Twin peaks of in-hospital mortality among patients with STEMI across five phases of COVID-19 outbreak in China: a nation-wide study

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Lockdown and re-opening may become cyclical due to the recurrent waves of the COVID-19 epidemic. Few studies have examined temporal trends and determinants of in-hospital mortality among patients with ST-segment elevation myocardial infarction (STEMI), a life-threatening condition that requires emergency medical care. Using nation-wide data before, during and after the Wuhan lockdown, we aimed to depict temporal patterns and major determinants of STEMI in-hospital mortality in China across five time periods of the COVID-19 epidemic. We analyzed the data of 283,661 STEMI patients who were admitted to 4,487 chest-pain-centers across China, from January 1, 2019 to May 31, 2020. Compared with the period before the lockdown, STEMI in-hospital mortality increased by 25% (OR 1.25, 95%CI 1.16–1.34) during Early Lockdown, by 12% (OR 1.12, 95%CI 1.03–1.22) during Later Lockdown, by 35% (OR 1.35, 95%CI 1.21–1.50) during Early Lift, and returned to pre-COVID risk (OR 1.04, 95%CI 0.95–1.14) during Later Lift. For each time-period, we observed a clear mortality gradient by timing and types of revascularization procedure. In conclusion, the COVID-19 epidemic had a significant adverse impact on STEMI in-hospital

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mortality, with bimodal peaks during early lockdown and early lift periods and clear mortality gradients by timing and types of revascularization procedure, independent of the time periods.

COVID-19, STEMI, mortality, lockdown, re-opening

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INTRODUCTION

The COVID-19 pandemic remains to be a major threat in many parts of the world, and has led to a multitude of disruptions at the individual, family, and community level, additionally affecting the entire ecosystem (Wang et al., 2020). The SARS-CoV-2 B.1.617.2 (also termed variant Delta), first detected in India, is now the main variant worldwide (Callyaway, 2021). Studies have shown that the Delta variant has a 60% higher risk of household transmission than the Alpha variant, and is responsible for new waves of outbreaks in many countries and regions (Mahase, 2021a). Facing this threat, affected countries have to implement a new round of lockdown or strict social distancing measures (Mahase, 2021b). It is foreseeable that lockdown, social distancing and re-opening may become cyclical due to the recurrent waves of the COVID epidemic. A critical but understudied question is whether each phase of the COVID lockdown-reopening cycle, impacts cardiovascular outcomes differently and if so, what factors contribute to the differences (Auriemma et al., 2021; Biamonte et al., 2021; Califf, 2021).

This study focuses on ST-segment elevation myocardial infarction (STEMI), a life-threatening condition that requires emergency medical care. The impact of COVID-19 on the timely diagnosis and treatment of STEMI patients has been demonstrated in several nation-wide studies, which revealed a reduction in hospital admissions and an increased risk of death during the lockdown (Gluckman et al., 2020; Mafham et al., 2020; Rattka et al., 2021). To our knowledge, few studies have examined the temporal trends and determinants of in-hospital mortality among patients with STEMI across all phases of the COVID-19 pandemic. To fill in this gap, we analyzed the data from 283,661 STEMI patients who were admitted to 4,487 chest-pain-centers across China, from January 1, 2019 to May 31, 2020, spanning all five phases of the COVID-19 outbreak in China: Before the pandemic; Early Lockdown; Later Lockdown; Early Lift and Later Lift. We sought to examine temporal trends and influencing factors of in-hospital mortality among patients with STEMI. Given that lockdown and re-opening may become cyclical due to the recurrent waves of the COVID-19 epidemic, our findings have implications on responses to and preparedness for current and future pandemics.

