary model. Within Model IV, the only other covariates independently associated with the outcome were anterior infarct loca-

Table 4. Cardiogenic-shock statistical pathway analysis and standardized cross-sectional decomposition

Analysis	Term	OR (95% CI)	*P* value
Pathway models (Model IV covariates)			
Pathway model A	Prolonged symptom-to-door time → cardiogenic-shock status	4.57 (2.77-7.53)	<0.001
Pathway model B	Cardiogenic-shock status → adverse outcome status	3.45 (2.02-5.88)	<0.001
Pathway model B	Prolonged symptom-to-door time, residual association	1.79 (1.13-2.83)	0.013
Standardized decomposition (500 bootstrap resamples)			
Overall association	Total cross-sectional association	2.20 (1.44-3.31)	-
Indirect component	Represented by cardiogenic-shock status	1.28 (1.12-1.49)	-
Residual component	Not represented by cardiogenic-shock status	1.72 (1.11-2.64)	-
Proportion represented	Share of the log-scale association, %	30.9 (13.0-75.1)	-

Estimates are cross-sectional associations between status variables summarized from the same completed hospital episode at a single record-closure assessment. They constitute a statistical decomposition and must not be interpreted as natural direct or natural indirect effects, or as evidence of causal mediation. CI, confidence interval; OR, odds ratio.

tion (OR 2.21, 95% CI 1.45-3.34, P<0.001) and age per additional year (OR 1.02, 95% CI 1.00-1.04, P=0.049). Modelled continuously, each doubling of symptom-to-door time carried an adjusted OR of 1.34 (95% CI 1.14-1.58, P<0.001). Categorical modelling revealed a graded pattern: relative to presentation within 2 h, the adjusted odds were 1.17 (95% CI 0.69-2.00) for 2 to 6 h, 2.08 (95% CI 1.12-3.89) for 6 to 12 h and 3.62 (95% CI 1.77-7.40) for more than 12 h, with a significant trend across categories (P<0.001). Observed outcome prevalence rose monotonically from 11.4% to 32.3% across these strata. The sequential models, the alternative exposure parameterizations, the sensitivity analyses and the subgroup estimates are displayed together in **Figure 1**.

Cardiogenic-shock statistical pathway analysis

Pathway results and the standardized decomposition are summarized in **Table 4**, and the pathway structure is depicted in **Figure 2**. In pathway model A, prolonged symptom-to-door time was strongly associated with cardiogenic-shock status after full adjustment (OR 4.57, 95% CI 2.77-7.53, P<0.001). In pathway model B, cardiogenic-shock status was independently associated with adverse outcome status (OR 3.45, 95% CI 2.02-5.88, P<0.001), and the exposure retained a significant residual association once shock status was included (OR 1.79, 95% CI 1.13-2.83, P=0.013), indicating that the exposure-outcome association was attenuated but not abolished. The standardized decomposition produced an overall association of OR 2.20 (95% CI 1.44-3.31), an indirect component statistically represented by cardiogenic shock of OR 1.28 (95% CI 1.12-1.49) whose interval excluded unity, and a residual component of OR 1.72 (95% CI 1.11-2.64). Cardiogenic-shock status therefore represented 30.9% of the log-scale association (95% CI 13.0-75.1%). Consistent with substantial clinical heterogeneity rather than a deterministic rule, 142 of 186 late presenters (76.3%) had no documented shock, 38 of 574 earlier presenters (6.6%) did have shock, 49 of 82 patients with shock (59.8%) had no composite adverse outcome, and 86 of 678 patients without shock (12.7%) nevertheless had one.

Component-specific decomposition and robustness to unmeasured confounding

Because the composite outcome aggregates events of differing severity and pathophysiology, the decomposition was repeated for each component separately (**Table 7**). Cardiogenic-shock status was associated with every component, most strongly with in-hospital death (OR 4.61, 95% CI 1.76-12.07) and resuscitated cardiac arrest (OR 3.12, 95% CI 1.45-6.73), and least clearly with in-hospital stroke (OR 1.76, 95% CI 0.51-6.12). The indirect component represented by shock excluded unity for in-hospital death (OR 1.41, 95% CI 1.09-2.13) and for resuscitated cardiac arrest (OR 1.29, 95% CI 1.03-1.65) but not for sustained ventricular tachycardia or fibrillation (OR 1.21, 95% CI 0.99-1.52), in-hospital stroke (OR 1.12, 95% CI 0.81-1.61) or acute mechanical complication (OR 1.28, 95% CI 0.91-1.81). A proportion could be estimated with usable precision only for resuscitated cardiac arrest (23.3%, 95% CI

