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## Clinical characteristics and outcomes of acute myocardial infarction during the COVID-19 pandemic: a multicenter retrospective cohort study in Northern China

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### Abstract

**Background** The impacts of COVID-19 on acute myocardial infarction (AMI) care were heterogeneous. The study aims to analyze the clinical characteristics and outcomes of AMI patients in China during different stages of the COVID-19 pandemic.

**Methods** This is a multicenter retrospective cohort study in Shanxi Province of northern China. Patients diagnosed with AMI during the zero-case, lockdown, and outbreak periods were included. Characteristics and outcomes were analyzed according to time periods and COVID-19 infection. The primary outcome was in-hospital mortality. Additional outcomes included reperfusion times, coronary angiographic measures, procedure or AMI-associated complications, arrhythmia, other adverse events, and left ventricular systolic dysfunction (LVSD).

**Results** The study included 1021 AMI patients, with 393, 250, and 378 from the zero-case, lockdown, and outbreak periods. No differences in in-hospital mortality or other adverse events were found by time periods. By infection status, 264 patients were COVID-positive, and 706 were COVID-negative. The COVID-positive ST-elevation myocardial infarction population had longer symptom-to-first medical contact (3.07 vs. 2.31, p = 0.026), pre-hospital time (4.58 vs. 3.67, p = 0.032), door-to-balloon (1.20 vs. 1.08, p = 0.046), and total ischemic time (5.80 vs. 4.70, p = 0.011). No differences in other in-hospital outcomes were found, except that multivariate logistic regression analysis demonstrated COVID-19 infection was correlated with increased risks of LVSD (OR 1.73, 95% Cl 1.11–2.69, p = 0.015).

**Conclusions** In-hospital mortality did not differ by time period or COVID-19 infection status. The COVID-positive AMI patients had longer reperfusion times and higher risks of LVSD. AMI treatments were impacted during the pandemic, and measures are warranted to minimize the reperfusion time.

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Keywords Acute myocardial infarction, COVID-19, In-hospital outcomes, Reperfusion time

#### Background

Since COVID-19 was first reported in December 2019 in Wuhan, China [1], it has caused more than 7 million deaths across the world until April 2024 [2]. According to the Global Burden of Disease Study, globally increased mortality rates and reduced life expectancy were found during the COVID-19 pandemic [3]. During the outbreak, the treatment of acute myocardial infarction (AMI) was greatly affected, and admissions decreased significantly for both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) patients [4-6]. For STEMI patients, metaanalyses demonstrated increasing time from symptom onset to first medical contact (FMC) and door-to-balloon (D-to-B) during the pandemic [6, 7], with increasing risks of in-hospital mortality [8]. Among STEMI patients, COVID-19 infection was associated with increased thrombus burden, worse post-procedural Thrombolysis in Myocardial Infarction (TIMI) flow, and higher in-hospital mortality rates [9, 10]. However, these studies were from different countries and were highly heterogeneous [7, 11], which might have affected the results because of the disparity in healthcare resources and social lockdown policy.

Multiple waves of COVID-19 infections occurred in China. After the first COVID-19 outbreak in 2019 and 2020, strict lockdown measures were controlled. With the decreasing virulence of the COVID-19 variant (Omicron), the lockdown measures were loosened, and another outbreak across the country was seen since December 2022. Previous studies compared the clinical outcomes of AMI patients during the first COVID-19 outbreak with the pre-COVID era in China [12, 13]. However, few studies have analyzed AMI patients through different stages of the pandemic in China. In this study, we retrospectively analyzed in-hospital statistics of AMI patients from Shanxi Province during the outbreak period, using the zero-case and the lockdown periods as comparisons. The study aims to analyze the clinical characteristics and outcomes across different periods of the pandemic or by COVID-19 infection status and to provide insights into managing AMI while facing emerging infectious diseases.

#### Methods

#### Study design

This is a multicenter retrospective cohort study that aims to summarize the clinical characteristics and outcomes of AMI during the COVID-19 pandemic. The study was conducted in four tertiary hospitals from Taiyuan, Shanxi Province, including Taiyuan Central Hospital, Taigang General Hospital, the Second Hospital of Shanxi Medical University, and Shanxi Cardiovascular Hospital. AMI patients admitted to these tertiary hospitals from three different periods during the COVID-19 pandemic were consecutively enrolled in the study, including period 1 (the zero-case period, from December 8th, 2021 to January 20th, 2022), period 2 (the lockdown period, from November 1st, 2022 to December 7th, 2022), and period 3 (the outbreak period, from December 8th, 2022 to January 20th, 2023). Details of COVID-19 epidemiology and quarantine policies in China were demonstrated in Supplementary Methods 1. Patients were screened for COVID-19 infection at admission and categorized into the COVID-19 positive and COVID-19 negative groups. The COVID-19 positive group was defined as positive COVID-19 nucleic acid or antigen test, or, if admitted during the outbreak period, having fever or computed tomography (CT) scans demonstrated pulmonary infections. The COVID-19 negative group was defined as negative COVID-19 nucleic acid or antigen test without fever or pulmonary infections on CT scans. The study evaluated baseline characteristics and in-hospital outcomes of AMI patients according to time periods and COVID-19 infection status.