RESULTS

Baseline characteristics stratified by different time periods of COVID-19

A total of 283,661 STEMI patients were included in the analysis. Table 1 presents the characteristics of the participants according to different time periods of COVID-19. Among the overall sample, compared with the period prior to the lockdown, after the Wuhan lockdown, admission numbers decreased, in-hospital mortality rates increased, symptoms to first medical contact (S2FMC) were prolonged, and STEMI patients tended to be slightly younger, had higher blood pressure, and a lower percentage of them were female. By the early stage of Wuhan Lift in Lockdown, admissions had decreased further, in-hospital mortality had risen to 5.0%, the S2FMC time had fallen back, and the Timely S to FMC (symptom to first medical contact) rate had increased. The in-hospital mortality rates of STEMI patients during the five periods were 3.6%, 4.4%, 4.0%, 5.0% and 3.8%, respectively. When stratified by revascularization procedures, among primary percutaneous coronary intervention (PPCI) patients, door to wire (D2W) time increased, and the percentage of timely PPCI decreased. The in-hospital mortality rates of PPCI patients during the five periods were 2.3%, 2.8%, 2.3%, 3.2% and 2.7%, respectively. Among fibrinolytic therapy (FT) patients, door to needle (D2N) time decreased and percentage of timely FT increased. The in-hospital mortality rates of FT patients during the five periods were 3.2%, 4.1%, 5.0%, 5.1% and 4.0%, respectively. For patients without any revascularization, S2FMC substantially increased. The in-hospital mortality rates for patients without any revascularization during the five periods were 6.1%, 7.7%, 6.8%, 8.4% and 6.2%, respectively.