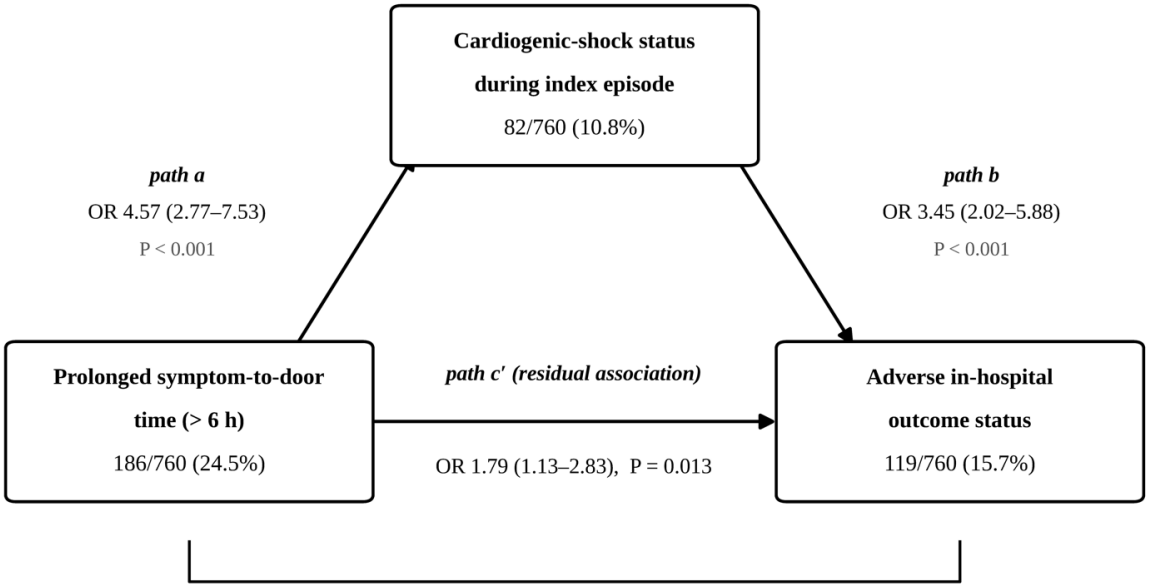


Figure 2. Cardiogenic-shock statistical pathway structure in the fully adjusted analysis. Path a represents the association between prolonged symptom-to-door time and cardiogenic-shock status, path b the association between cardiogenic-shock status and adverse in-hospital outcome status, and path c' the residual association of prolonged symptom-to-door time with the outcome once cardiogenic-shock status is included in the same model. Path c denotes the total association estimated in the fully adjusted primary model without the pathway variable. Cardiogenic shock is excluded from the composite adverse outcome, so the pathway variable and the outcome share no definitional overlap. The corresponding standardized cross-sectional decomposition is reported in **Table 4**. Because symptom-to-door time, cardiogenic-shock status and adverse in-hospital outcome status were all summarized from the same completed hospital episode at a single record-closure index assessment, no temporal ordering is measured within the episode; the estimates shown describe cross-sectional associations and must not be interpreted as natural direct or natural indirect effects, or as evidence of causal mediation. CI, confidence interval; OR, odds ratio.

Table 5. Prespecified sensitivity analyses of the association between prolonged symptom-to-door time and adverse in-hospital outcome status

Sensitivity analysis	n	OR (95% CI)	*P* value
Primary model (Model IV) for reference	760	2.28 (1.48-3.53)	<0.001
1. Continuous exposure, per doubling of symptom-to-door time	760	1.34 (1.14-1.58)	<0.001
2. Delay redefined as >12 h	760	2.80 (1.53-5.14)	<0.001
3. Excluding cardiogenic shock already present at ED arrival	718	2.22 (1.38-3.56)	<0.001
4. Restricted to patients treated with primary PCI	700	2.57 (1.62-4.08)	<0.001
5. Excluding symptom-to-door time >24 h	744	2.19 (1.40-3.43)	<0.001
6. Additional adjustment for ED vital signs and admission lactate	760	2.05 (1.31-3.22)	0.002
7. Additional adjustment for calendar year of admission	760	2.28 (1.47-3.53)	<0.001
8. Outcome restricted to in-hospital death alone	760	1.60 (0.69-3.72)	0.271

All analyses retain the Model IV covariate set unless the analysis itself modifies it. CI, confidence interval; ED, emergency department; OR, odds ratio; PCI, percutaneous coronary intervention.