Baseline characteristics and in-hospital outcomes were retrospectively collected from the electronic medical records, including demographics, past medical history, COVID-19 infection status, laboratory tests, coronary angiographic and echocardiographic imaging, medical therapies, chest pain center time targets, in-hospital outcomes, length of stay and hospital costs.

The study was approved by the institutional ethics committee of Taiyuan Central Hospital (No. 2023001), and written informed consent was waived. The investigation was conducted according to the principles outlined in the Declaration of Helsinki. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

#### Study population

Detailed inclusion and exclusion criteria of the study population are shown below. Patients were included if meeting the following requirements: (1) age more than 18 years; (2) diagnosed with AMI using the fourth universal definition of myocardial infarction (2018) [14], with details shown in Supplementary Methods 2; (3) admitted from chest pain centers of the emergency departments. Patients presented with electrocardiographic changes and elevated troponins but had a final diagnosis of aortic dissection, acute pulmonary embolism, myocarditis, or gastrointestinal bleeding were excluded from the study.

#### Study outcomes

The primary study outcome was in-hospital mortality. Additional outcomes included reperfusion targets for STEMI patients (symptom-to-FMC, pre-hospital time, D-to-B, door-to-needle [D-to-N], total ischemic time [TIT], percentages of coronary angiogram, emergent percutaneous coronary intervention [PCI], thrombolysis, and rescue PCI), coronary angiographic measures (coronary thrombosis, multivessel coronary artery disease, post-procedural TIMI flow grade 0 to 2, slow-flow [defined as post-procedural TIMI flow grade 2], noreflow [defined as post-procedural TIMI flow grade 0 to 1]), PCI-associated complications (coronary artery dissection, coronary artery perforation, cardiac arrest, emergent revascularization, peri-procedural mortality), AMI-associated complications (cardiac tamponade, papillary muscle rupture, pericardial effusion), arrhythmias (atrial fibrillation, ventricular tachycardia or ventricular fibrillation, sinus bradycardia or sinus pause, third-degree atrioventricular block, defibrillation), cardiopulmonary resuscitation, cerebrovascular events, gastrointestinal bleeding, acute kidney injury, pre-discharge Killip classification, and left ventricular systolic dysfunction (LVSD) which was defined as left ventricular ejection fraction (LVEF) less than 50%.

#### Statistical analysis

For baseline characteristics and in-hospital outcomes, categorical variables were shown as counts and percentages and compared using the chi-squared or Fisher's exact test. For continuous variables, distributions were tested using the Shapiro-Wilk normality test. Continuous variables were presented with means and standard deviations (SD) and compared using the student's t-test if normally distributed, while presented with medians and interquartile ranges (IQR) and compared using the Mann-Whitney U test if skewed distribution. In-hospital outcomes were compared and adjusted odds ratios (OR) of time periods or COVID-19 infections were calculated using multivariable logistic regression models. A multivariate logistic regression model was built to testify to the association between COVID-19 infection and LVSD. In the model, all variables with a p-value less than 0.10 in univariate analysis were selected, and ORs and 95% confidence intervals (CI) were calculated. An interaction analysis was further conducted to find out the correlations between COVID-19 infection and LVSD across different subgroups. A minority of the in-hospital outcomes during period 1 from Shanxi Cardiovascular Hospital were not documented and were regarded as missing variables during the analysis. A two-tailed p-value less than 0.05 was considered significant. All statistical analyses were performed using R Version 4.4.1.

#### Results

#### Baseline characteristics by time periods

A total of 1021 AMI patients were included in the analysis, including 393 (38.5%), 250 (24.5%), and 378 (37.0%) patients from periods 1 to 3. Overall, 787 (77.1%) patients were diagnosed with STEMI, and 234 (22.9%) patients were diagnosed with NSTEMI. Detailed baseline characteristics by time periods are shown in Supplementary Table 1. Baseline characteristics were comparable among the groups, and no differences in cardiac arrest, ventricular fibrillation, or cardiogenic shock at admission were found.

