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The Effect of Covid-19 Pandemic on Treatment Management, and Clinical Outcome of Patients with Acute Coronary Syndromes (ACS): A Systematic Review and Meta-Analysis

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ABSTRACT

This systematic review and meta-analysis aimed to summarize the available evidence on the impacts of the COVID-19 pandemic on treatment management, and clinical outcomes among patients with acute coronary syndrome (ACS). PubMed and ScienceDirect were searched from January 2020 to September 2021 to identify relevant studies. For dichotomous variables, meta-analysis was performed using the random-effects model. For continuous variables, descriptive synthesis was conducted. Sixty-three articles were included in the review. The time from symptom onset to First Medical Contact (FMC) was significantly longer during the COVID-19 pandemic in 50% of the studies (17/34). One-third of the studies (9/26) observed significantly longer door-to-balloon (DTB) times during the pandemic. Approximately 73 % of studies (11/15) indicated a significantly longer total ischemic time during the pandemic era. The pooled results did not show a significant difference in in-hospital mortality during the COVID-19 pandemic among patients with ST-elevation myocardial infarction (STEMI) (RD = -0.01, 95% CI -0.02, 0.00) and non-ST-elevation myocardial infarction (NSTEMI) (RD = -0.01, 95% CI -0.01, 0.00). No significant difference in the proportion of patients who underwent Percutaneous Coronary Intervention (PCI) was found across the pandemic period. The COVID-19 pandemic seemed to prolong the time to receive treatment in most settings. Education campaigns and well-planned ACS pathways to ensure timely treatment for patients with ACS during the pandemic/crisis are warranted.

Keywords: COVID-19; STEMI; NSTEMI; Acute Coronary Syndrome; Impact

INTRODUCTION

Coronavirus (COVID-19) is an emerging infectious disease firstly identified in 2019. The disease then rapidly spread globally and was declared a pandemic by the World Health Organization (WHO) in March 2020 (World Health Organization, 2020). As of October 25, 2022, the pandemic had resulted in 628 million cases and 6.58 million deaths worldwide (European Centre for Disease Prevention and Control, 2021). Moreover, the pandemic has been reported as a devastating event ruining the global healthcare system and patients' willingness to visit health facilities. Several studies have reported a significant reduction in health service utilization during the COVID-19 pandemic (Moynihan *et al.*, 2021), possibly derived from the reluctance of patients to seek medical care due to the fear of

getting infected by COVID-19 and the adaptation of health systems to reduce less urgent and unnecessary services.

Cardiovascular disease is one of the leading causes of death and Disability-Adjusted Life Year (DALY) loss globally (Ritchie, 2017). Acute Coronary Syndrome (ACS) is an acute cardiovascular disease that necessitates immediate care (Valgimigli *et al*., 2018). Effective and timely reperfusion is critical for patients with ACS and is associated with a decrease in mortality rate, length of stay, reinfarction, and other major adverse cardiac events (Bagai *et al*., 2014; DeVon *et al*., 2010; Ibanez *et al*., 2017). According to the guidelines (Collet *et al*., 2020; Ibanez *et al*., 2017; Jneid *et al*., 2017), the time from symptom onset to the first medical contact (FMC) and the duration from the onset of symptoms to hospital arrival (Ibanez *et al*., 2017) should be less than 12 hours, while the door-to-balloon time (DTB), which is the difference between the date/time of hospital arrival and the date/time of first device activation (Ibanez *et al*., 2017), should be within 90 minutes (Ibanez *et al*., 2017; Jneid *et al*., 2017). However, the ideal recommended time from symptom onset to receiving reperfusion therapy (total ischemic time) should be within 120 minutes (Collet *et al*., 2020; Ibanez *et al*., 2017). During the COVID-19 pandemic, one of the challenges for ACS management is to find a balance between risks related to delayed treatment and COVID-19 transmission control. Prior studies have reported the elevated rates of cardiac arrest (Perrin *et al*., 2020), death (Calvão *et al*., 2021), and other significant cardiac events in patients with ACS (Erol *et al*., 2020) as a result of delays in receiving treatment during COVID-19 pandemic.

To date, four systematic reviews examining the impacts of COVID-19 on the number of ACS admissions have been identified (Helal *et al*., 2021; Kiss *et al*., 2021; Moynihan *et al*., 2021; Pourasghari *et al*., 2022). Of these, only two studies summarized the impacts of COVID-19 on treatment patterns and treatment delays among patients with ACS (Kiss *et al*., 2021; Rattka *et al*., 2020). Nevertheless, such impacts were not comprehensively described (Kiss *et al*., 2021), and only patients with ST-elevation myocardial infarction (*STEMI*) were included (Rattka *et al*., 2020). Two studies examined the impact of COVID-19 on the mortality of patients with STEMI (Pourasghari *et al*., 2022; Rattka *et al*., 2020). Importantly, it should be noted that the search period of all previous systematic reviews (Helal *et al*., 2021; Kiss *et al*., 2021; Moynihan *et al*., 2021; Pourasghari *et al*., 2022) ended in 2020, when COVID-19 had not yet reached its peak. Therefore, this systematic review and meta-analysis aimed to comprehensively review and update the impacts of the COVID-19 pandemic on the treatment management (i.e., time from symptom onset to FMC, DTB time, total ischemic time, and the proportion of patients who underwent PCI), and clinical outcome (i.e., in-hospital mortality) among patients with ACS.

