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## Effect of Fibrinolytic Therapy on ST-Elevation Myocardial Infarction Clinical Outcomes during the COVID-19 Pandemic: A Systematic Review and Meta-Analysis

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## Abstract

### BACKGROUND

ST-elevation myocardial infarction (STEMI) is the result of transmural ischemia of the myocardium and is associated with a high mortality rate. Primary percutaneous coronary intervention (PPCI) is the recommended first-line treatment strategy for patients with STEMI. The timely delivery of PPCI became extremely challenging for STEMI patients during the coronavirus disease 2019 (COVID-19) pandemic, leading to a projected steep rise in mortality. These delays were overcome by the shift from first-line therapy and the development of modern fibrinolytic-based reperfusion. It is unclear whether fibrinolytic-based reperfusion therapy is effective in improving STEMI endpoints.

### AIM

To determine the incidence of fibrinolytic therapy during the COVID-19 pandemic and its effects on STEMI clinical outcomes.

### METHODS

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were queried from January 2020 up to February 2022 to identify studies investigating the effect of fibrinolytic therapy on the prognostic outcome of STEMI patients during the pandemic. Primary outcomes were the incidence of fibrinolysis and the risk of all-cause mortality. Data were meta-analyzed using the random effects model to derive odds ratios (OR) and 95% confidence intervals. Quality assessment was carried out using the Newcastle-Ottawa scale.

### RESULTS

Fourteen studies including 50136 STEMI patients ( $n = 15142$  in the pandemic arm;  $n = 34994$  in the pre-pandemic arm) were included. The mean age was 61 years; 79% were male, 27% had type 2 diabetes, and 47% were smokers. Compared with the pre-pandemic period, there was a significantly increased overall incidence of fibrinolysis during the pandemic period [OR: 1.80 (1.18 to 2.75);  $I^2 = 78\%$ ;  $P = 0.00$ ; GRADE: Very low]. The incidence of fibrinolysis was not associated with the risk of all-cause mortality in any setting. The countries with a low-and middle-income status reported a higher incidence of fibrinolysis [OR: 5.16 (2.18 to 12.22);  $I^2 = 81\%$ ;  $P = 0.00$ ; GRADE: Very low] and an increased risk of all-cause mortality in STEMI patients [OR: 1.16 (1.03 to 1.30);  $I^2 = 0\%$ ;  $P = 0.01$ ; GRADE: Very low]. Meta-regression analysis showed a positive correlation of hyperlipidemia ( $P = 0.001$ ) and hypertension ( $P < 0.001$ ) with all-cause mortality.

### CONCLUSION

There is an increased incidence of fibrinolysis during the pandemic period, but it has no effect on the risk of all-cause mortality. The low- and middle-income status has a significant impact on the all-cause mortality rate and the incidence of fibrinolysis.

**Key Words:** ST-elevation myocardial infarction; Myocardial infarction; Thrombolytic therapy; Fibrinolysis; COVID-19; Pandemics

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**Core Tip:** The guideline-recommended time goals for primary percutaneous coronary intervention (PPCI) could not be met during the coronavirus disease 2019 (COVID-19) pandemic for the treatment of ST-elevation myocardial infarction (STEMI) patients. Leading cardiology societies recommended considering a new fibrinolytic-based reperfusion strategy during the time of the COVID-19 pandemic; however, previous large-scale studies have indicated that fibrinolytic therapy may offer a reduced prognostic value and poor survival outcomes in patients with STEMI compared to PPCI. We investigated the differential prevalence of the use of fibrinolytic therapy by healthcare systems belonging to countries with distinct income status, and its effect on the risk of all-cause mortality in STEMI patients.

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## INTRODUCTION

ST-elevation myocardial infarction (STEMI) is a severe form of coronary artery disease caused by transmural ischemia that affects the entire thickness of the myocardium. This condition is associated with high morbidity and mortality rates, making it a significant public health concern[1]. According to the Global Registry of Acute Coronary Syndrome Events (GRACE), STEMI accounts for approximately 30% of all acute coronary syndrome events[2].

The preferred treatment for STEMI is primary percutaneous coronary intervention (PPCI)[3]. However, the coronavirus disease 2019 (COVID-19) pandemic placed a significant strain on healthcare resources and providers, leading some experts to recommend changes in STEMI management. Fibrinolytic therapy was suggested as an alternative treatment for patients with severe resource limitations, a shortage of personal protective equipment, low-risk STEMI, systems of care delays, and the inability to provide PPCI in a timely fashion[4-8]. In a recent systematic review and meta-analysis conducted by Kamarullah and colleagues, it was found that the performance of STEMI care declined and clinical outcomes deteriorated in STEMI patients during the COVID-19 pandemic[9]. Despite this, the impact of fibrinolytic therapy on clinical outcomes during the pandemic remains largely unknown.