In-hospital mortality during different time periods of COVID-19

Figure 1A depicts the weekly in-hospital mortality of STEMI patients across the five time periods in 2020: Before Wuhan Lockdown; Early Wuhan Lockdown; Later Wuhan Lockdown; Early Wuhan Lift in Lockdown and Later Wuhan Lift in Lockdown, and mortality during the equivalent time periods in 2019. Weekly in-hospital mortality was basically the same before COVID-19 in 2020 compared with the equivalent time in 2019. Since the outbreak of COVID-19,
| Variables | All time periods (2019.01.01–2020.05.31) | Before Wuhan Lockdown (2019.01.01–2020.01.22) | Early Wuhan Lockdown (2020.01.23–2020.03.04) | Later Wuhan Lockdown (2020.03.05–2020.04.07) | Early Wuhan Lift in Lockdown (2020.04.08–2020.04.28) | Later Wuhan Lift in Lockdown (2020.04.29–2020.05.31) |
|---|---|---|---|---|---|---|
| **Number of days for each period** | 517 | 387 | 42 | 34 | 21 | 33 |
| **Admissions during the periods** | 283,661 | 216,846 | 22,934 | 19,674 | 8,513 | 15,694 |
| **Average admissions per day** | 548 | 560 | 546 | 578 | 405 | 475 |
| **Age at admission, years** | 62.9 (12.6) | 63.1 (12.6) | 62.5 (12.5) | 62.7 (12.4) | 62.8 (12.7) | 62.3 (12.6) |
| **Female, No. (%)** | 68,174 (24.0) | 52,476 (24.2) | 5,438 (23.7) | 4,589 (23.3) | 2,036 (23.9) | 3,635 (23.2) |
| **In-hospital mortality, No. (%)** | 10,703 (3.8) | 7,872 (3.6) | 1,009 (4.4) | 795 (4.0) | 423 (5.0) | 604 (3.8) |
| **Systolic blood pressure, mmHg** | 131.8 (26.6) | 131.5 (26.4) | 133.3 (27.1) | 132.8 (27.0) | 132.5 (27.2) | 131.2 (26.8) |
| **Diastolic blood pressure, mmHg** | 81.5 (17.3) | 81.3 (17.1) | 82.6 (17.7) | 82.3 (17.6) | 82.2 (17.5) | 81.6 (17.6) |
| **S to FMC, min** | 124.0 (60.0, 290.0) | 121.0 (60.0, 280.0) | 137.0 (65.0, 321.0) | 135.0 (63.0, 313.0) | 132.0 (62.0, 309.0) | 131.0 (61.0, 306.0) |
| **Timely S to FMC (<30 min), No. (%)** | 22,788 (9.3) | 18,072 (9.6) | 1,526 (7.7) | 1,351 (8.1) | 666 (9.1) | 1,173 (8.7) |
| **Patients with PPCI** | | | | | | |
| **Age at admission, years** | 61.9 (12.3) | 62.0 (12.3) | 61.4 (12.2) | 61.5 (12.2) | 61.8 (12.7) | 61.3 (12.3) |
| **Female, No. (%)** | 36,606 (21.6) | 28,386 (21.7) | 2,845 (21.4) | 2,341 (20.9) | 1,045 (21.5) | 1,989 (21.3) |
| **In-hospital mortality, No. (%)** | 4,050 (2.4) | 3,004 (2.3) | 376 (2.8) | 262 (2.3) | 154 (3.2) | 254 (2.7) |
| **Systolic blood pressure, mmHg** | 131.9 (26.5) | 131.6 (26.3) | 134.1 (27.1) | 133.1 (27.0) | 132.5 (26.8) | 131.4 (26.5) |
| **Diastolic blood pressure, mmHg** | 81.8 (17.3) | 81.6 (17.2) | 83.1 (17.7) | 82.8 (17.7) | 82.3 (17.4) | 81.8 (17.6) |
| **Door to wire, min** | 71.0 (53.0, 90.0) | 71.0 (52.0, 90.0) | 73.0 (55.0, 91.8) | 74.0 (55.0, 95.0) | 72.0 (54.0, 91.0) | 73.0 (55.0, 92.0) |
| **Timely PPCI (<90 min), No. (%)** | 115,716 (74.0) | 91,439 (74.6) | 8,449 (72.4) | 6,829 (70.1) | 3,137 (73.3) | 5,862 (72.3) |
| **Patients with FT** | | | | | | |
| **Age at admission, years** | 60.5 (11.6) | 60.4 (11.6) | 60.3 (11.5) | 60.9 (11.6) | 60.9 (12.0) | 60.5 (11.7) |
| **Female, No. (%)** | 4,784 (21.2) | 2,935 (21.1) | 667 (21.4) | 534 (21.6) | 253 (21.9) | 395 (20.3) |
| **In-hospital mortality, No. (%)** | 829 (3.7) | 441 (3.2) | 128 (4.1) | 124 (5.0) | 59 (5.1) | 77 (4.0) |
| **Systolic blood pressure, mmHg** | 129.5 (26.2) | 128.4 (25.4) | 132.0 (27.1) | 131.4 (27.4) | 131.1 (27.9) | 129.4 (27.4) |
| **Diastolic blood pressure, mmHg** | 81.5 (17.3) | 81.6 (17.2) | 83.1 (17.7) | 82.8 (17.7) | 82.3 (17.4) | 81.8 (17.6) |
| **Door to needle, min** | 30.0 (24.0, 51.0) | 31.0 (25.0, 52.0) | 30.0 (24.0, 48.0) | 30.0 (24.0, 47.0) | 30.0 (24.0, 50.0) | 30.0 (24.0, 50.0) |
| **Timely FT (<30 min), No. (%)** | 5,362 (44.2) | 2,556 (43.1) | 954 (43.1) | 800 (45.7) | 412 (49.5) | 640 (44.9) |
| **Patients without revascularization** | | | | | | |
| **Age at admission, years** | 65.5 (13.0) | 65.5 (13.0) | 65.6 (12.9) | 65.5 (12.7) | 65.7 (13.2) | 65.4 (12.9) |
| **Female, No. (%)** | 26,784 (29.2) | 21,155 (29.2) | 1,926 (29.4) | 1,714 (28.5) | 738 (29.5) | 1,251 (28.5) |
| **In-hospital mortality, No. (%)** | 5,824 (6.3) | 4,427 (6.1) | 505 (7.7) | 409 (6.8) | 210 (8.4) | 273 (6.2) |
| **Systolic blood pressure, mmHg** | 132.0 (26.9) | 131.8 (26.8) | 132.3 (27.1) | 133.0 (27.0) | 133.2 (27.7) | 131.5 (26.9) |
| **Diastolic blood pressure, mmHg** | 81.0 (17.1) | 81.0 (17.1) | 81.3 (17.5) | 81.4 (17.2) | 81.8 (17.1) | 80.8 (17.1) |
| **S to FMC, min** | 160.0 (66.0, 436.0) | 151.0 (64.0, 414.0) | 205.0 (80.0, 558.0) | 181.0 (76.0, 547.8) | 180.0 (76.0, 511.2) | 188.0 (75.0, 560.0) |
| **Timely S to FMC (<30 min), No. (%)** | 2,001 (9.3) | 1,305 (9.9) | 225 (7.5) | 187 (8.0) | 118 (10.6) | 166 (8.9) |