MATERIALS AND METHODS

This systematic review and meta-analysis protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021277640. All authors contributed to the study's conception and design. Searching (PEND), study selection (PEND, BR, WH, MT), quality assessment and data extraction (PEND, BR, WH), and data analysis (PEND, MT) were performed. The first draft of the manuscript was written by PEND, and all authors commented on previous versions. Afterward, all authors read and approved the final manuscript.

Data sources and search strategies

To identify relevant studies, the PubMed and ScienceDirect databases were searched from January 2020 to September 2021. The researchers conducted a term search based on the population domain (acute coronary syndrome) and intervention domain (Sars-Cov2 or COVID-19 period). A combination of Medical Subject Heading (MeSH) terms and keywords was used for each domain (supplement table I). The search process was performed by one reviewer (PEND) and verified by other reviewers (BR, WH, MT, QT).

Study selection

By screening titles and abstracts, two reviewers (BR and WH) independently selected studies. Full texts were then reviewed by other reviewers (PEND, MT, QT) based on the following criteria: (1) were conducted among patients with ACS (i.e., STEMI, NSTEMI, and NSTEACS), (2) compared the situation before and during the COVID-19 pandemic, (3) reported any of the following outcomes: proportion of patients who underwent Percutaneous Coronary Intervention (PCI), time from symptom onset to FMC, total ischemic time, DTB time, and in-hospital mortality rate, and (4) published in English. On the

other hand, studies were excluded if they were a review study, expert opinion, case study, research letter, or discussion forum. Studies with insufficient information on this study's outcome of interests or whose full texts were unavailable were also excluded. Any discrepancy was resolved by discussion within the research team.

Data extraction

The data were extracted by two independent reviewers (PEND and BR) using a pre-designed data extraction form. The following data were extracted: study characteristics (i.e., setting, sample size, and study period), types of patients with ACS (i.e., STEMI, NSTEMI). The following outcomes were extracted for both before and during the COVID-19 pandemic period: time from symptom onset to FMC, DTB time, total ischemic time, number of patients who underwent PCI, and in-hospital mortality. Any disagreement was resolved by discussion and consensus with the research team.

Risk of bias assessment

The risk of bias was assessed independently by four reviewers (PEND, WH, QT, MT) using the Newcastle-Ottawa Scale (NOS). NOS comprised eight items grouped into three domains. A study with a score of <2 indicated a high risk of bias, 2–6 represented a moderate risk of bias, and 7-9 denoted a low risk of bias (McPheeters Ml Fau - Kripalani *et al*., 2012). In addition, the reporting quality of each study was assessed using the ***Strengthening the Reporting of Observational Studies in Epidemiology*** (STROBE) checklist (von Elm *et al*., 2014). The checklist contained 22 items. The STROBE score was calculated as the total number of items adequately reported divided by the number of applicable items and expressed as a percentage. The scores of < 50%, 50% to <70%, 70% to <85%, and ≥85% indicated the poor, fair, good, and excellent quality of reporting, respectively (Cuschieri, 2019; Limaye *et al*., 2018).

Data synthesis

For dichotomous variables (i.e., the proportion of patients who underwent PCI and in-hospital mortality), meta-analysis was performed by pooling risk differences (RDs) if there were at least three studies. The Q test and I^2 statistics were applied to assess heterogeneity. The random-effects model by DerSimonian and Laird was applied if heterogeneity was present (i.e., $I^2 > 25\%$ or Cochran Q test < 0.1); otherwise, fixed-effects by the inverse variance method were used. Publication bias was assessed using the funnel plot. All analyses were performed with Review Manager software version 5.4 and stratified by types of patients with ACS (i.e., STEMI and NSTEMI). For continuous variables, a meta-analysis could not be conducted as most studies reported outcomes regarding medians, and there is no well-established statistical method to pool the difference between medians. Therefore, descriptive synthesis was conducted for the following outcomes: time from symptom onset to FMC, DTB time, and total ischemic time. Significant difference in the descriptive synthesis was extracted from the included studies.