2.3-85.2%) and sustained ventricular tachycardia or fibrillation (16.4%, 95% CI -2.0-48.9%); for the other components the bootstrap intervals were too wide to be informative, which follows directly from event counts of 17 to 29. With respect to unmeasured confounding, the E-value for the primary estimate was 3.34 and 2.14 for the bound of its confidence interval

Table 6. Subgroup analyses of the association between prolonged symptom-to-door time and adverse in-hospital outcome status

Subgroup	n	Events, n (%)	Adjusted OR (95% CI)	P for interaction
Age <65 years	419	60 (14.3)	3.09 (1.68-5.70)	0.483
Age ≥65 years	341	59 (17.3)	1.65 (0.85-3.23)	
Male	551	80 (14.5)	2.57 (1.51-4.37)	0.369
Female	209	39 (18.7)	1.51 (0.64-3.58)	
Anterior STEMI	355	74 (20.8)	2.45 (1.38-4.35)	0.587
Non-anterior STEMI	405	45 (11.1)	1.89 (0.94-3.81)	
Diabetes mellitus	188	39 (20.7)	3.18 (1.44-6.99)	0.191
No diabetes mellitus	572	80 (14.0)	1.93 (1.12-3.32)	
Arrival by emergency medical services	298	43 (14.4)	2.12 (0.99-4.55)	0.995
Self-transport	462	76 (16.5)	2.39 (1.39-4.13)	
Typical presenting symptoms	663	103 (15.5)	2.84 (1.78-4.55)	0.015
Atypical presenting symptoms	97	16 (16.5)	0.54 (0.13-2.22)	
Treated with primary PCI	700	110 (15.7)	2.57 (1.62-4.08)	0.126
Not treated with primary PCI	60	9 (15.0)	0.72 (0.11-4.77)	

Each subgroup estimate was obtained within the stratum using the Model IV covariate set excluding the stratifying variable. P for interaction derives from a multiplicative exposure-by-subgroup product term fitted in the full sample. CI, confidence interval; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

nearest the null, and the corresponding E-values for the association with cardiogenic-shock status were 6.85 and 4.39.

Sensitivity analyses

All eight prespecified sensitivity analyses were directionally consistent with the primary model (**Table 5**; **Figure 1**). Redefining delay as more than 12 h strengthened the association (OR 2.80, 95% CI 1.53-5.14). Excluding the 42 patients whose shock was already documented at ED arrival left the estimate essentially unchanged (n=718; OR 2.22, 95% CI 1.38-3.56), which argues against the association being generated solely by patients who were already in shock when they reached the door. Restriction to primary PCI recipients gave OR 2.57 (95% CI 1.62-4.08) and exclusion of symptom-to-door times beyond 24 h gave OR 2.19 (95% CI 1.40-3.43), showing that the finding is not driven by extreme outliers or by patients who never received acute reperfusion. Additional adjustment for first ED vital signs and admission lactate attenuated but did not eliminate the association (OR 2.05, 95% CI 1.31-3.22, P=0.002), and additional adjustment for calendar year left it unchanged (OR 2.28, 95% CI 1.47-3.53). When the outcome was restricted to in-hospital death alone, the point estimate remained above unity but the confidence interval was wide and included it (OR 1.60, 95% CI 0.69-3.72, P=0.271), which is unsurprising given only 29 deaths.