Therefore, the aim of this systematic review is to examine the significance of the increase in fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-COVID-19 era, and to assess the impact of this treatment strategy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to patients who received standard-care before or during the pandemic.

## MATERIALS AND METHODS

### *Protocol and registration*

To ensure transparent reporting, this systematic review and meta-analysis follow the PRISMA guidelines[10] and the MOOSE group's reporting guidelines[11] for observational studies in epidemiology. The research protocol has been registered with PROSPERO, the international prospective register of systematic reviews, under registration number CRD42022300242.

### *Literature search*

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched systematically for articles in the English language between the time when severe acute respiratory syndrome coronavirus 2 was declared a Public Health emergency of international concern-PHIEC (January 2020) up until February 2022. We used the following keywords: STEMI, fibrinolysis, and COVID-19. We utilized minimum keywords to maximize the initial scope of research in order to ensure the largest number of articles recorded. Complete search strategies used for all electronic databases were developed by an experienced librarian and are reported in the [Supplementary material](#). Reference mining included scanning reference lists of relevant papers, included studies, and systematic reviews published during the analysis of literature.

**Eligibility criteria and study selection**

Our study population consisted of patients with confirmed STEMI. We included studies that reported the impact of the COVID-19 pandemic on STEMI care. We searched for clinical trials, cohort studies, case-control studies, and case series. Animal studies, expert opinions, literature reviews, news articles, letters, editorials, case reports, guidelines, and any studies that did not mention the timing, population, intervention, and outcomes of interest were excluded.

We imported articles retrieved from the systematic search and exported them to EndNote reference library software (Thomson Reuters), where duplicates were identified and removed. Initially, articles were screened based on titles and abstracts by two independent reviewers (H.A.H. and E.P), then filtered relevant articles underwent full-text screening by another two reviewers working independently (H.A.M. and A.B.J). Another reviewer (A.K.) was consulted for decisions regarding any discrepancies during screening.

**Data extraction**

Data were extracted in a standardized data extraction form. We extracted data related to the following: (1) Summary of the included studies: Authors, year, timing, country, study design, sample size, inclusion criteria, duration of symptoms to intervention, study arms, and duration of follow up; (2) baseline characteristics of the included patients for regression purpose: Age, gender, race, body mass index, comorbidities, smoking status, and type of STEMI; and (3) the study outcomes as stated below. Any disagreements during data extraction were discussed to reach a consensus.

**Risk of bias and quality assessment**

The Newcastle–Ottawa Scale for observational studies was used by two independent reviewers (M.E. and M.K.K.) to evaluate quality on three diverse characteristics: Selection of study groups, comparability of groups, and ascertainment of the outcome of interest[12]. Each article was given a score that indicated how biased it was. Studies with a total score of seven or above were regarded to have a minimal probability of bias. If a study had a total score of six or less, it was determined to have a significant risk of bias. Disagreements in quality ratings were solved by a third reviewer (A.K.).

**Study outcomes**

We included studies that reported the incidence of the use of fibrinolytic therapy for STEMI patients during the pandemic compared to the timeline before the pandemic. The primary outcomes were the incidence of fibrinolysis and all-cause mortality.

**Data synthesis and analysis**

The analysis was performed in a sequence of calculations; the odds ratio (OR) of the incidence of fibrinolysis was calculated, followed by the subgrouping of studies based on significant increase in the incidence of fibrinolysis, no change in the incidence of fibrinolysis, and economic status of the countries where the studies were carried out, respecting the World Bank's classification of developed and developing countries into high-income and low- and middle-income countries (HICs and LMICs), respectively[13]. The effect sizes and the corresponding 95% confidence intervals (CIs) were calculated from raw data and variability measures or extracted directly from the studies. The outcomes were calculated using the DerSimonian and Laird random-effects model. The Higgin  $I^2$  test was used to evaluate the heterogeneity between studies, and higher percentages indicated higher heterogeneity. The summation effect measures were calculated as OR with 95% CIs. Statistical significance was set at  $< 0.05$  for all calculations.

Publication bias was assessed using the Begg funnel plot test[14]. Sensitivity analysis was performed by adding and removing studies one after another. Meta-regression analysis was executed for all-cause mortality. Two covariates having significant correlation among all the tested ones were displayed in the results. MetaXL version 5.3 (Epigear) add-on for Microsoft Excel 365 and Review Manager 5.4 was used to perform all analyzes. The statistical methods of the study were reviewed by a biomedical statistician.