*For continuous variables, values are presented as mean (SD). b Values are presented as median (IQR).*
in-hospital mortality increased significantly, especially during the Early Wuhan Lockdown and Early Wuhan Lift in Lockdown periods, and was substantially higher than the same periods of 2019. Figure 1B shows the trend in in-hospital mortality during the epidemic and during the same period in 2019. As shown in the figure, the in-hospital mortality rate of STEMI was higher during the epidemic and showed a bimodal pattern. Figure S1 in Supporting Information shows STEMI mortality for the five time periods in 2020 compared with the same period in 2019. Consistent with Figure 1, we found a higher mortality in the Early Lockdown and Early Lift periods compared with the same period the year before (4.4% vs. 3.6%, \( P < 0.001 \); 5.0% vs. 3.6%, \( P < 0.001 \)).

Table 2 shows the crude and adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) of in-hospital mortality of STEMI patients during the different time periods of COVID-19 (using the pre-COVID time period as the reference group), using logistic regression models. Model 1 adjusted for baseline characteristics including age, sex, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status and history of diabetes. Model 2 further adjusted for rescue time. When analyzing the patients as a whole, the highest in-hospital mortality occurred in the periods of early lockdown and early lifting of the lockdown, even after adjustment of potential confounders. Compared with the Before Wuhan Lockdown period, STEMI in-hospital mortality increased by 25% (OR 1.25, 95%CI 1.16–1.34) during Early Wuhan Lockdown, by 12% (OR 1.12, 95%CI 1.03–1.22) during Later Wuhan Lockdown, and 18% (OR 1.18, 95%CI 1.09–1.28) during Early Wuhan Lift in Lockdown.
Table 2  Crude and adjusted odds ratios of in-hospital mortality for STEMI patients during different time periods of COVID-19 in total sample and in subgroups defined by revascularization procedures

| Time periods of COVID-19          | N     | Events (%) | Crude Model | Adjusted Model 1 | Adjusted Model 2 |
|----------------------------------|-------|------------|-------------|------------------|------------------|
|                                 |       |            | OR (95%CI)  | P-value          | OR (95%CI)       | P-value          |
|                                 |       |            | P-value     |                  |                  |                  |
| Total sample                     | 216,846 | 7,872 (3.6) | reference   | reference        | reference        | reference        |
| Before Wuhan Lockdown (2019.01.01–2020.01.22) | 22,934 | 1,009 (4.4) | 1.22 (1.14, 1.31) | <0.001 | 1.28 (1.19, 1.38) | <0.001 |
| Early Wuhan Lockdown (2020.01.23–2020.03.04) | 19,674 | 795 (4.0)  | 1.12 (1.04, 1.20) | 0.003 | 1.17 (1.08, 1.27) | <0.001 |
| Later Wuhan Lockdown (2020.03.05–2020.04.07) | 8,513  | 423 (5.0)  | 1.39 (1.26, 1.53) | <0.001 | 1.39 (1.25, 1.55) | <0.001 |
| Early Wuhan Lift in Lockdown (2020.04.08–2020.04.28) | 15,694 | 604 (3.8)  | 1.06 (0.98, 1.16) | 0.159 | 1.07 (0.98, 1.17) | 0.140 |
| Later Wuhan Lift in Lockdown (2020.04.29–2020.05.31) | 130,582 | 3,004 (2.3) | reference | reference | reference | reference |
| Patients with PPCI              | 13,276 | 376 (2.8)  | 1.24 (1.11, 1.38) | <0.001 | 1.31 (1.16, 1.48) | <0.001 |
| Before Wuhan Lockdown (2019.01.01–2020.01.22) | 11,192 | 262 (2.3)  | 1.02 (0.90, 1.16) | 0.784 | 1.08 (0.94, 1.23) | 0.304 |
| Early Wuhan Lockdown (2020.01.23–2020.03.04) | 4,855  | 154 (3.2)  | 1.39 (1.18, 1.64) | <0.001 | 1.40 (1.18, 1.67) | <0.001 |
| Later Wuhan Lockdown (2020.03.05–2020.04.07) | 9,356  | 254 (2.7)  | 1.19 (1.04, 1.35) | 0.010 | 1.19 (1.04, 1.37) | 0.014 |
| Patients with FT                 | 13,924 | 441 (3.2)  | reference | reference | reference | reference |
| Before Wuhan Lockdown (2019.01.01–2020.01.22) | 3,110  | 128 (4.1)  | 1.31 (1.07, 1.60) | 0.008 | 1.05 (0.84, 1.31) | 0.660 |
| Early Wuhan Lockdown (2020.01.23–2020.03.04) | 2,469  | 124 (5.0)  | 1.62 (1.32, 1.98) | <0.001 | 1.20 (0.96, 1.49) | 0.115 |
| Later Wuhan Lockdown (2020.03.05–2020.04.07) | 1,155  | 59 (5.1)   | 1.65 (1.25, 2.17) | <0.001 | 1.15 (0.85, 1.55) | 0.354 |
| Early Wuhan Lift in Lockdown (2020.04.08–2020.04.28) | 1,945  | 77 (4.0)   | 1.26 (0.98, 1.61) | 0.066 | 0.93 (0.71, 1.21) | 0.585 |
| Later Wuhan Lift in Lockdown (2020.04.29–2020.05.31) | 72,340 | 4,427 (6.1) | reference | reference | reference | reference |
| Patients without revascularization | 6,548  | 505 (7.7)  | 1.28 (1.16, 1.41) | <0.001 | 1.25 (1.12, 1.39) | <0.001 |
| Before Wuhan Lockdown (2019.01.01–2020.01.22) | 6,013  | 409 (6.8)  | 1.12 (1.01, 1.24) | 0.035 | 1.13 (1.01, 1.27) | 0.037 |
| Early Wuhan Lockdown (2020.01.23–2020.03.04) | 2,503  | 210 (8.4)  | 1.40 (1.22, 1.62) | <0.001 | 1.38 (1.18, 1.61) | <0.001 |
| Later Wuhan Lockdown (2020.03.05–2020.04.07) | 4,393  | 273 (6.2)  | 1.02 (0.90, 1.15) | 0.799 | 0.97 (0.84, 1.11) | 0.640 |