Subgroup analyses

Subgroup estimates are shown in **Table 6** and in the lower panel of **Figure 1**. The direction of association was positive in twelve of the fourteen strata examined, and interaction tests were non-significant for age, sex, infarct location, diabetes status, mode of arrival and receipt of primary PCI. Point estimates were numerically larger in patients younger than 65 years (OR 3.09, 95% CI 1.68-5.70) than in older patients (OR 1.65, 95% CI 0.85-3.23), and in patients with diabetes (OR 3.18, 95% CI 1.44-6.99) than in those without (OR 1.93, 95% CI 1.12-3.32), but neither contrast met the threshold for effect modification (P for interaction 0.483 and 0.191, respectively). The single significant interaction involved symptom typicality (P for interaction 0.015): among the 663 patients with typical presentations the adjusted OR was 2.84 (95% CI 1.78-4.55), whereas among the 97 patients with atypical presentations no association was detected (OR 0.54, 95% CI 0.13-2.22), a stratum containing only 16 outcome events.

Table 7. Component-specific standardized decomposition of the cross-sectional association between prolonged symptom-to-door time and each adverse in-hospital outcome component

Outcome component	Events, n (%)	Shock-component OR (95% CI)	Total association OR (95% CI)	Indirect component OR (95% CI)	Proportion, % (95% CI)
Composite adverse outcome	119 (15.7)	3.45 (2.02-5.88)	2.20 (1.44-3.31)	1.28 (1.12-1.49)	30.9 (13.0-75.1)
In-hospital death	29 (3.8)	4.61 (1.76-12.07)	1.48 (0.60-3.15)	1.41 (1.09-2.13)	Not estimable
Resuscitated cardiac arrest	42 (5.5)	3.12 (1.45-6.73)	2.95 (1.54-5.90)	1.29 (1.03-1.65)	23.3 (2.3-85.2)
Sustained ventricular tachycardia or fibrillation	34 (4.5)	2.43 (1.04-5.69)	3.25 (1.45-6.53)	1.21 (0.99-1.52)	16.4 (-2.0-48.9)
In-hospital stroke	17 (2.2)	1.76 (0.51-6.12)	3.10 (0.95-10.14)	1.12 (0.81-1.61)	Not estimable
Acute mechanical complication	18 (2.4)	2.82 (0.90-8.90)	1.99 (0.61-5.96)	1.28 (0.91-1.81)	Not estimable

All estimates are adjusted for the Model IV covariate set and derive from the same standardized cross-sectional decomposition described for the composite outcome, with 500 bootstrap resamples. The shock-component column reports the association between cardiogenic-shock status and that component in a model containing both the exposure and shock. A proportion is reported only where the bootstrap interval was finite and interpretable; for in-hospital death, in-hospital stroke and acute mechanical com plication the intervals spanned implausible values and the proportion is therefore reported as not estimable. Component analyses rest on 17 to 42 events and are exploratory. CI, confidence interval; OR, odds ratio.

Discussion

In this record-based retrospective cross-sectional analysis of 760 completed index hospital episodes, prolonged symptom-to-door time was associated with more than a twofold increase in the odds of adverse in-hospital outcome status, and the estimate proved remarkably stable across four sequential adjustment blocks, finishing at OR 2.28 (95% CI 1.48-3.53) in the fully adjusted primary model. The association was graded rather than threshold-like, with adjusted odds rising from 1.17 to 3.62 across symptom-to-door strata and an adjusted OR of 1.34 per doubling of the interval. Prolonged delay was associated even more strongly with cardiogenic-shock status (OR 4.57, 95% CI 2.77-7.53) than with the composite outcome itself, and standardized decomposition indicated that cardiogenic shock statistically represented 30.9% (95% CI 13.0-75.1%) of the observed cross-sectional association, leaving a residual component of OR 1.72 (95% CI 1.11-2.64) that shock did not account for. To our knowledge this is the first study to provide quantitative evidence partitioning the symptom-to-door association in STEMI into a component represented by cardiogenic-shock status and a component that is not, and it does so within a design that makes no temporal or causal claim beyond what a single record-closure assessment can support.