RESULTS AND DISCUSSION

A total of 3,644 articles were identified from PubMed and ScienceDirect. Two thousand five hundred and sixty-one duplicates were removed, leaving 1,083 articles for the title and abstract screening. Then, 860 unrelated articles were excluded, resulting in 223 articles for full-text screening. Finally, 63 articles (Abdelaziz *et al*., 2020; Aldujeli *et al*., 2020; Aldujeli *et al*., 2021; Arai *et al*., 2021; Araiza-Garaygordobil *et al*., 2021; Ayad *et al*., 2021; Azul Freitas *et al*., 2021; Baldi *et al*., 2021; Balghith, 2020; Boeddinghaus *et al*., 2021; Bonnet *et al*., 2021; Braiteh *et al*., 2020; Bruoha *et al*., 2021; Calvão *et al*., 2021; Cammalleri *et al*., 2020; Chen *et al*., 2021; Chew *et al*., 2021; Cinier *et al*., 2020; Claeys *et al*., 2020; Coughlan *et al*., 2020; D'Amario *et al*., 2020; Daoulah *et al*., 2021; De Luca *et al*., 2020; Dharma *et al*., 2021; Erol *et al*., 2020; Fabris *et al*., 2021; Fardman *et al*., 2021; Firman *et al*., 2021; Gluckman *et al*., 2020; Gramegna *et al*., 2020; Haddad *et al*., 2021; Hannan *et al*., 2021; Hauguel-Moreau *et al*., 2021; Kiris *et al*., 2021; Kobo *et al*., 2020; Leng *et al*., 2021; Little *et al*., 2020; Liu *et al*., 2021; Lu *et al*., 2021; Ma *et al*., 2021; Mafham *et al*., 2020; Mao *et al*., 2021; Medranda *et al*., 2021; Mengal *et al*., 2020; Natarajan *et al*., 2020; Papafaklis *et al*., 2020; Perrin *et al*., 2020; Petrović *et al*., 2021; Phua *et al*., 2021; Popovic *et al*., 2021; Rodríguez-Leor *et al*., 2020; Rodriguez-Ramos, 2021; Scholz *et al*., 2020; Soylu *et al*., 2021; Su *et al*., 2021; Sutherland *et al*., 2022; Tomasoni *et al*., 2020; Toušek *et al*., 2020; Ullah *et al*., 2021; Wienbergen *et al*., 2021; Xiang *et al*., 2020; Zachariah *et al*., 2021; Zhang *et al*., 2021) were eligible for inclusion in this systematic review (Figure1).

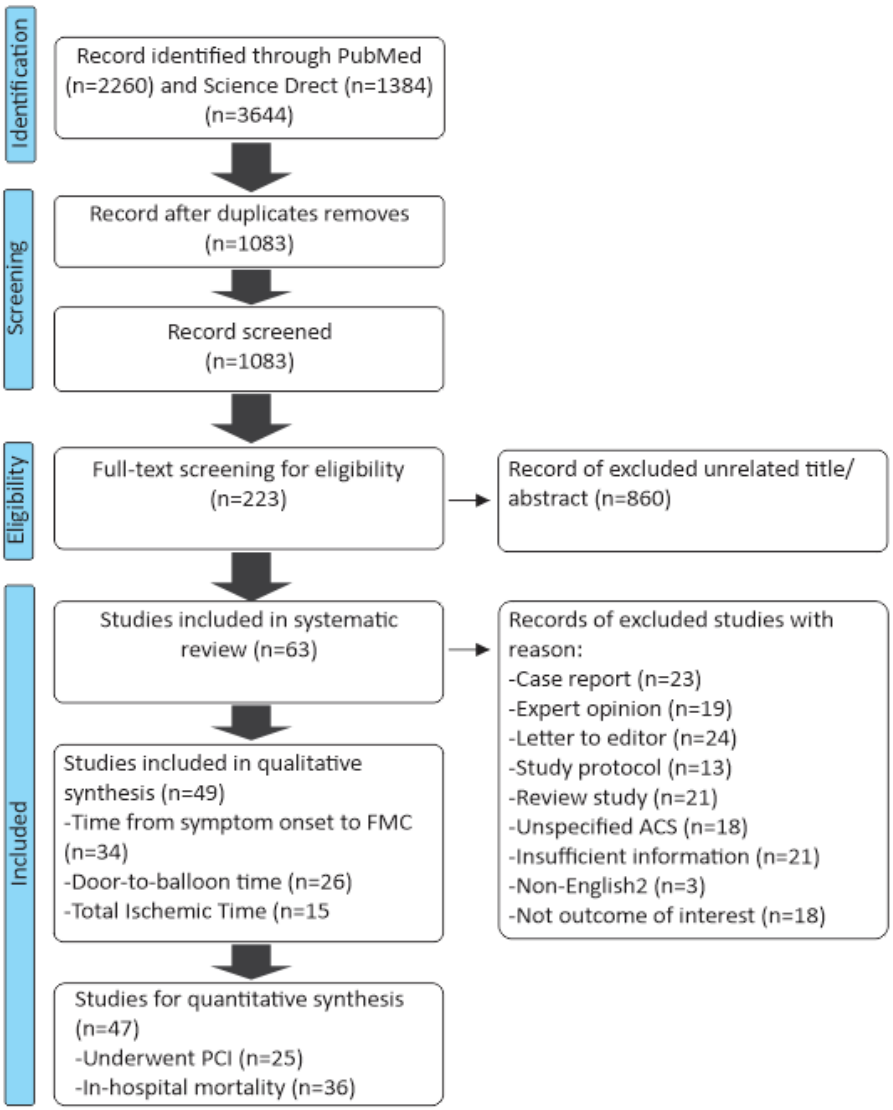

Figure 1. PRISMA flow chart of search procedure

Study characteristics

Of the 63 included studies, 45 (71.43 %) were conducted in high-income countries (Supplement table II). Two (3.17%) studies were multi-country studies (Araiza-Garaygordobil *et al*., 2021; De Luca *et al*., 2020) Twenty-two studies (34.92%) were conducted in Asia (i.e., India (Zachariah *et al*., 2021) , Israel(Bruoha *et al*., 2021; Fardman *et al*., 2021; Kobo *et al*., 2020) , China (Leng *et al*., 2021; Liu *et al*., 2021; Lu *et al*., 2021; Ma *et al*., 2021; Mao *et al*., 2021; Xiang *et al*., 2020; Zhang *et al*., 2021) , Pakistan (Mengal *et al*., 2020), Turkey (Cinier *et al*., 2020; Erol *et al*., 2020; Kiris *et al*., 2021; Soylu *et al*., 2021), Singapore (Chew *et al*., 2021; Phua *et al*., 2021) , Taiwan (Su *et al*., 2021) , Japan (Arai *et al*., 2021) , and Indonesia (Dharma *et al*., 2021; Firman *et al*., 2021)).