#### In-hospital outcomes and time periods

For the AMI population, in-hospital outcomes according to time periods are demonstrated in Table 1. A lower percentage of PCI treatment was found in period 3 (p = 0.042). No differences in arrhythmia, AMI-associated complications, in-hospital mortality, or adverse events were found. During period 3, reduced lengths of hospital (p < 0.001) and cardiac care unit (CCU) stay (p = 0.042)were found. The crude and adjusted ORs of in-hospital outcomes are shown in Supplementary Table 2. Compared with the outbreak period, the zero-case period had lower risks of D-to-B exceeding the 90-minute target (adjusted OR 0.51, 95% CI 0.31–0.83; *p* = 0.007) and were less likely to present with multivessel CAD (adjusted OR 0.42, 95% CI 0.28–0.63; *p* < 0.001). STEMI patients were more likely to be treated with thrombolysis during the lockdown period (adjusted OR 1.77, 95% CI 1.08-2.88; p = 0.022) compared with the outbreak period. No differences were found in other in-hospital outcomes. Medications at discharge are detailed in Supplementary Table 3.

For the STEMI patients, reperfusion time targets according to time periods are shown in Supplementary Table 4. During period 3, the D-to-B was significantly longer than the other periods (p = 0.011), and a smaller population met the 90-minute target of D-to-B (p = 0.022). Other time targets, including symptom-to-FMC and TIT, did not differ significantly. A higher percentage of thrombolysis was found in period 2 (p = 0.044), while no differences in D-to-Needle or rescue PCI were found.

### Baseline characteristics and in-hospital outcomes by COVID-19 infection status

Among those with COVID-19 infection status, 264 (27.2%) patients were in the COVID-positive group, while 706 (72.8%) were in the COVID-negative group. Baseline characteristics of the study population by COVID-19 infection status are shown in Supplementary Table 5. No differences in demographics or past medical history were found, except the COVID-positive group had a higher proportion of smoking history and chronic lung

,,, _,, _	Period 1 ( <i>n</i> =393)	Period 2 ( <i>n</i> =250)	Period 3 ( <i>n</i> = 378)	<i>p</i> value	<i>p</i> value (Period 1 vs. 3)	p value (Period 2 vs. 3)
CAG	380 (96.7)	246 (98.4)	374 (98.9)	0.075	0.060	0.819
PCI	325 (82.7)	205 (82.0)	287 (75.9)	0.042	0.025	0.087
IABP/ECMO	16 (4.7)	17 (6.8)	22 (5.8)	0.520	0.592	0.732
Coronary angiographic measures						
Multivessel CAD	75 (50.3)	183 (73.2)	254 (67.7)	< 0.001	< 0.001	0.170
Coronary thrombosis	57 (38.0)	116 (46.4)	168 (44.8)	0.238	0.185	0.755
Post-procedural TIMI flow grade 0–2	24 (8.0)	23 (11.0)	29 (9.0)	0.517	0.761	0.551
No-reflow	11 (3.7)	2 (1.0)	6 (1.9)	0.111	0.271	0.623
Slow-flow	13 (4.3)	21 (10.0)	23 (7.2)	0.043	0.185	0.310
PCI-associated complications						
Coronary artery dissection	2 (1.3)	0 (0.0)	1 (0.3)	0.105	0.411	1
Coronary artery perforation	0 (0.0)	0 (0.0)	1 (0.3)	0.592	1	1
Cardiac arrest	3 (2.0)	2 (0.8)	2 (0.5)	0.276	0.287	1
Emergent revascularization	1 (0.7)	6 (2.5)	3 (0.8)	0.153	1	0.176
Peri-procedural mortality	1 (0.3)	0 (0.0)	0 (0.0)	0.409	0.967	NA
AMI-associated complications						
Cardiac tamponade	0 (0.0)	1 (0.4)	3 (0.8)	0.493	0.655	0.921
Papillary muscle rupture	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA
Pericardial effusion 18 (12.2)		38 (15.2)	50 (13.3)	0.663	0.838	0.580
Arrhythmia						
AF	19 (4.8)	18 (7.2)	19 (5.1)	0.395	1	0.346
VT or VF	11 (7.4)	13 (5.2)	20 (5.3)	0.605	0.485	1
Sinus bradycardia or sinus pause	4 (2.7)	7 (2.8)	6 (1.6)	0.543	0.639	0.454
Third-degree AVB	3 (2.0)	7 (2.8)	8 (2.1)	0.828	1	0.786
Defibrillation	5 (3.4)	9 (3.6)	9 (2.4)	0.646	0.739	0.518
LVEF	53.50 [46.00, 60.00]	52.00 [45.00, 57.00]	51.00 [45.00, 58.00]	0.013	0.015	0.798
LVSD	143 (38.6)	104 (45.2)	140 (44.3)	0.188	0.155	0.901
Pre-discharge Killip class 3–4	19 (12.8)	30 (12.1)	39 (10.3)	0.658	0.506	0.580
Cardiopulmonary resuscitation	8 (5.4)	10 (4.0)	14 (3.7)	0.676	0.530	1
In-hospital mortality	5 (1.3)	5 (2.0)	7 (1.9)	0.728	0.713	1
Gastrointestinal bleeding	13 (9.0)	28 (11.4)	35 (10.2)	0.736	0.800	0.735
Cerebrovascular events	0 (0.0)	1 (0.4)	4 (1.1)	0.331	0.488	0.647
AKI	7 (4.8)	17 (6.8)	15 (4.0)	0.292	0.887	0.173
Length of CCU stay (days, median [IQR])	3.00 [0.00, 6.00]	3.00 [2.00, 4.00]	2.00 [0.00, 5.00]	0.042	0.077	0.023
Length of Hospital stay (days, median [IQR])	10.00 [8.00, 13.00]	10.00 [8.00, 13.00]	9.00 [7.00, 11.75]	< 0.001	< 0.001	< 0.001
Hospital costs (10,000 CNY, median [IQR])	3.43 [2.71, 5.17]	3.58 [2.77, 4.54]	3.25 [2.55, 4.34]	0.017	0.011	0.022