a) Model 1 adjusted for sex, age, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status, and history of diabetes. For total sample, adjusted for sex, age, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status, history of diabetes, symptom to first medical contact, and revascularization procedures. For patients with PPCI, adjusted for sex, age, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status, history of diabetes, symptom to first medical contact, and door to wire. For patients with FT, adjusted for sex, age, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status, history of diabetes, symptom to first medical contact, and door to needle. For patients without revascularization, adjusted for sex, age, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status, history of diabetes, and symptom to first medical contact.
Lockdown, by 35% (OR 1.35, 95%CI 1.21–1.50) during Early Wuhan Lift in Lockdown, and returned to the pre-COVID risk (OR 1.04, 95%CI 0.95–1.14) during Later Wuhan Lift in Lockdown. When patients were stratified by revascularization procedures, in-hospital mortality risk during the early lockdown period and the early lift in lockdown period remained elevated for PPCI and non-revascularization patients, but not for FT patients.

Table S1 in Supporting Information shows the sensitivity analyses of in-hospital mortality risk in relation to the Wuhan lockdown periods, where the Wuhan population, the Hubei population, and patients with COVID-19 were removed, respectively, and the results remained unchanged.

**Joint influence of COVID-19 and timing and types of revascularization procedure**

Figure 2 is a 3D display of the joint influence of the five time periods and timing and type of revascularization procedures on in-hospital mortality. Regardless of time period, the lowest mortality rate was observed among patients who received timely PPCI, and the highest mortality rate was among patients who did not receive any revascularization. During the outbreak of COVID-19, both PPCI and non-revascularization patients showed a bimodal peak in mortality during the Early Wuhan Lockdown and Early Wuhan Lift in Lockdown periods, but such a pattern was not observed for FT patients.

Table 3 presents results from logistic regression analyses used to estimate the crude and adjusted odds ratios (95% CIs) of in-hospital mortality across the groups defined by the timing and types of revascularization procedures (using PPCI with D2W<90 min as the reference group), stratified by the five COVID time periods. The adjusted models included patient baseline characteristics and symptom to first
medical contact. The regression results further confirm and quantify what was observed in Figure 2. That is, regardless of COVID time period, the lowest mortality rate was observed among patients who received timely PPCI, and the highest mortality was among patients who did not receive revascularization. This pattern remained after adjusting for baseline demographic and clinical characteristics and timeliness to care.