Risk of bias of included studies

The average score for the STROBE checklist was 58.80% ± 10.76%. Nine studies (14.29%), fourty-nine studies (77.78%), three studies (4.76%), and two studies (3.17%) were found to have a poor, fair, good, and excellent quality of reporting, respectively. According to NOS, twenty-nine studies (46.03%) were considered high-quality studies, while thirty-four studies (53.97%) were deemed moderate-quality studies (Supplement table II).

Table I. Time from symptom onset to FMC among STEMI patients before and during COVID-19 pandemic

No	Study	Median (Q1, Q3) or mean ±SD (minute)		Condition compared to before the pandemic
		Before pandemic	During pandemic	
1	Abdelaziz HK, 2020 (19)	119 (27, 203)	227 (65, 790)	Significantly Longer
2	Aldujeli A, 2020 (20)	349 (146, 659)	620 (255, 1500)	Significantly Longer
3	Aldujeli A, 2021 (21)	262 (120, 525)	582 (180, 1212)	Significantly Longer
4	Azul Freitas, 2021 (25)	240 (120, 570)	360 (120, 600)	Longer
5	Baldi E, 2021 (26)	122.3 (62.6, 527.1)	371.2 (125.6, 1895.4)	Significantly Longer
6	Boeddinghaus J, 2020 (28)	202 (120, 630)	210 (120, 540)	Longer
7	Bonnet G, 2021 (29)	125 (60, 360)	150 (60, 420)	Significantly Longer
8	Bruoha S, 2021 (31)	174.6±213.8	158.5±162.3	Shorter
9	Calvao J, 2021 (32)	145±178	180±360	Longer
10	Cammalleri V, 2020 (33)	80 (60, 207)	120 (52.5, 3600)	Longer
11	Chew NW, 2021 (35)	126 (73, 259)	121 (70, 229)	Shorter
12	Claeys MJ, 2020 (37)	114 (50, 240)	138 (67, 331)	Significantly Longer
13	D'Amario D, 2020 (39)	311 (188, 649)	216.5 (117.5, 880.2)	Longer
14	Dharma S, 2021 (42)	360 (270, 480)	360 (240, 540)	No difference
15	Erol M, 2020 (43)	32.5 (15, 120)	80 (30, 195)	Significantly Longer
16	Fabris E, 2020 (44)	96 (35, 171)	90 (47,195)	Shorter
17	Fardman A, 2021 (45)	130 (75, 243)	186 (97, 732)	Significantly Longer
18	Gramegna M, 2020 (48)	120 (60, 180)	900 (120, 2880)	Significantly Longer
19	Haddad K, 2020 (49)	103 (42.5, 263)	189 (70, 840)	Significantly Longer
20	Hauguel-Moreau M, 2020 (51)	121 (55, 291)	600 (298, 632)	Significantly Longer
21	Kiris T, 2021 (52)	100 (60, 180)	120 (75, 240)	Significantly Longer
22	Leng WX, 2020 (54)	266.4±178.2	273.6±163.8	Longer
23	Little CD, 2020 (55)	90 (22, 269)	82 (30, 360)	Shorter
24	Lu Q, 2021 (57)	154.8 (78.2, 348.6)	261 (80.4, 540)	Longer
25	Ma T, 2021 (58)	309 (84.25, 1267.5)	251 (80, 1080)	Shorter
26	Mao Q, 2021 (60)	180 (120, 270)	300 (180,600)	Significantly Longer
27	Perrin N, 2020 (65)	60 (20, 165)	112 (16, 211)	Significantly Longer
28	Rodriguez Leor O, 2020 (68)	71 (30, 180)	105 (45, 222)	Significantly Longer
29	Scholz KH, 2020 (70)	163.1±7.9	150.4±13.6	Shorter
30	Soylu K, 2021 (71)	61 (20, 6932)	190 (15, 3660)	Significantly Longer
31	Sutherland N, 2021 (73)	191 (80, 764)	292 (97, 1767)	Longer
32	Tomasoni D, 2020 (74)	130 (30, 185)	148 (79, 781)	Significantly Longer
33	Xiang D, 2020 (78)	154.2 (67.2, 460.2)	193.2 (80.4, 471.6)	Longer
34	Zhang F, 2020 (80)	91 (38, 201)	230 (156, 464)	Longer

Time from symptom onset to FMC
STEMI

The time from symptom onset to *FMC* during the pandemic was longer in 27 of 34 studies (79.4%). The longest time was reported by a study in Italy, which reached 900 min or 15 h during the COVID-19 pandemic (Gramegna *et al*., 2020). However, only 17 of 27 studies (62.96%) (Abdelaziz *et al*., 2020; Aldujeli *et al*., 2020; Aldujeli *et al*., 2021; Baldi *et al*., 2021; Bonnet *et al*., 2021; Claeys *et al*., 2020; Erol *et al*., 2020; Fardman *et al*., 2021; Gramegna *et al*., 2020; Haddad *et al*., 2021; Hauguel-Moreau *et al*., 2021; Kiris *et al*., 2021; Mao *et al*., 2021; Perrin *et al*., 2020; Rodríguez-Leor *et al*., 2020; Soylu *et al*., 2021; Tomasoni *et al*., 2020) revealed significantly longer time-from symptom onset to FMC during the pandemic, as compared to the condition before the pandemic (Table I).