#### Table 1 In-hospital outcomes by time periods

Variables are reported as numbers (percentages) if not indicated

AF: atrial fibrillation; AKI: acute kidney injury; AVB: atrioventricular block; CAD: coronary artery disease; CAG: coronary angiogram; CCU: cardiac care unit; CNY: Chinese Yuan; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; IQR: interquartile range; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; NA: not available; PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction; VF: ventricular fibrillation; VT: ventricular tachycardia

disease. Laboratory tests demonstrated higher levels of D-Dimer and N-terminal pro–B-type natriuretic peptide (NT-proBNP) in the COVID-positive group. In-hospital outcomes according to COVID-19 infection status are demonstrated in Table 2, while the crude and adjusted ORs of in-hospital outcomes are detailed in Supplementary Table 6. The COVID-positive group had lower LVEF (50% vs. 53%, p = 0.002), and a higher percentage of the population had LVSD (49.8% vs. 39.8%, p = 0.012). After

adjustment, the COVID-positive group had higher risks of LVSD (adjusted OR 1.54, 95% CI 1.12–2.12; p = 0.007). All the other in-hospital outcomes did not significantly differ between the groups. Medications at discharge are shown in Supplementary Table 7. The COVID-positive group was prescribed with a lower percentage of  $\beta$ -blockers (67.7% vs. 79.6%, p < 0.001) and a higher percentage of diuretics (26.5% vs. 15.6%, p = 0.001).

AKI

#### Table 2 In-hospital outcomes by COVID-19 infection status

	COVID-positive (n = 264)	COVID-negative (n = 706)	<i>p</i> value
CAG	262 (99.2)	688 (97.5)	0.135
PCI	189 (71.6)	583 (82.6)	< 0.001
IABP/ECMO	18 (6.8)	35 (5.3)	0.474
Coronary angiographic measures			
Multivessel CAD	180 (68.7)	298 (64.5)	0.287
Coronary thrombosis	117 (44.5)	207 (44.8)	0.996
Post-procedural TIMI flow grade 0–2	24 (11.1)	47 (8.3)	0.273
No-reflow	5 (2.4)	14 (2.5)	1
Slow-flow	19 (8.8)	33 (5.8)	0.180
PCI-associated complications			
Coronary artery dissection	1 (0.4)	2 (0.4)	1
Coronary artery perforation	1 (0.4)	0 (0.0)	0.781
Cardiac arrest	1 (0.4)	6 (1.3)	0.402
Emergent revascularization	3 (1.1)	7 (1.5)	0.906
Peri-procedural mortality	0 (0.0)	1 (0.2)	1
AMI-associated complications			
Cardiac tamponade	3 (1.1)	1 (0.2)	0.275
Papillary muscle rupture	0 (0.0)	0 (0.0)	NA
Pericardial effusion	39 (14.8)	62 (13.4)	0.686
Arrhythmia			
AF	14 (5.3)	39 (5.5)	1
VT or VF	15 (5.7)	27 (5.8)	1
Sinus bradycardia or sinus pause	6 (2.3)	11 (2.4)	1
Third-degree AVB	5 (1.9)	12 (2.6)	0.734
Defibrillation	7 (2.7)	15 (3.3)	0.825
LVEF	50.00 [45.00, 57.00]	53.00 [45.00, 60.00]	0.002
LVSD	108 (49.8)	261 (39.8)	0.012
Pre-discharge Killip class 3–4	29 (11.0)	52 (11.4)	0.977
Cardiopulmonary resuscitation	10 (3.8)	20 (4.3)	0.877
In-hospital mortality	5 (1.9)	10 (1.4)	0.799
Gastrointestinal bleeding	25 (10.7)	48 (10.6)	1
Cerebrovascular events	2 (0.8)	2 (0.4)	0.964