Our headline estimate sits comfortably within the existing evidence on delayed presentation, while adding a dimension that this evidence has not previously addressed. Yang and colleagues analyzed 458,260 patients with STEMI undergoing primary PCI across 2,529 centers and found that each additional hour of patient delay raised the adjusted odds of in-hospital death by 2.2% (OR 1.022, 95% CI 1.017-1.027), concluding that patient delay carries an impact comparable to system delay [4]. Extrapolated across the roughly seven-hour median difference separating our exposure groups, that per-hour figure is of a similar order to the continuous estimate we observed per doubling of the interval. Cho and colleagues, studying 5,826 patients with STEMI from a national registry, showed that the 624 who presented between 12 and 48 h had substantially worse long-term outcomes than the 5,202 early presenters, and concluded that late presentation identifies a group whose prognosis is not fully rescued by revascularization [5]. Cha and colleagues extended the same principle beyond ST elevation, reporting among 6,544 patients with non-ST-elevation myocardial infarction that a symptom-to-door time of 24 h or more was associated with higher in-hospital and 3-year all-cause mortality irrespective of baseline risk, with older age, female sex, atypical chest pain, diabetes and non-use of EMS emerging as independent predictors of delay [16]. Oh and colleagues, analyzing 5,364 patients with STEMI from the same national registry, found that 36-month outcomes after primary PCI performed during off-hours were similar to those after on-hours procedures, which is consistent with the view that in mature STEMI networks residual variation in outcome arises mainly before, rather than after, arrival at the door [17], and Bouisset and colleagues, comparing revascularized with non-revascularized late presenters, reported markedly divergent long-term death rates and argued that late arrival should not by itself withhold an invasive strategy [18]. Our study contributes three pieces of novel evidence to this body of work. First, it shows that the delay signal is detectable on a composite of in-hospital events to which death is only a minor contributor, meaning that the harm associated with delay manifests through arrhythmic, mechanical and neurological events and not through mortality alone. Second, it demonstrates that the association persists in a setting where in-hospital process efficiency was demonstrably preserved, since median door-to-wire time was identical at 82 min in both exposure groups. Third, and most importantly, it quantifies for the first time how much of the association travels with cardiogenic-shock status and how much does not.

The pathway findings invite a specific interpretation. Prolonged occlusion enlarges the infarct, and once the mass of non-contractile myocardium crosses a threshold, stroke volume falls, filling pressures rise and systemic perfusion becomes dependent on vasoconstriction and inotropic reserve. Cardiogenic shock is the clinical expression of that transition, and it remains the dominant proximate cause of in-hospital death after myocardial infarction [9], with reported incidence after infarction ranging from 2.7% to 10% [10]. A Danish population-

based analysis of temporal trends confirmed that shock complicating infarction has remained both common and lethal despite contemporary reperfusion practice [19], while imaging-based evidence has established the underlying gradient directly, showing that longer ischemic delay is associated with larger infarct size and greater microvascular obstruction after primary PCI [20]. Our observation that shock accounted for roughly a third of the cross-sectional association, but no more, is therefore biologically coherent in both directions. The proportion is large enough to confirm that hemodynamic decompensation is a major conduit through which delay and adverse outcome co-occur, and small enough to indicate that most of the association runs through channels that shock status does not capture, including electrical instability in freshly reperfused or non-reperfused myocardium, the structural fragility of transmural necrosis, and thrombotic burden. That reading is supported by our component-level data, in which resuscitated cardiac arrest and sustained ventricular arrhythmia showed the clearest separation between exposure groups. It is also worth noting that the consequences of shock physiology extend beyond the heart: in critical illness more broadly, the balance between perfusion pressure and vasopressor burden has measurable end-organ effects, as shown in a retrospective database analysis of 5,524 patients with septic shock in which the blood pressure response index displayed an L-shaped association with acute kidney injury, with risk rising steeply below an inflection point of 3.98 (fully adjusted OR 0.988, 95% CI 0.979-0.996) [21]. The wide confidence interval around our proportion estimate deserves emphasis and reflects the modest number of patients with both shock and an adverse outcome. Most fundamentally, because symptom-to-door time, shock status and outcome status were all summarized from the same completed episode at a single record-closure assessment, this partition describes how the three status variables co-vary in cross-section. It does not establish that shock preceded the outcome, and it should not be read as a natural indirect effect.