Door-To-Balloon (DTB) time
STEMI

Of the 26 studies comparing DTB time before and during the COVID pandemic, 18 reported longer DTB time during the pandemic period. Nevertheless, only nine out of 18 studies (50.0%) uncovered significantly longer DTB during the pandemic (Bruoha *et al*., 2021; Cinier *et al*., 2020; Claeys *et al*., 2020; De Luca *et al*., 2020; Firman *et al*., 2021; Leng *et al*., 2021; Lu *et al*., 2021;

Table II. Door-to-balloon time among STEMI patients before and during COVID-19 pandemic

No	Study	Median (Q1, Q3) or mean ±SD (minute)		Condition compared to before the pandemic
		Before pandemic	During pandemic	
1	Abdelaziz HK, 2020 (19)	48 (39, 70)	47(38, 63)	Shorter
2	Arai R, 2021 (22)	127.6±145.2	103.1±62.5	Shorter
3	Boeddinghaus J, 2020 (28)	38 (15, 68)	37 (21, 60)	Shorter
4	Bruoha, 2021 (31)	57.41±27.52	69.31±54.14	Significantly Longer
5	Chen Y, 2021 (34)	51±54	50±100	Shorter
6	Chew NW, 2021 (35)	52 (39, 74)	55 (39, 74)	Longer
7	Cinier G, 2020 (36)	26.4 (11, 40)	54.6 (9, 55)	Significantly Longer
8	Claeys MJ, 2020 (37)	39 (22, 69)	45 (30, 83)	Significantly Longer
9	De Luca G, 2020 (41)	34 (21, 36)	36 (24, 60)	Significantly Longer
10	Erol M, 2020 (43)	37 (25, 65)	40 (25, 68)	Longer
11	Firman D, 2021 (46)	97.79±60.29	125.56±66.35	Significantly Longer
12	Kobo O, 2020 (53)	49 (31, 75)	56 (30,89)	Longer
13	Leng WX, 2020 (54)	115 (83, 160)	175 (121, 213)	Significantly Longer
14	Little CD, 2020 (55)	48 (35,70)	48 (34, 65)	No difference
15	Lu Q, 2021 (56)	70 (63.5, 81.5)	87 (76, 108)	Significantly Longer
16	Ma T, 2021 (58)	57.5 (41.5, 76.5)	79 (63.75, 105.25)	Significantly Longer
17	Medranda GA, 2021 (61)	74.4±46.1	95.9±66.9	Longer
18	Petrovic M, 2021 (66)	50.5±31.3	69.2±58.4	Significantly Longer
19	Phua K, 2021 (67)	67±83	66±65	Shorter
20	Scholz KH, 2020 (70)	51.3±1.1	53.2±2	Longer
21	Soylu K, 2021 (71)	69(11, 455)	83 (28, 488)	Longer
22	Sutherland N, 2021 (73)	59(48, 78)	62 (52, 150)	Longer
23	Su YH, 2021 (72)	59 (34, 74)	68 (48, 98)	Longer
24	Wienberg H, 2021 (77)	45±22	39±15	Significantly Shorter
25	Zachariah G, 2021 (79)	45 (30, 70)	45 (30, 75)	No difference
26	Popovic B, 2020 (81)	72±138	78±138	Longer

Ma *et al*., 2021; Petrović *et al*., 2021) (Table II). Notably, one study reported a significantly shorter DTB time (Wienbergen *et al*., 2021).

Total Ischemic Time

STEMI

Thirteen of 15 studies reported a longer total ischemic time during the pandemic (supplement table III). Nonetheless, a significantly longer total ischemic time during the pandemic was reported in 11 of 13 studies (Bonnet *et al*., 2021; De Luca *et al*., 2020; Erol *et al*., 2020; Fardman *et al*., 2021; Firman *et al*., 2021; Little *et al*., 2020; Mao *et al*., 2021; Mengal *et al*., 2020; Petrović *et al*., 2021; Popovic *et al*., 2021; Rodríguez-Leor *et al*., 2020). One study reported significant shorter total ischemic time during the pandemic (Rodriguez-Ramos, 2021).

In-hospital mortality

The meta-analysis of 35 and 7 indicated a non-significant increase in in-hospital mortality rate during the COVID-19 pandemic among patients with STEMI (Pooled RD -0.01, 95% CI: -0.02, 0.00), I^2 = 65%) and NSTEMI (Pooled RD = -0.01, 95% CI: -0.01, 0.00, I^2 = 31%), respectively (Figure 2). For STEMI, an asymmetric funnel plot indicated publication bias (supplement figure 1).