Variables are reported as numbers (percentages) if not indicated

Length of CCU stay (days, median [IQR])

Length of Hospital stay (days, median [IQR])

Hospital costs (10,000 CNY, median [IQR])

AF: atrial fibrillation; AKI: acute kidney injury; AVB: atrioventricular block; CAD: coronary artery disease; CAG: coronary angiogram; CCU: cardiac care unit; CNY: Chinese Yuan; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; IQR: interguartile range; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; NA: not available; PCI: percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction; VF: ventricular fibrillation; VT: ventricular tachycardia

12 (4.6)

2.00 [0.00, 5.00]

9.00 [7.00, 13.00]

3.39 [2.52, 4.62]

For STEMI patients, the reperfusion time targets are shown in Table 3; Fig. 1. The COVID-positive STEMI population had longer symptom-to-FMC (3.07 vs. 2.31, p = 0.026), pre-hospital time (4.58 vs. 3.67, p = 0.032), D-to-B (1.20 vs. 1.08, p = 0.046), and TIT (5.80 vs. 4.70, p = 0.011). No differences in emergent CAG, PCI, thrombolysis, D-to-Needle, or rescue PCI were found. The association between prolonged reperfusion times and in-hospital mortality is shown in Supplementary Tables 8, and prolonged D-to-B was correlated with increasing risks of mortality in STEMI patients (adjusted OR 1.60, 95% CI 1.07–2.38; *p* = 0.021).

#### Multivariate logistic regression analysis of LVSD

23 (5.0)

3.00 [1.00, 5.00]

10.00 [8.00, 13.00]

3.45 [2.72, 4.75]

Since LVSD was found to be correlated with COVID-19 infection, a multivariate logistic regression analysis was conducted to further adjust any confounding factors. The results are illustrated in Table 4. The multivariate logistic model showed that STEMI (OR 1.76, 95% CI 1.03-3.00, *p* = 0.039), COVID-19 infection (OR 1.73, 95% CI 1.11-2.69, p=0.015), symptom-to-FMC (OR 1.03, 95% CI 1.00-1.05, p = 0.028), and peak creatine kinase-MB (CK-MB) (OR 1.003, 95% CI 1.002–1.005, *p* < 0.001) were positively associated with LVSD.

0.942

0.002

0.240

0.249

Table 3	Reperfusion	time targets in S	STEMI patients acro	oss COVID-positive and	COVID-negative groups
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	COVID-positive (n=201)	COVID-negative (n = 547)	<i>p</i> value
Symptom-to-FMC (h, median [IQR])	3.07 [1.60, 7.00]	2.31 [1.00, 6.25]	0.026
Symptom-to-FMC≤5 h	132 (69.8)	364 (70.5)	0.930
Pre-hospital time (h, median [IQR])	4.58 [2.00, 9.65]	3.67 [1.33, 8.73]	0.032
TIT (h, median [IQR])	5.80 [3.25, 11.03]	4.70 [2.53, 9.00]	0.011
TIT≤12 h	112 (78.3)	354 (82.5)	0.320
D-to-B (h, median [IQR])	1.20 [0.94, 1.50]	1.08 [0.90, 1.42]	0.046
D-to-B≤90 min	103 (76.3)	340 (81.9)	0.190
Emergent CAG	199 (99.0)	536 (98.0)	0.531
Emergent PCI	155 (77.1)	456 (83.4)	0.064
Thrombolysis	32 (16.0)	101 (18.5)	0.502
D-to-Needle (h, median [IQR])	0.60 [0.48, 1.00]	0.58 [0.44, 1.04]	0.923
D-to-Needle≤30 min	11 (40.7)	42 (46.2)	0.782
Rescue PCI	31 (100.0)	88 (88.9)	0.116

Variables are reported as numbers (percentages) if not indicated

CAG: coronary angiogram; D-to-B: door-to-balloon; D-to-Needle: door-to-needle; FMC: first medical contact; IQR: interquartile range; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIT: total ischemic time



Fig. 1 Reperfusion time in STEMI patients according to COVID-19 infection status D-to-B: door-to-balloon; D-to-Needle: door-to-needle; Sx-to-FMC: symptom to first medical contact; STEMI: ST-elevation myocardial infarction; TIT: total ischemic time

For STEMI patients, a separate multivariate logistic regression model for LVSD was built, as shown in Supplementary Table 9. COVID-19 infection (OR 2.31, 95% CI 1.28–4.17, p = 0.005) and peak CK-MB (OR 1.003, 95% CI 1.001–1.005, p < 0.001) were positively correlated with LVSD, while hypertension (OR 0.57, 95% CI 0.33–0.97,

p = 0.037) was negatively associated with LVSD. Total ischemic time (OR 1.04, 95% CI 1.00-1.08, p = 0.068) had a nonsignificant tendency towards increasing risks of LVSD.