**Evaluating certainty of evidence**

A summary of estimated effects and the certainty of each piece of evidence was produced using the GRADE approach (Supplementary Table 1). The GRADE criteria categorize the certainty of evidence as High, Moderate, Low, and Very low. The rating process followed the GRADE manual. GRADEpro GDT was used to construct the certainty of evidence and the summary of findings table.

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**RESULTS**

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**Search results**

The process of study selection and the characteristics of the included studies are summarized in Figure 1 and Tables 1 and 2, respectively. A total of 2938 studies were initially identified through database

Table 1 Characteristics of included studies

Ref.	Country	Study design/Sa	Study group/time period of study / sample size
Daoulah <i>et al</i> [15]	Saudi Arabia	Retrospective Cohort/500	Pandemic period STEMI/01/01/2020–30/04/2020/500 Pre-pandemic period STEMI/2018–2019/1285
Leng <i>et al</i> [16]	China	Retrospective Cohort	Pandemic period STEMI/23/01/2020–30/04/2020/164 Pre-pandemic period STEMI/Equivalent period in 2019/240
Song <i>et al</i> [17]	China	Retrospective Cohort	Pandemic period STEMI/24/01/2020–31/03/2020/73 Pre-pandemic period STEMI/24/01/2019–31/03/2019/95
Wang <i>et al</i> [18]	China	Retrospective Cohort	Pandemic period STEMI/23/01/2020–20/03/2020/37 Pre-pandemic period STEMI/01/09/2019–02/12/2019/41
Wu <i>et al</i> [19]	England	Retrospective Cohort	Pandemic period STEMI/01/01/2019/1600 Pre-pandemic period STEMI/22/05/2020/15646
Xiang <i>et al</i> [20]	China	Retrospective Cohort	Pandemic period STEMI/20/02/2020/10516 Pre-pandemic period STEMI/27/12/2019/14634
Zhang <i>et al</i> [21]	China	Retrospective Cohort	Pandemic period STEMI/01/01/2020–31/03/2020/119 Pre-pandemic period STEMI/2018 and 2019/276
Huang <i>et al</i> [22]	China	Retrospective Cohort	Pandemic period STEMI/01/02/2020–15/04/2020/31 Pre-pandemic period STEMI/01/01/2019–31/12/2019/31
Erol <i>et al</i> [23]	Turkey	Retrospective Cohort	Pandemic period STEMI/2020/485 Pre-pandemic period STEMI/2018/711
Mesnier <i>et al</i> [24]	France	Retrospective Cohort	Pandemic period STEMI/16/03/2020–12/02/2020/252 Pre-pandemic period STEMI/17/02/2020–15/03/2020/331
Balghith[25]	Saudi Arabia	Retrospective Cohort	Pandemic period STEMI/01/2020–05/2020/81 Pre-pandemic period STEMI/08/2019–12/2019/92
Clifford <i>et al</i> [26]	Canada	Retrospective Cohort	Pandemic period STEMI/17/03/2020–16/07/2020/193 Pre-pandemic period STEMI/15/11/2019–16/03/2020/238
Rodríguez-Leor <i>et al</i> [27]	Spain	Retrospective Cohort	Pandemic period STEMI/16/03/2020–14/04/2020/1009 Pre-pandemic period STEMI/01/04/2019–30/04/2019/1305
Calvão <i>et al</i> [28]	Portugal	Retrospective Cohort	Pandemic period STEMI/03/2020–04/2020/71 Pre-pandemic period STEMI/03/2020–04/2020/80

STEMI: ST-elevation myocardial infarction.

searches, and after removing duplicates, 14 studies were found to be eligible for inclusion in this meta-analysis[15-28]. These studies involved 50136 adult STEMI patients, with 15142 patients receiving fibrinolytic therapy during the pandemic era and 34994 patients receiving standard of care before or during the pre-pandemic era. Our meta-analysis assessed the impact of fibrinolytic therapy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to standard-care before or during the pandemic.

### Quality assessment

To assess the quality of the included studies, we used the Newcastle-Ottawa Scale for observational studies. Out of the 14 included studies, two were cohort studies, while the remaining 12 were case-control studies. Five studies had a low risk of bias (total score: 7-9), while the remaining studies were found to have a moderate risk of bias (total score: 4-6). None of the included studies had a high risk of bias (total score: 0-3). The detailed quality assessment of each study is provided in the (Supplementary Figure 1). The symmetrical funnel plot (Figure 2) indicated no small study or publication bias.