Several secondary findings merit comment. The monotonic gradient across symptom-to-door categories, with outcome prevalence rising from 11.4% below 2 h to 32.3% beyond 12 h and a significant trend, is consistent with a dose-dependent relationship rather than an artefact of an arbitrary cut-point, and it is reassuring that redefining delay at 12 h strengthened rather than weakened the estimate (OR 2.80, 95% CI 1.53-5.14). The stability of the association after exclusion of patients already in shock at ED arrival (OR 2.22, 95% CI 1.38-3.56) is analytically important, since it indicates that the finding is not merely a restatement of the fact that the sickest patients arrive latest. Our exposure-group comparison also reproduced well-described correlates of delay: patients arriving late were more often diabetic, more often had atypical symptoms and were less likely to use EMS, echoing the predictors identified in the non-ST-elevation registry analysis [16] and in single-center work on very late presentation, where women, patients with diabetes and patients without chest pain were disproportionately represented among those arriving at or beyond 12 h [6]. A systematic review of age and sex differences in pre-hospital delay reached similar conclusions across multiple health systems [22]. Under-use of EMS is a modifiable part of this picture; in a registry analysis of 5,602 patients undergoing primary PCI, 74% used EMS, and EMS use was associated with shorter adjusted door-to-balloon time (53 versus 72 min) and shorter symptom-to-balloon time (183 versus 212 min) [23]. Subgroup analyses were largely homogeneous, with the sole significant interaction arising for symptom typicality; the apparent absence of association among the 97 patients with atypical presentations rests on only 16 events and, given that the atypical stratum is precisely the group in which onset timing is least reliably recorded, is most plausibly explained by exposure misclassification and limited power rather than by a genuine protective effect. Finally, the association between prolonged delay and mechanical complications, although not statistically significant here, is directionally aligned with a contemporary single-center series of 2,508 patients with STEMI in which the 26 patients suffering a mechanical complication were far more likely to have had an interval from symptom onset to angiography exceeding 24 h (42.3% versus 16.2%, P=0.002) [24].

These findings carry practical implications for emergency and cardiovascular care. The first is that patient-side delay deserves the same sys-

tematic attention that has transformed in-hospital process metrics. Our data show a center achieving a median door-to-wire time of 82 min irrespective of how late the patient arrived, yet still observing a doubling of adverse outcome odds in late presenters; procedural excellence downstream cannot compensate for time already lost upstream. Community-level symptom education, targeted outreach to patients with diabetes and to those prone to atypical presentation, and measures that increase EMS utilization are therefore not peripheral quality initiatives but core determinants of in-hospital outcome. The second implication concerns triage. Because cardiogenic-shock status represented only about a third of the association, prolonged symptom-to-door time carries prognostic information that is not reducible to hemodynamic status at presentation, and a patient who arrives late but appears hemodynamically stable should not be assumed to be at low risk. Symptom-to-door time is recorded at zero marginal cost in every chest pain pathway and could reasonably be incorporated into ED risk stratification alongside infarct location, which was the only other independent correlate of the outcome in our primary model. The third implication is that anticipatory monitoring for arrhythmic and mechanical complications, rather than for shock alone, is the more complete response to a late-presenting patient with STEMI. This matters because established shock therapeutics remain demanding and only incrementally beneficial. Early revascularization conferred a durable survival advantage in the landmark randomized evidence, yet six-year survival remained near one third [25]; culprit-lesion-only intervention proved superior to immediate multivessel intervention rather than the reverse [26], a conclusion supported by pooled evidence [27]; and although mechanical circulatory support lowered 180-day mortality in selected patients, it did so at the cost of substantially more adverse events including renal complications [12, 28], with attenuated benefit in older patients [29]. Upstream time reduction therefore retains a value that no downstream device can replicate.