DISCUSSION

To our knowledge, this is the first large-scale, nation-wide study in China to examine the impact of COVID-19 on in-hospital mortality of STEMI patients across the five phases of the pandemic. Compared with the period before the lockdown, and after adjusting for relevant variables, we found two peaks for STEMI in-hospital mortality, which increased by 25% during Early Lockdown, and again, by 35% during Early Lift. For each time-period, we also observed a clear mortality gradient by timing and types of revascularization procedure. We speculate that there are multiple explanations for the observed twin peaks, including hospital, individual factors, and societal factors mixed in, as discussed below.

Previous studies in several countries have reported the impact of COVID-19 outbreaks on STEMI, primarily at the hospital level, and mostly during the lockdown period, and
the findings included reductions in hospital admissions, reductions in the volume of cardiac procedures, including PCI, changes in reperfusion strategies, delays in total ischemic time and in-hospital rescue time, and an increase in in-hospital mortality (Gluckman et al., 2020; Mafham et al., 2020; Park and Yang, 2020; Rattka et al., 2021). Our research was consistent with the available literature. We found a decrease in STEMI admissions and a decrease in performing PCI during the COVID-19 lockdown. Our data showed that in-hospital rescue time for PCI was prolonged during the COVID-19 lockdown compared with the pre-COVID-19 period. Changes in in-hospital factors due to the epidemic may all have had an impact on STEMI death. As health systems continue to adjust their response strategies, the impact caused at the hospital level has improved to some extent.

In contrast to most previous studies, we examined STEMI mortality across time periods from before the pandemic, during the lockdown, and to the lifting of lockdown. Compared with the same period before lockdown, STEMI in-hospital mortality increased by 25% during Early Wuhan Lockdown. The observed increase in in-hospital mortality adjusted for patients’ baseline demographic and clinical characteristics, and timing and types of revascularization procedure, underscores the real impact of COVID-19. Notably, for the first time, this study observed a 35% spike in the risk of in-hospital mortality among STEMI patients, even in patients who underwent timely PCI, during the period of the early lifting of the lockdown. Hospital-level factors alone are not sufficient to explain the bimodal phenomenon observed for in-hospital mortality in STEMI patients, especially the second peak that occurred during the early lifting of the lockdown.

Individual factors, mixed of course with social factors, may at least partially explain the phenomenon. During the epidemic, patient health care seeking behavior changed, which was manifested as a prolonged S2FMC time. Previous studies observed significantly prolonged pre-hospital time during the outbreak (Kite et al., 2021). Similar findings were observed in our study, where the pre-hospital time was prolonged from 121 to 137 min early in the outbreak and only gradually decreased after the lifting. However, this still does not explain the twin peaks. We speculate that lockdown-related personal factors may contribute to the appearance of the second peak, which include poor chronic disease management, psychological problems associated with social isolation and the epidemic itself, and reduced physical activity.