**Table 2** Baseline characteristics of the included subjects

Ref.	Study group	Age, years (SD)	Male, n (%)	Hypertension, n (%)	Diabetes mellitus, n (%)	Hyperlipidemia, n (%)	Smoking, n (%)
Daoulah <i>et al</i> [15]	Pandemic period STEMI	55.4 (11.8)	454 (90.8)	229 (46.7)	257 (52.1)	190 (38.9)	213 (43)
	Pre-pandemic period STEMI	56.5 (12.8)	1123 (87.5)	599 (47.6)	632 (50.4)	450 (35.8)	318 (41.6)
Leng <i>et al</i> [16]	Pandemic period STEMI	63.13 (13.6)	131 (79.9)	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	62.21 (13.14)	178 (73.9)	N/A	N/A	N/A	N/A
Song <i>et al</i> [17]	Pandemic period STEMI	61.6 (13.1)	59 (80.82)	43 (58.9)	16 (21.9)	39 (53.4)	36 (49.3)
	Pre-pandemic period STEMI	60.6 (13.9)	68 (71.57)	56 (59)	22 (23.2)	51 (53.7)	55 (57.9)
Wang <i>et al</i> [18]	Pandemic period STEMI	59.29 (11.46)	33 (89.18)	20 (54.05)	6 (16.21)	13 (35.13)	37 (100)
	Pre-pandemic period STEMI	55.49 (11.89)	35 (85.36)	18 (43.90)	5 (12.19)	15 (36.58)	31 (75.60)
Wu <i>et al</i> [19]	Pandemic period STEMI	65.1 (13.6)	1181 (73.81)	581 (36.31)	309 (19.31)	368 (23)	450 (28.12)
	Pre-pandemic period STEMI	65.76 (13.44)	11263 (71.98)	6060 (38.73)	3005 (19.20)	3645 (23.29)	4704 (30.06)
Xiang <i>et al</i> [20]	Pandemic period STEMI	61.59 (13.10)	7986 (75.94)	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	62.86 (12.33)	11019 (75.29)	N/A	N/A	N/A	N/A
Zhang <i>et al</i> [21]	Pandemic period STEMI	N/A	N/A	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	N/A	N/A	N/A	N/A	N/A	N/A
Huang <i>et al</i> [22]	Pandemic period STEMI	61	25 (80.6)	16 (51.6)	8 (25.8)	7 (22.6)	18 (58.1)
	Pre-pandemic period STEMI	60	25 (80.6)	18 (58.1)	6 (19.4)	8 (25.8)	20 (64.5)
Erol <i>et al</i> [23]	Pandemic period STEMI	59 (13)	552 (77.63)	221 (45.56)	151 (31.13)	108 (22.26)	248 (50.30)
	Pre-pandemic period STEMI	60 (14)	387 (79.79)	273 (38.39)	201 (28.27)	67 (9.4)	401 (56.39)
Mesnier <i>et al</i> [24]	Pandemic period STEMI	63.4 (12.5)	357 (74)	116 (24.11)	35 (7.27)	N/A	96 (19.95)
	Pre-pandemic period STEMI	64.4 (13.6)	509 (74)	139 (20.26)	55 (8.01)	N/A	131 (19.09)
Balgith[25]	Pandemic period STEMI	57.2 (12.6)	83 (90.21)	44 (54.32)	45 (48.91)	36 (39.13)	41 (44.56)
	Pre-pandemic period STEMI	51.3 (11.5)	81 (100)	38 (41.3)	41 (44.56)	31 (33.69)	35 (38.04)
Clifford <i>et al</i> [26]	Pandemic period STEMI	65 (12)	169 (71)	99 (51.29)	55 (28.49)	86 (44.55)	53 (27.46)
	Pre-pandemic period STEMI	64 (13)	135 (70)	123 (51.68)	54 (22.68)	99 (41.5)	93 (39.07)
Rodríguez-Leor <i>et al</i> [27]	Pandemic period STEMI	63.1 (12.5)	786 (78.4)	520 (51.9)	226 (22.6)	466 (46.7)	442 (44.6)
	Pre-pandemic period STEMI	63.7 (13.2)	1023 (78.4)	647 (50)	224 (25.2)	592 (45.8)	581 (45.7)



Calvão <i>et al</i> [28]	Pandemic period STEMI	63.3 (12.7)	56 (78.9)	49 (69.01)	23 (32.39)	38 (53.52)	40 (56.33)
	Pre-pandemic period STEMI	65.7 (12.8)	60 (75)	48 (60)	26 (32.5)	49 (57.5)	39 (48.75)

N/A: Not available; STEMI: ST-elevation myocardial infarction.