Underwent PCI

The pooled rate of patients with STEMI who underwent PCI from 24 studies (Aldujeli *et al*., 2020; Araiza-Garaygordobil *et al*., 2021; Ayad *et al*., 2021; Balghith, 2020; Braiteh *et al*., 2020; Calvão *et al*., 2021; Cammalleri *et al*., 2020; Chen *et al*., 2021; Claeys *et al*., 2020; Daoulah *et al*., 2021; Erol *et al*., 2020; Firman *et al*., 2021; Flori *et al*., 2021; Gluckman *et al*., 2020; Gramegna *et al*., 2020; Mafham *et al*., 2020; Natarajan *et al*., 2020; Papafaklis *et al*., 2020; Rodríguez-Leor *et al*., 2020; Scholz *et al*., 2020; Soylu *et al*., 2021; Ullah *et al*., 2021; Zachariah *et al*., 2021; Zhang *et al*., 2021) indicated a non-significant difference when comparing between the COVID-19 period and the pre-COVID-19 period (Pooled RDs -0.02; 95% CI: -0.06, 0.02, I^2 = 97%).

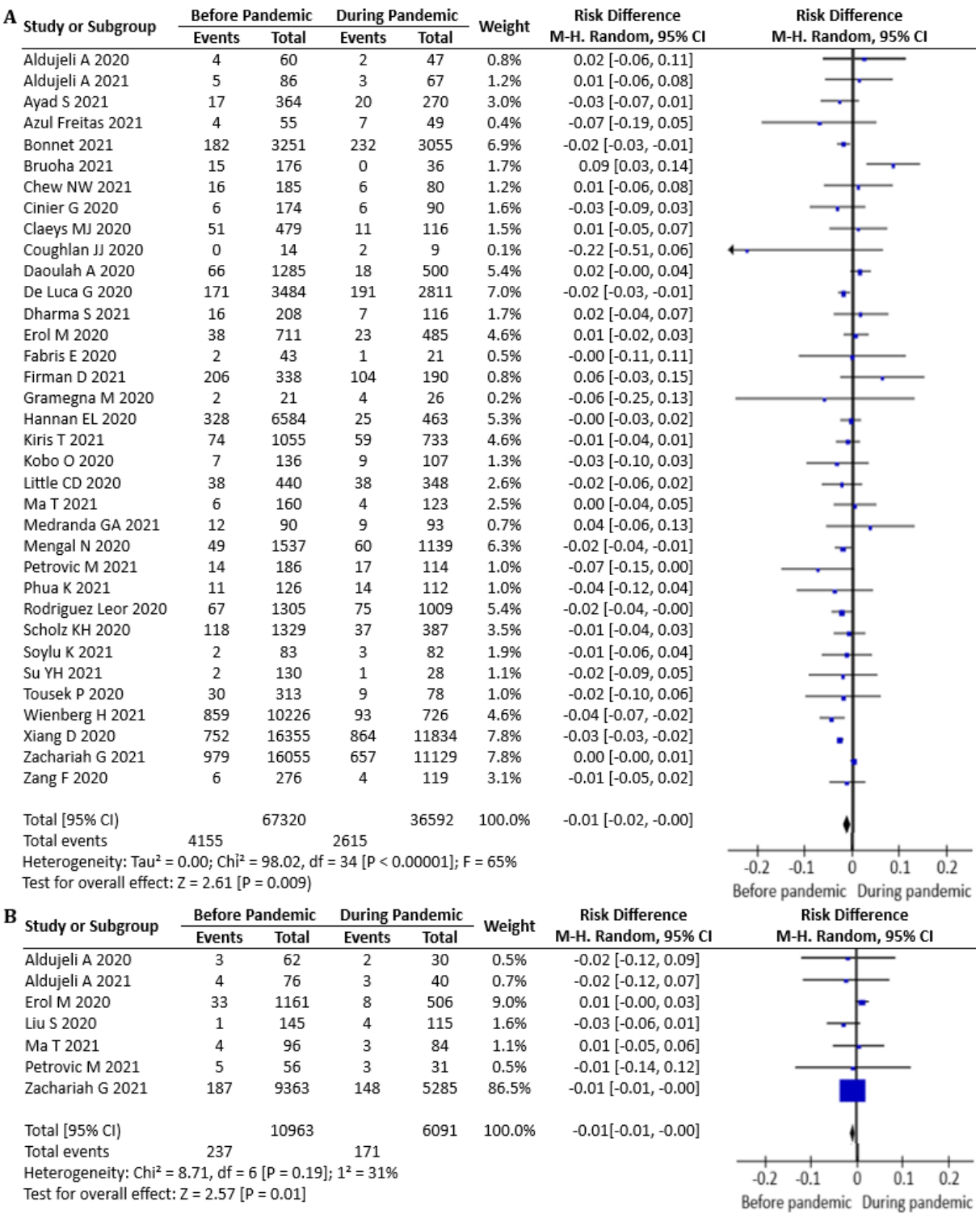

Figure 2. (A) Forest plot for in-hospital mortality among STEMI patients, (B) Forest plot for In-Hospital mortality among NSTEMI patients.