Table 4	Univariate and mult	ivariate logistic re	gression analysis of LVS	D

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	<i>p</i> value
Age	1.02 (1.00-1.03)	0.053	1.01 (1.00-1.03)	0.124
Female (vs. Male)	1.49 (0.84–2.65)	0.170		
STEMI (vs. NSTEMI)	1.87 (1.15–3.04)	0.012	1.76 (1.03-3.00)	0.039
COVID-19 infection	1.68 (1.11–2.56)	0.015	1.73 (1.11–2.69)	0.015
DM	1.38 (0.90–2.10)	0.140		
Hypertension	0.83 (0.56–1.22)	0.340		
Cerebrovascular diseases	1.69 (0.94–3.04)	0.081	1.52 (0.80–2.88)	0.197
Chronic lung diseases	1.35 (0.68–2.69)	0.391		
Smoking history	1.01 (0.67–1.53)	0.949		
Symptom-to-FMC	1.02 (1.00-1.05)	0.052	1.03 (1.00-1.05)	0.028
Killip class 3–4 at admission (vs. Killip class 1–2)	2.16 (0.99–4.75)	0.054	1.34 (0.55–3.22)	0.518
Antiplatelet therapies	1.44 (0.54–3.82)	0.464		
Multivessel CAD	1.21 (0.81–1.81)	0.360		
PCI	0.68 (0.41-1.12)	0.127		
Peak CK-MB	1.003 (1.002–1.005)	< 0.001	1.003 (1.002–1.005)	< 0.001
Creatinine	1.00 (1.00-1.01)	0.057	1.004 (1.000-1.009)	0.079
D-Dimer	0.99 (0.96–1.01)	0.333		

CAD: coronary artery disease; CK-MB: creatine kinase-MB; CI: confidence interval; DM: diabetes mellitus; FMC: first medical contact; LVSD: left ventricular systolic dysfunction; NSTEMI: non-ST-elevation myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

## Interaction analysis between COVID-19 infection and LVSD across subgroups

An interaction analysis was conducted to evaluate the association between COVID-19 infection and LVSD through different subgroups. The results of the interaction analysis are shown in Fig. 2. No differences were found in different groups of age, sex category, AMI type, previous medical histories, levels of C-reactive protein, D-Dimer, or peak CK-MB. Therefore, the risks of LVSD were increased with COVID-19 infection across all the subgroups.

#### Discussion

In this multicenter retrospective cohort study, clinical characteristics and outcomes of AMI patients from multiple phases throughout the pandemic were analyzed. By time periods, higher risks of prolonged D-to-B and shorter lengths of hospital and CCU stay during the outbreak period were found, while higher percentages of thrombolysis during the lockdown period were found. The study also found that COVID-positive patients had longer symptom-to-FMC, pre-hospital time, D-to-B, and TIT. Higher risks of LVSD were found in COVID-positive patients. As for in-hospital mortality or other adverse events, no differences were found by time period or COVID-19 infection status.

From previous studies, the impact of the COVID-19 pandemic on AMI patient care was heterogeneous. A study from the United States demonstrated increased in-hospital mortality and decreased use of coronary angiography and PCI for AMI patients during the early pandemic [15]. However, no differences in fatality rates in AMI patients were found before and during the

pandemic in a nationwide study from Sweden [16]. A study from Northern American countries demonstrated COVID-positive STEMI patients had longer D-to-B and higher mortality rates [17], while another nationwide database analysis from the United States found no differences in 30-day major adverse cardiac events (MACE) in COVID-positive STEMI patients [18].

During the early outbreak of COVID-19, reductions in AMI hospitalizations were found with increasing mortality [19]. Strict lockdown measures, care avoidance, and inequalities in healthcare resources all contribute to the results [20, 21]. A previous nationwide study from China also demonstrated that the risk of in-hospital mortality of STEMI patients increased during the early outbreak of COVID-19 in 2020 and gradually returned to the pre-COVID era [12]. However, in this study, no differences in in-hospital mortality were found across the pandemic, including the outbreak seen in December 2022. Since strict lockdown measures were taken before the end of 2022 in China, the healthcare systems were more prepared for the outbreak, and treatment strategies were improved compared with the early COVID-19 outbreak in 2020. This could be one of the reasons for the lack of increase in mortality rates in this study. Besides, the improvements in outcomes could be caused by promotions of COVID-19 vaccinations and changes in dominant variants of COVID-19, since the Omicron variant has reduced pathogenicity [22]. According to a study from the United Kingdom, in-hospital mortality of STEMI patients comorbid with COVID-19 increased during the first wave of the pandemic but declined significantly during the subsequent second and third waves [10].