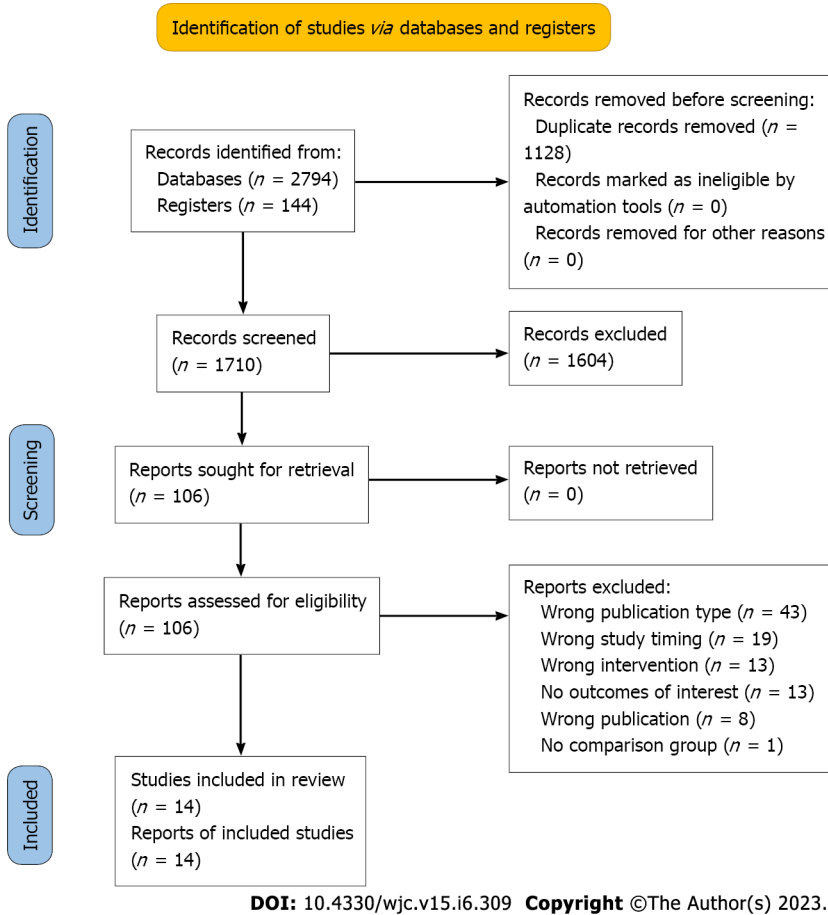


Figure 1 PRISMA chart displaying the process of search to study selection.

### Frequency of fibrinolytic therapy

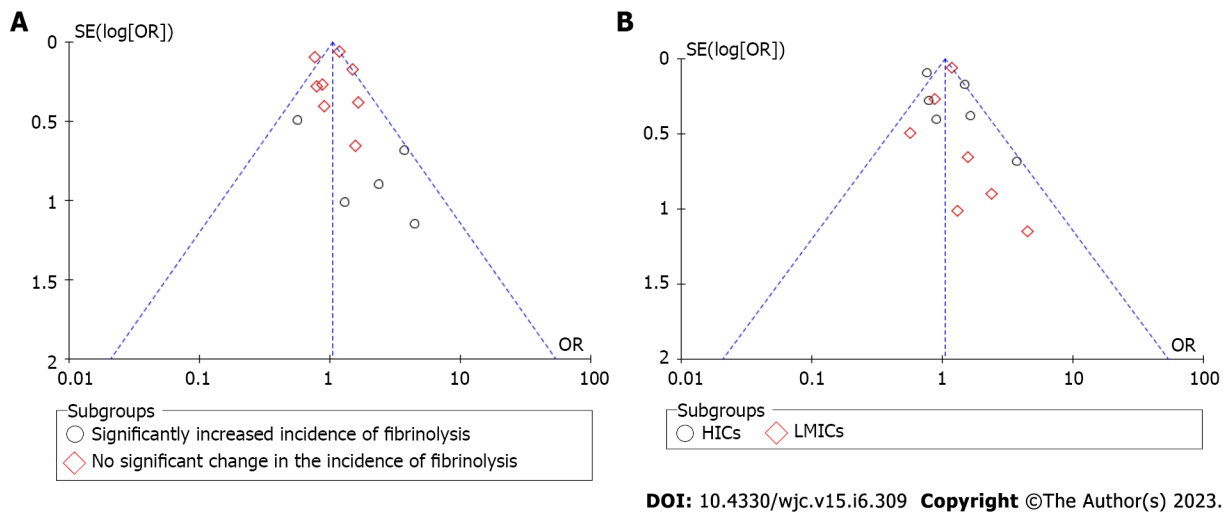
All 14 studies included in this meta-analysis investigated the frequency of fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-pandemic era. Our analysis revealed a significantly higher incidence of fibrinolytic therapy during the pandemic [OR: 1.80 (95% CI: 1.18-2.75);  $I^2 = 78\%$ ;  $P = 0.00$ ; GRADE: Very low] (Figure 3A). Moreover, we observed that patients treated in LMICs had a higher probability of receiving fibrinolytic therapy [OR: 5.16 (95% CI: 2.18-12.22);  $I^2 = 81\%$ ;  $P = 0.00$ ; GRADE: Very low] (Figure 3B).