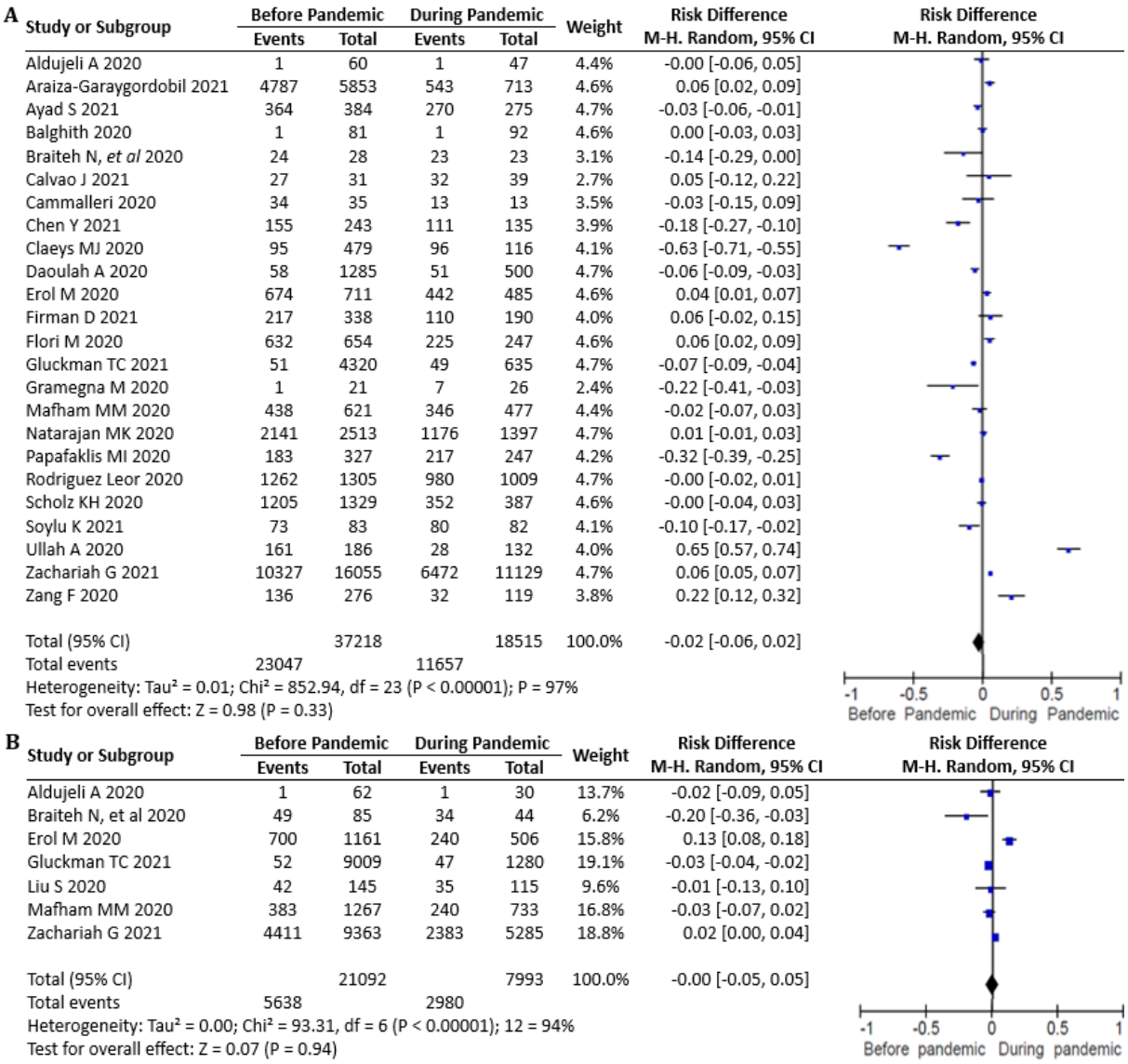

Figure 3. (A) Forest plot for proportion underwent PCI among STEMI patients, (B) Forest plot for proportion underwent PCI among NSTEMI patients.

Similarly, the pooled rate of patients with NSTEMI who underwent PCI from 7 studies (Aldujeli *et al*., 2020; Braiteh *et al*., 2020; Erol *et al*., 2020; Gluckman *et al*., 2020; Liu *et al*., 2021; Mafham *et al*., 2020; Zachariah *et al*., 2021) suggested a non-significant difference when comparing the COVID-19 period and the pre-COVID-19 period (Pooled RD: -0.00; 95% CI: -0.05, 0.05; I^2 = 94%), (Figure 3). Asymmetry in the funnel plot among patients with STEMI denoted publication bias (see supplement figure 2).

As expected, this review indicated that the pandemic increased the time from symptom onset to FMC, DTB time, and total ischemic time. Possible reasons for such a longer time include reluctance to visit health facilities due to fear of contracting COVID-19, avoidance of medical care due to lockdown measures, and difficulty getting transportation to PCI facilities during lockdown policy (Braiteh *et al*., 2020; Félix-Oliveira *et al*., 2020; Wu *et al*., 2021; Zitelny *et al*., 2020). As expected, while none of the included studies reported a significant decrease in time from

symptom onset to FMC, 50% of the studies revealed a significant increase in time from symptom onset to FMC during the COVID-19 pandemic. According to this study, none of the studies reported a time from onset to FMC longer than the recommendation of 12 h (Ibanez *et al*., 2017) during the pre-COVID-19 pandemic period. On the other hand, two studies reported a time from onset to FMC of longer than 12 hours during the COVID-19 pandemic (D'Amario *et al*., 2020; Gramegna *et al*., 2020). Nevertheless, this study's finding was in contrast with a previous study in which no significant difference in time from symptom onset to FMC was found (Rattka *et al*., 2020). It might be partly explained by the previous study conducted during the pandemic's beginning (Rattka *et al*., 2020).