This study has notable strengths. The analytic framework was specified in advance and applied with unusual internal discipline: one completed episode per patient, one fixed record-closure assessment, a single row per patient, and a pathway variable deliberately excluded from the outcome composite so that the decomposition could not be inflated by definitional overlap. Exclusion of inter-hospital transfers and of patients given reperfusion before arrival ensured that symptom-to-door time meant the same thing for every participant, and post-arrival treatment variables were kept out of the primary confounder set to avoid conditioning on consequences of the exposure. Robustness was probed from eight independent directions, and the conclusions did not depend on any one of them. Several limitations must nonetheless be acknowledged. This is a single-center study from one region of China, and the distribution of delay, the 92.1% rate of primary PCI and the 3.8% in-hospital mortality may not transfer to systems with different pre-hospital architecture. Symptom onset was reconstructed from the medical record and is subject to recall and documentation error, most acutely in patients with atypical or stuttering symptoms, which biases the exposure towards misclassification. To gauge how much this matters we repeated the primary analysis after excluding the 97 patients with atypical presentations, in whom onset timing is least reliably recorded, and the estimate strengthened rather than weakened (OR 2.88, 95% CI 1.81-4.59); additionally excluding night-time onset gave OR 2.44 (95% CI 1.28-4.65). Because non-differential misclassification of a binary exposure biases an association towards the null, the reported estimates, including the decomposition proportion, are more likely to be conservative than inflated, although differential misclassification cannot be excluded. Cardiogenic shock was captured as a documented clinical status rather than through prospective hemodynamic criteria or standardized severity staging [13], so milder or transient episodes may have been missed. Shock was not staged by SCAI SHOCK severity, and neither its duration nor the timing of its onset relative to the outcome was recorded, so the pathway variable is a coarse binary summary of a graded and dynamic state. If the episodes most likely to have been missed are the mild and transient ones, which plausibly carry lower outcome risk, their omission would tend to understate rather than inflate the share of the association represented by shock; the direction of this bias cannot, however, be established from these data. Residual confounding by unmeasured

factors such as socioeconomic position, health literacy, distance to hospital and pre-hospital electrocardiographic transmission is likely. To bound that possibility we computed E-values: an unmeasured confounder would need to be associated with both prolonged delay and the outcome by a risk ratio of at least 3.34, and at least 2.14 to move the confidence interval to the null, after accounting for the measured covariates. None of the measured confounders in Model IV approached that strength, but a socioeconomic or access-related factor of that magnitude cannot be ruled out. The composite outcome, while clinically coherent, aggregates events of differing severity, and the sample provided limited power for individual components, in particular in-hospital death. The component-specific decomposition now reported addresses this only partly: it localizes the shock-represented share to in-hospital death and resuscitated cardiac arrest, but the intervals for stroke and mechanical complications are too wide to support inference and should be treated as exploratory. No a priori sample size calculation was possible in a design that used every eligible record; post hoc the study had 80% power to detect an odds ratio of 1.87, yet precision around the decomposition proportion was low, as the interval from 13.0% to 75.1% makes plain. That interval is best read as showing that shock represents a non-trivial but imprecisely determined share of the association, and the point estimate of 30.9% should not be quoted without it. Most fundamentally, the cross-sectional index assessment provides no measured temporal ordering between exposure, cardiogenic-shock status and outcome status within the episode; the decomposition is therefore a statistical partition of co-varying status variables and cannot be interpreted as causal mediation. Specifically, the design cannot establish that cardiogenic shock preceded the adverse outcome, and the word pathway is used throughout in a purely statistical sense, denoting a partition of covariation among status variables rather than a biological mechanism. Prospective studies with time-stamped documentation of shock onset, standardized shock phenotyping and multicenter recruitment are needed before these associations can be given a causal reading.

Conclusions

In this record-based retrospective cross-sectional study of completed index hospital episodes among adults presenting directly to the emergency department with ST-segment elevation myocardial infarction, prolonged symptom-to-door time was associated with a consistent pattern of less favorable in-hospital status, including higher odds of a composite adverse in-hospital outcome across four sequentially adjusted models, a graded increase in odds across symptom-to-door categories, a significant association per doubling of the continuous interval, and higher odds of cardiogenic-shock status. Standardized cross-sectional decomposition suggested that cardiogenic-shock status statistically represented a measurable portion of the observed association, indicating that differences in hemodynamic status may account for roughly one third of the association with adverse in-hospital outcome status, alongside a substantial residual association not represented by shock. Component-level and subgroup analyses identified anterior infarct location and typical symptom presentation as the contexts in which the association was most clearly expressed, and eight prespecified sensitivity analyses, including exclusion of patients already in shock at emergency department arrival and restriction to patients treated with primary percutaneous coronary intervention, supported the robustness of the primary estimate. Overall, these findings suggest that reducing patient-side delay and recognizing hemodynamic vulnerability at the point of arrival are complementary rather than interchangeable targets, and they highlight the need for prospective multicenter studies with time-stamped shock documentation and standardized shock phenotyping to strengthen causal inference and inform implementation.

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Disclosure of conflict of interest

None.

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