### All-cause mortality

We evaluated all-cause mortality in 13 of the included studies. The increased incidence of fibrinolytic therapy was not found to be associated with an increased risk of all-cause mortality [OR: 1.65 (95% CI: 0.67-4.06);  $I^2 = 40\%$ ;  $P = 0.27$ ; GRADE: Very low] (Figure 4). However, patients who received fibrinolytic therapy in LMICs were at a higher risk of all-cause mortality [OR: 1.16 (95% CI: 1.03-1.30);  $I^2 = 0\%$ ;  $P = 0.01$ ; GRADE: Very low]. Overall, we found no significant association between the all-cause mortality rate and the incidence of fibrinolytic therapy [OR: 1.09 (95% CI: 0.87-1.37);  $I^2 = 58\%$ ;  $P = 0.47$ ; GRADE: Very low] (Figure 5).

### Meta-regression for exploring specific covariates

Meta-regression of heterogeneity was performed for the outcome of all-cause mortality, as it is one of our primary outcomes and more clinically relevant. Hyperlipidemia (reported in 9 studies[15,17-19,22,23,24-28]) and hypertension (reported in 10 studies[15,17-19,22-28]) were tested as covariates. The meta-



**Figure 2** No evidence of publication bias. A: When studies have been divided based on the incidence of fibrinolysis; B: When studies have been divided based on the income status of countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

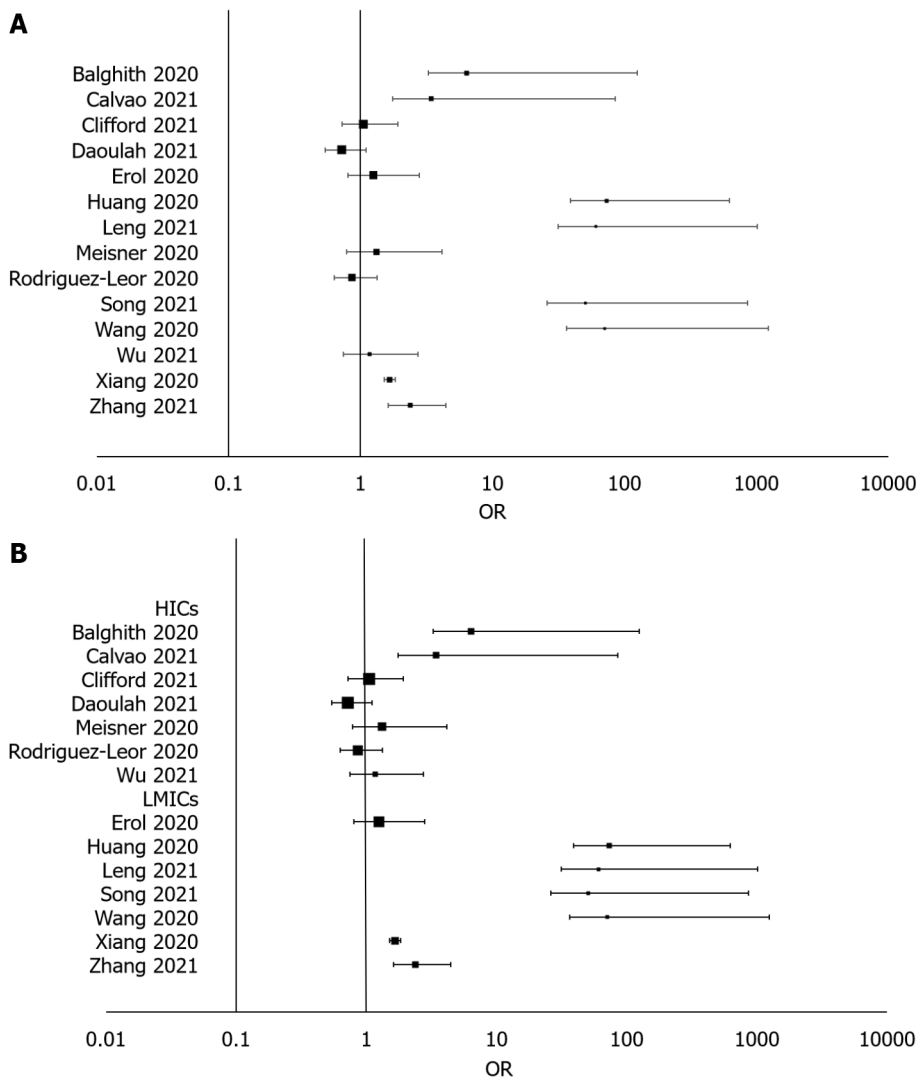
regression analysis provide evidence that hyperlipidemia is associated with an increased risk of all-cause mortality ( $P = 0.001$ ) (Figure 6A). The meta-regression analysis further revealed that hypertension is also a significant predictor of all-cause mortality ( $P < 0.001$ ) (Figure 6B). These findings suggest that managing hyperlipidemia and hypertension may be crucial for reducing the risk of all-cause mortality.