While it was recommended that DTB time should not exceed 90 minutes (101), three studies (Arai *et al*., 2021; Firman *et al*., 2021; Leng *et al*., 2021) reported longer than 90 minutes in both pre-COVID and during the COVID-19 pandemic. On the other hand, four study reported a DTB time of longer than 90 minutes during the COVID-19 pandemic (Arai *et al*., 2021; Firman *et al*., 2021; Leng *et al*., 2021; Medranda *et al*., 2021). Furthermore, this review uncovered that 34.61% of the studies reported significantly longer DTB time during the COVID-19 pandemic, while 3.85% reported significantly shorter DTB time, implying that DTB time tended to be longer during the COVID-19 pandemic as compared with the pre-COVID pandemic. The longer DTB during the pandemic period was also identified in a previous review (Rattka *et al*., 2020) and could be due to the extra time spent to prevent the in-hospital spread of the COVID-19 virus, such as testing for COVID-19, wearing personal protective equipment (PPE), and terminal cleaning of the CATH lab (Han, 2020; Rattka *et al*., 2020).

Inaccessibility to PCI facilities due to national lockdown was also mentioned as the reason for the reduction in PCI procedure rate among patients with ACS, especially in the first year of the COVID-19 outbreak (Boeddinghaus *et al*., 2021; Braiteh *et al*., 2020; Showkathali *et al*., 2020). Although the previous review (Kiss *et al*., 2021) indicated that the COVID-19 pandemic might reduce the number of procedures, this study's pooled results found no significant difference in the proportion of patients who underwent PCI between pre-COVID and during the COVID-19 pandemic. Recommendations from the Society for Cardiovascular Angiography and Interventions (SCAI) Emerging Leader Mentorship and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), which emphasized the importance of PCI among patients with ACS even during the COVID-19 pandemic (Alaide *et al*., 2020; Szerlip *et al*., 2020), may have accounted for the non-significant reduction in the proportion of patients that underwent PCI during the pandemic period.

Similar to the previous study (Pourasghari *et al*., 2022; Rattka *et al*., 2020), the authors could not observe a significant impact of the COVID-19 pandemic on in-hospital mortality. It could be partly explained by the fact that the COVID-19 pandemic might lead to an increase in out-of-hospital arrest/mortality (Husain *et al*., 2023; Mountantonakis *et al*., 2020; Scquizzato *et al*., 2021) and that those who presented at the hospital have already survived the period with the highest mortality risk or survivor-cohort effect.

This study constitutes a thorough and current systematic review of the impacts of the COVID-19 pandemic on ACS. To ensure a comprehensive dataset, this review encompassed NSTEMI patients as well as STEMI patients. By conducting a longer search period in comparison to the previous review, this study gathered data from the inception of COVID-19 until the conclusion of the peak surge of cases. This additional time period may enhance the comprehensiveness and novelty of this study. However, there are some limitations to this review. Firstly, a meta-analysis of time from onset to FMC, DTB time, and total ischemic time could not be performed as most studies reported median instead of mean. Second, approximately one-half of the included studies were of moderate quality based on NOS assessment results, and three-quarters were of fair quality based on STROBE assessment results. Notably, unadjusted comparisons between pre-COVID-19 and during COVID-19 periods might lead to biased estimates of the impacts of COVID-19. Furthermore, this review did not investigate the long-term impact of COVID-19 among patients with ACS or out-of-hospital mortality. Third, this study opted to use two databases as source of study selection process. More databases might be needed to obtain more articles in review process. Nevertheless, the databases we have chosen are widely regarded as the most popular online databases for scientific and medical research. Both databases are extensively utilized for conducting literature research.

CONCLUSION

This review confirmed that the COVID-19 pandemic tended to increase the time from symptom onset to FMC, DTB time, and total ischemic time. Nevertheless, the impact on in-hospital mortality and the proportion of patients who underwent PCI were not observed. This phenomenon was an important lesson for health systems to better respond to future pandemics/emergencies. This pandemic also offers an opportunity for health systems worldwide to reset their priorities by reducing unnecessary care and non-urgent health services. As ACS is a time-sensitive health condition, health systems and policies should prepare to adapt to the pandemic by reducing utilization for non-urgent cases/unnecessary services while prioritizing patients with ACS who require urgent treatment to receive timely and appropriate medical attention. Innovative medical service delivery methods, such as telemedicine, should be further developed to handle non-severe cases and reduce in-person contact in health facilities during the pandemic. Standardized patients with ACS pathways and in-hospital processes during the pandemic period should also be clearly developed by related organizations. Finally, a public health campaign should be launched to encourage patients with symptoms or signs of ACS to seek immediate medical attention, even during the pandemic.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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