Variable	Count	Percent (%)						OR (95% CI)	p value	p for interaction
Age				1						0.319
Less than 65	546	62.5						• 1.70 (1.14 to 2.51)	0.009	
Greater than 65	327	37.5	·					1.23 (0.75 to 2.02)	0.421	
Gender										0.879
Male	737	84.4						1.48 (1.05 to 2.07)	0.023	
Female	136	15.6		1				• 1.58 (0.73 to 3.41)	0.245	
AMI types										0.446
NSTEMI	190	21.8	H	-				1.16 (0.56 to 2.39)	0.697	
STEMI	683	78.2			-			1.58 (1.12 to 2.24)	0.010	
Diabetes mellitus										0.267
No	616	70.8						1.69 (1.16 to 2.45)	0.006	
Yes	254	29.2	·	-				1.16 (0.67 to 2.00)	0.603	
Hypertension										0.611
No	426	49	⊢	1			-	1.39 (0.89 to 2.16)	0.144	
Yes	444	51						• 1.63 (1.06 to 2.51)	0.027	
Chronic lung disease				1						0.208
No	784	94.1		·				1.58 (1.13 to 2.20)	0.007	
Yes	49	5.9	<b>← =</b>					0.73 (0.23 to 2.32)	0.590	
Smoking history										0.996
No	380	43.7	,					+ 1.52 (0.92 to 2.50)	0.099	
Yes	490	56.3		·				1.52 (1.02 to 2.26)	0.040	
CRP										0.319
Less than 10 mg/L	65	34.2	1					• 2.61 (0.94 to 7.20)	0.065	
Greater than 10 mg/L	125	65.8	<b></b>					• 1.39 (0.68 to 2.83)	0.369	
D-Dimer										0.933
Less than 0.5 ng/mL	416	61.9		H				1.52 (0.96 to 2.40)	0.074	
Greater than 0.5 ng/mL	256	38.1	۰					• 1.57 (0.90 to 2.72)	0.111	
Peak CK-MB										0.491
Less than 60 ng/mL	230	38.2				•		• 1.86 (1.02 to 3.37)	0.042	
Greater than 60 ng/mL	372	61.8	•					1.43 (0.92 to 2.23)	0.115	
Overall	873	100		¦ —				1.50 (1.10 to 2.04)	0.010	
		(	0.5	1	1.5	2	2	.5		

Fig. 2 Interaction analysis between COVID-19 infection and LVSD across subgroups

AMI: acute myocardial infarction; CK-MB: creatine kinase-MB; CI: confidence interval; CRP: C-reactive protein; LVSD: left ventricular systolic dysfunction; NSTEMI: non-ST-elevation myocardial infarction; OR: odds ratio; STEMI: ST-elevation myocardial infarction

During the lockdown period, a higher percentage of patients were treated with thrombolysis, which could be explained by the potential system delay for transfer. However, the TIT and in-hospital outcomes were not increased during the lockdown period. Similar to previous research [23], the study found increasing D-to-B during the outbreak period, despite the majority of patients meeting reperfusion targets. The length of CCU and hospital stays were shorter during the outbreak period, most likely caused by the inadequacy of healthcare resources. Meanwhile, in-hospital outcomes were similar, suggesting chest pain centers remained high standards during the pandemic.

In COVID-positive patients, prolonged symptom-to-FMC, pre-hospital time, D-to-B, and TIT were found in STEMI patients, although there were no differences in the percentages of patients who met reperfusion time targets. The results are consistent with prior global analysis [24]. The reasons for exceeding the time targets include mandatory COVID-19 screening tests, shortage of personnel, overwhelmed emergency department, and strict infection control measures [7]. The prolongation of pre-hospital time might exceed PCI's therapeutic window, as our study found that COVID-positive STEMI patients were less likely to be treated with emergent PCI.

As for in-hospital outcomes, no differences except for LVSD were found in the COVID-positive group. Using multivariable logistic regression analysis, our study found that COVID-19 infection was significantly associated with LVSD in both AMI and STEMI patients. Higher NT-proBNP and lower LVEF were found in the COVIDpositive group. COVID-19 infection is associated with cardiovascular damage, manifesting as myocardial ischemia, arrhythmia, myocarditis, cardiomyopathy, or