## DISCUSSION

After conducting a thorough meta-analysis, we observed a significant increase in the use of fibrinolytic reperfusion in STEMI cases during the COVID-19 pandemic. Interestingly, we found no significant association between fibrinolysis and all-cause mortality rates. However, our analysis revealed that countries with lower-middle-income and low-income status reported a higher incidence of fibrinolysis, which in turn was associated with an elevated risk of all-cause mortality for STEMI patients.

In our meta-regression analysis, we found out that patients having hyperlipidemia and hypertension tend have an increased risk of all-cause mortality. Hyperlipidemia decreases the stability of plaques that are most likely to rupture and decreases endothelial function[29]. It also promotes the formation of platelet thromboses at the site of the injury[30]. LIPID trial also showed a decrease in the risk of mortality for those patients who were treated for hypercholesteremia with the help of Statins therapy [31]. hypertension is also a crucial prognostic factor for STEMI. Hypertension reduces the elastic ability of blood vessels and causes atherosclerosis[32].

The COVID-19 pandemic has added to the already existing challenges of chronically strained healthcare systems worldwide. Among the many areas of healthcare that have been impacted, primary cardiac interventions for STEMI patients have also faced significant obstacles[33]. In high-income countries, meeting the recommended time goals for such interventions was difficult even before the pandemic, with only 25%-50% of patients receiving PPCI within the recommended time frame of 120 minutes from first medical contact (FMC) to balloon[34]. Unfortunately, the pandemic has further exacerbated delays in symptoms-to-FMC and door-to-balloon time, creating an additional challenge for healthcare systems to provide timely and effective care to STEMI patients. A study reported that the mean time from symptoms to intervention was longer during the COVID-19 pandemic compared to the previous year[35]. The need to screen for COVID-19, which includes procedures such as chest radiographs, epidemiological screening, polymerase chain reaction swab tests, and other laboratory tests, has potentially contributed to delays in providing PPCI for STEMI patients. The goal of these screening measures is to prevent the spread of COVID-19 within healthcare settings. However, delays in PPCI have been linked to a significant increase in mortality rates for STEMI patients[36]. Moreover, the incidence of STEMI has been reported to decrease during the COVID-19 pandemic. A study by Furnica *et al*[37] found that the incidence of STEMI decreased by 48.8% during the COVID-19 pandemic compared to the same time in the previous year[37]. Another study by Oettinger *et al*[38] reported a similar increase in STEMI incidence of 22.9% during the COVID-19 pandemic[38]. These findings suggest that there may be an association between the declining incidence of STEMI and the COVID-19 pandemic. The use of fibrinolysis and PCI in the management of STEMI has been reported to differ before and during the COVID-19 pandemic. A study found that the use of fibrinolysis increased by 20.2% during the COVID-19 pandemic, while the use of PCI decreased by 74.6% [16]. While the use of