Firstly, poor management of common chronic diseases, especially of chronic metabolic diseases, during the lockdown period can affect cardiometabolic health. An Italian study showed significant increases in the prevalence of various metabolic diseases at the end of the lockdown period: obesity, from 37.8% to 51.3%, \( P<0.0001 \); dyslipidemia, from 28.4% to 48.6%, \( P=0.003 \); and metabolic syndrome, from 14.9% to 27%, \( P<0.0001 \) (Auriemma et al., 2021). Meanwhile, another study also noted that weight and glycemic control in patients with type 2 diabetes mellitus (T2DM) during the lockdown period were suboptimal (Biamonte et al., 2021). After the lockdown period, T2DM patients had a significant increase in weight, BMI and waist circumference. Fasting blood glucose and glycated hemoglobin levels were significantly higher, especially in patients receiving insulin therapy (OR: 2.40, 95%CI: 1.06–5.45; \( P=0.035 \)). In a recent commentary, Dr. Robert Califf pointed out that if the epidemic is compared with a submarine earthquake, death from chronic disease is, as he terms it, “the Coming Tsunami”, with incalculable consequences if left unattended, and with cardiometabolic disease being the most affected (Califf, 2021). Secondly, lockdown or social restrictions have an impact on personal mental health, especially for those with underlying diseases (Chandola et al., 2020; Shah et al., 2020). An adverse mental state can contribute to the progression of myocardial infarction and even increase the risk of death (Batelaan et al., 2016; Li et al., 2020; Martens et al., 2010). British academics found that the incidence of common mental disorders reached 29% since the outbreak and remained at 9% until the early days of lifting the lockdown (Chandola et al., 2020). In a survey conducted in five provinces of China, including Hubei Province, the mental health burden of Chinese people did not ease with the gradual lifting of the country, but rather tended to increase (Du et al., 2020). We speculate that an ongoing adverse state of mental health may have contributed to the elevated risk of death in the early stage of lifting. Additionally, several studies have specifically identified “lockdown loneliness” as a significant public health issue that increases morbidity and mortality in those with underlying diseases (Shah et al., 2020). While on the one hand, it has been shown that those with bad to very bad health are more likely to develop “lockdown loneliness”, on the other hand, “lockdown loneliness” can exacerbate the progression of cardiovascular disease in this group, which contributed to the rising risk of in-hospital mortality in the early lockdown and in the early lifting of lockdown periods, as seen in our study (Reynolds et al., 2008). Thirdly, physical inactivity during the lockdown may have also contributed. A study in Shanghai, China, found a sharp decline in the average daily step count during the city’s lockdown, but a slow increase in daily step count was observed at the end of lockdown (Ding et al., 2021). However, among those with underlying disease, the increase in step count remained slow. The impact of a sudden change in lifestyle cannot be underestimated either.

What are the clinical and public health implications of our findings? Firstly, in this present study, we observed that regardless of the COVID-19 time period, the lowest mortality rate was observed among patients who received timely PCI, and the highest mortality was among patients who did not
receive revascularization. Our data provide strong evidence that timely PPCI remains the best option as measured by in-hospital mortality across all the time periods from pre-COVID to the later lifting of the lockdown. Our data also indicate that when PPCI is not possible or not available, timely FT saves lives compared with no-revascularization. Secondly, the management of chronic diseases needs to be optimized during lockdown, especially the high-risk groups at home. While patients need to closely manage themselves during the lockdown period: taking their medication regularly, monitoring their condition, maintaining a moderate level of activity, and ensuring a good state of mental health, patient self-management, however, must include guidance from professionals. To the extent that the epidemic prevention allows, medical input and information should be reinforced, and timely intervention should be initiated. The government and health authorities can support the effort by encouraging and promoting telemedicine for high-risk populations to optimize home-based, self-management models. Thirdly, psychological support should be strengthened. Studies have shown that the psychological burden associated with COVID-19 can be relieved by having active access to news about the epidemic, and taking active measures to cope with the epidemic, such as disinfection and temperature testing and moderate recreational activities (Reynolds et al., 2008). “Lockdown loneliness” can be reduced through the use of digital technology tools in moderation (Shah et al., 2020). All of this depends on active government promotion. Finally, remote monitoring of high-risk groups, both during and after the lockdown, is essential (Duffy et al., 2020). In cases where lockdown-related factors have already had an impact on cardiovascular health, timely treatment can also save lives.

Our study also has limitations. First, cardiology practice varies widely across China. As 64.7% of the China Chest Pain Centers (CCPCs) are located in urban areas, our data still have limited representativeness. Second, we lacked detailed information on the causes of death and therefore, were not able to make further explorations in this regard. However, preliminary data suggest that approximately 96% of deaths were due to cardiac origins. Third, we lacked detailed patient information during the lockdown, including psychological status, activity levels, and chronic disease management, so the impact of these factors on mortality cannot be quantified. These issues remain to be explored in future studies.

CONCLUSIONS

This large-scale, nation-wide study in China showed a significant impact of the COVID-19 epidemic on in-hospital mortality of STEMI patients, as reflected by bimodal mortality peaks (Early Wuhan Lockdown and Early Wuhan Lift in Lockdown). It also demonstrated clear mortality gradients by timing and type of revascularization, independent of COVID-19 time periods. These findings have implications on responses to and preparedness for current and future pandemics.