cardiogenic shock [25]. The mechanisms include inflammation, viral damage, endothelial dysfunction, hypoxemia, and hypercoagulation [26]. In our study, the decrease in LVEF could be explained by COVID-associated myocardial injury and systemic delay during the pandemic. Virus invasion of the myocardium might cause direct damage and myocarditis, while systemic inflammation caused by cytokine storms could lead to tissue hypoxia and microvascular thrombosis [27], in which the imbalance between oxygen delivery and myocardial oxygenation contributes to myocardial injury. Systemic delay also took part, as seen in the Magnetic Resonance Imaging in Acute STEMI (MARINA-STEMI) study, which showed that STEMI patients had increasing infarct size during major public health restriction periods of the pandemic [28]. As for treatment, more patients were prescribed diuretics, and fewer were prescribed  $\beta$ -blockers in the COVID-positive group. Since the COVID-positive group had a higher Killip class and lower LVEF, this group had a greater need for diuretics. The lower prescription rate of  $\beta$ -blockers in the COVID-positive group might be explained by the avoidance of respiratory adverse effects caused by  $\beta$ -blockers, including bronchospasm. However, standardized treatments, including β-blockers and reninangiotensin system inhibitors, should be promoted to improve long-term prognosis.

Studies on the long-term outcomes of AMI patients during the COVID-19 pandemic had inconsistent results. Previous studies did not find differences in long-term MACE of AMI patients between the pre-pandemic and the pandemic period [29, 30]. However, higher rates of long-term MACE, mortality, and hospitalization of heart failure were found in COVID-positive AMI patients compared with COVID-negative patients [31, 32]. Unfortunately, this study did not document long-term prognosis, which was a limitation of this study.

Overall, AMI patients were given appropriate treatments during the COVID-19 pandemic, although prolonged reperfusion time and impaired left ventricular systolic function were found in COVID-positive patients. Measures should be implemented to shorten the delay to reperfusion. The delays could be categorized into patient factors and healthcare systemic factors. From the patient's perspective, fear of co-infection and reluctance to seek medical care might lead to increasing time of symptom-to-FMC [33]. Awareness of AMI symptoms should be strengthened by education to the general public. From the emergency medical service perspective, the phone lines and ambulances were in shortage during the pandemic, which also increased the symptom-to-FMC time. The usage of telemedicine could reduce the time needed to diagnose and treat AMI [34]. As for the healthcare systemic delay, transfer time was prolonged because of less availability of ambulances and mandatory COVID testing, while the D-to-Needle and D-to-B prolongations were caused by a shortage of healthcare staff and personal protective equipment during the treatment process. Meanwhile, the time to transfer also impacts whether to choose thrombolysis or primary PCI strategy. A previous study showed that fibrinolysis-first strategy during the pandemic was associated with worse outcomes [35]. Therefore, additional capacity of healthcare staff and resources are needed to minimize the transfer and reperfusion delay as much as possible and ensure AMI patient's care pathway while facing the pandemic.

#### Limitation

The study had several limitations. First of all, despite being a multicenter study, this is a regional analysis of Shanxi Province of northern China. Therefore, the results reflect the characteristics of AMI patients in an urban area of China and might not be able to be generalized to the international level. Moreover, the study's retrospective design is susceptible to information bias, selection bias, and confounding bias. When analyzing the association between LVSD and COVID-19 infection, we used multivariable logistic regression models to minimize the effects of confounding factors, but there could be residual unknown confounders. Lastly, the study only focused on in-hospital outcomes. More comprehensive statistics, such as pre-hospital mortality or long-term outcomes, were unknown, and future studies are warranted.

#### Conclusions

This multicenter retrospective cohort study involved patients with comparable baseline characteristics from the zero-case, lockdown, and outbreak periods. Higher percentages of thrombolysis were found during the lockdown period, while prolonged D-to-B and reduced lengths of hospital stay were found during the outbreak period. The COVID-positive AMI patients had longer reperfusion times, lower LVEF, and higher risks of LVSD. In-hospital mortality or other adverse events did not differ by time period or COVID-19 infection status. The treatments of AMI patients were impacted during the pandemic, and more measures should be taken to minimize the reperfusion time further.

#### Abbreviations

AMI	Acute myocardial infarction
D-to-B	Door-to-balloon
D-to-N	Door-to-needle
MC	First medical contact
VSD	Left ventricular systolic dysfunction
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
ГIМI	Thrombolysis in Myocardial Infarction
ΓIT	Total ischemic time

#### **Supplementary Information**

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Supplementary Material 1

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#### Author contributions

All the authors have contributed significantly to the work, and correspondence should be directed to KL and DM. KL and DM designed and supervised the study. XS, BY, HW, FY, QL, XL, SZ, YY, ZZ, BZ, and FF collected and analyzed the patient data. YP did the statistical analysis and wrote the original draft. KL edited and revised the manuscript. All authors have read and approved the final version of the manuscript.

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#### Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

#### Declarations

#### Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the institutional ethics committee of Taiyuan Central Hospital (No. 2023001), and written informed consent was waived.

#### **Consent for publication**

Not applicable.

#### Competing interests

The authors declare no competing interests.

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