MATERIALS AND METHODS

Data source and participants
All data for this report are from the CCPC database, which included 4,487 CCPCs across 31 provinces in China. In China, CCPCs are part of the hospital emergency departments, and their mission is to provide fast access to treatment for patients with acute myocardial infarction and other critical illnesses, with acute chest pain as the main clinical manifestation. The CCPCs currently consist mainly of urban hospitals (64.7% of CCPCs are located in urban areas). The CCPC databases include epidemiological and clinical data of admitted patients, including diagnosis, treatment, and the timeline.

Study participants in the main analyses were STEMI patients admitted from January 1, 2019 to May 31, 2020. We excluded 18,045 transfer percutaneous coronary intervention patients (from a hospital with non-cardiology services to a hospital equipped to perform cardiac surgery) and 157 participants with missing values on province, for a total of 283,661 STEMI patients included in the final analysis (Figure S2 in Supporting Information).

The study received approval from the ethics committee of Peking University First Hospital, Beijing, China (institutional review board number 2020-242) and the institutional review board (IRB) of Anhui Medical University (Federal Wide Assurance Number: FWA00001263). All the datasets were de-identified before the data analyses to protect patients’ privacy and personal health information.

Timeline

From January 23, 2020, provinces across China enforced the “Major Public Health Emergency Level I Restrictions”, a mandate in which residents were required to stay at home and non-essential public places were closed, which affected a total population of over 1.2 billion (http://www.gov.cn/xinwen/2020-01/23/content_5471751.htm). In mid-to-late March 2020, all provinces and cities across China gradually and officially lifted their lockdown according to the epidemic situation at the local level, and by April 8, 2020, when Wuhan was lifted, the lifting was completed across the country. As Wuhan was the epicenter of the epidemic in China and one of the first cities to be on lockdown and the last to be lifted, the Wuhan city Lockdown and Re-opening dates are used in this paper to represent the nation-wide
Lockdown and Re-opening timeline in China. It should be noted that reopening was a gradual process in China and restrictions were regularly removed until the official lockdown was lifted, such as the gradual opening of public facilities and businesses.

As such, based on the sequence of events, we defined the following five time periods for the analyses: (i) Before Wuhan Lockdown (January 1, 2019 to January 22, 2020); (ii) Early Wuhan Lockdown (January 23, 2020 to March 4, 2020); (iii) Later Wuhan Lockdown (March 5, 2020 to April 7, 2020); (iv) Early Wuhan Lift in Lockdown (April 8, 2020 to April 28, 2020); and (v) Later Wuhan Lift in Lockdown (April 29, 2020 to May 31, 2020).

It should be noted that the five phases were first defined by official Wuhan lockdown and lift time, and within them, we further defined Early vs. Later Wuhan Lockdown and Early vs. Later Wuhan Lift in Lockdown, in order to observe more clearly the temporal trend of in-hospital mortality.

Clinical practice changes in STEMI treatment during the COVID-19 outbreak in China

During the outbreak, pre-screening triage tables were set up at both the emergency and outpatient entrances. Patients with STEMI were first screened for COVID-19, which included epidemiological surveys and measurement of body temperature. Thrombolytic therapy was recommended for patients with suspected COVID-19 identified through pre-screening.

Primary outcome

The primary endpoint was in-hospital all-cause mortality within each of the five defined time periods, according to hospital medical records and death certificates.

Statistical analysis

Means (SD) or medians (25th percentile-75th percentile) and proportions were used to describe STEMI patients’ characteristics by the five COVID-19 time periods. Multivariable logistic regression models, adjusted for age, sex, province, systolic blood pressure, diastolic blood pressure, dyslipidemia, body mass index, smoking status, history of diabetes, door to wire time, door to needle time, time of symptoms to first medical contact, and revascularization procedures were used to assess in-hospital mortality for STEMI patients during different time periods of COVID-19 in both the total sample and stratified by revascularization procedures. Similar regression analyses were also performed for the association between timing and types of revascularization procedure and in-hospital mortality, stratified by each of the five time periods. A 2-tailed \( P<0.05 \) was considered to be statistically significant in all analyses. EmpowerStats (http://www.empowerstats.com) and R software, version 4.0.0 (http://www.R-project.org/) were used for all statistical analyses.

Compliance and ethics

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.
The supporting information is available online at https://doi.org/10.1007/s11427-021-2046-4. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.