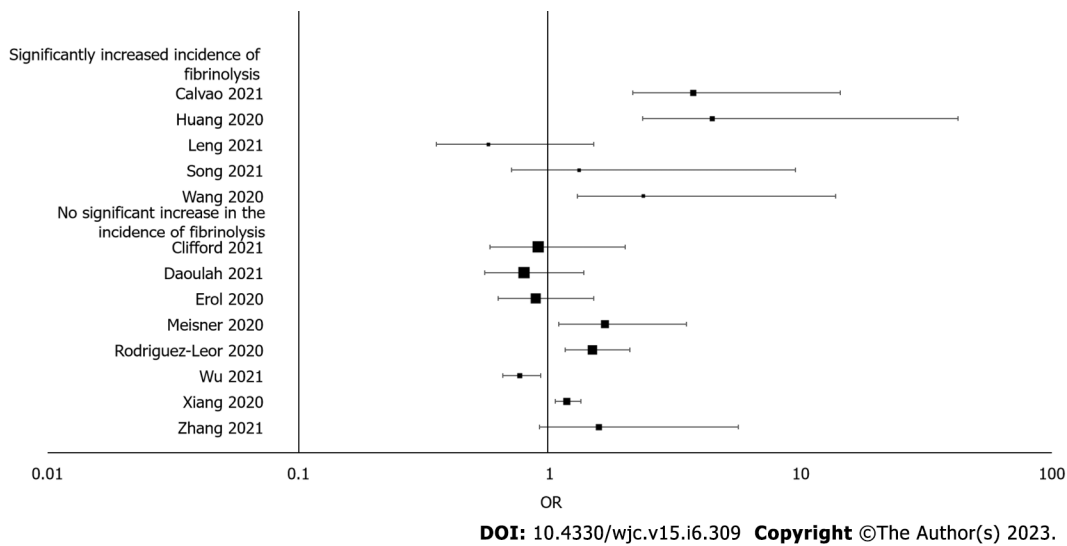
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**Figure 3 Increased incidence.** A: Fibrinolysis during the pandemic period; B: Fibrinolysis in low-and middle-income countries as compared to high-income countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

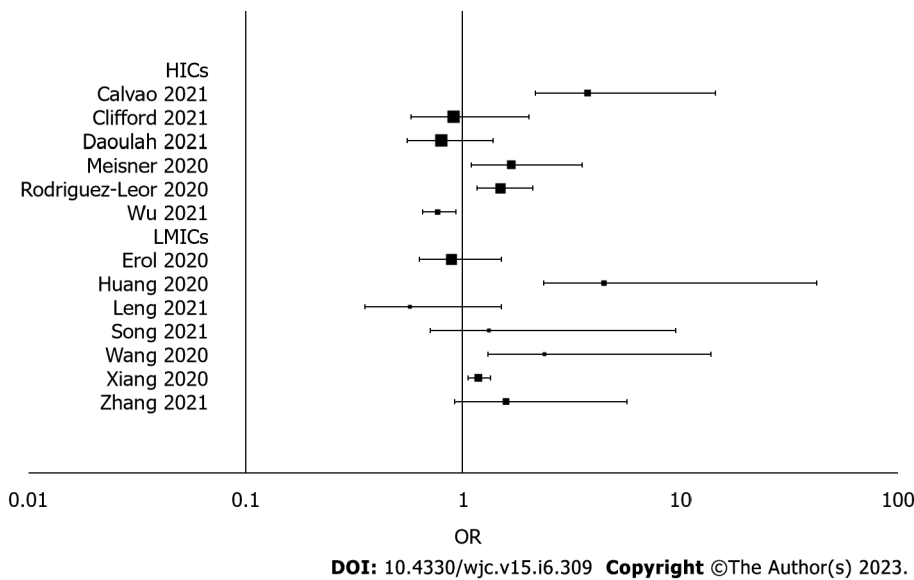
PPCI has become the standard of care for STEMI patients, fibrinolytic therapy may still be considered in situations where delays in PPCI are expected[39]. In light of major unexpected events like the COVID-19 pandemic, it is important to establish the effectiveness of fibrinolytic reperfusion therapy based on available evidence. Thus, the objective of this review is to critically evaluate the efficacy of fibrinolytic therapy in the context of such unprecedented and unpredictable events, like the COVID-19 pandemic.

The response to the COVID-19 pandemic has been rapidly evolving and may differ between countries based on their ability to adapt to the situation[40]. While previous studies have shown relatively consistent outcomes during the pandemic compared to the pre-pandemic period, our latest meta-analysis suggests a potential increase in the use of fibrinolytic therapy among countries with lower economic status, particularly in the eastern regions. Our subgroup analyses, which adjusted for income status, revealed that LMICs faced a higher incidence of fibrinolytic therapy and increased mortality rates for STEMI during the pandemic. Even before the pandemic, nearly three-quarters of myocardial infarction patients in such countries were treated with fibrinolytic therapy[41]. These findings raise concerns about the challenges faced by LMICs during the pandemic, as their lack of modern infrastructure may hinder their ability to provide timely reperfusion and cope with the pandemic's impact on STEMI care. Conversely, countries with high-income status and well-organized emergency systems have been able to continue using PPCI as the preferred treatment for patients requiring urgent intervention[42].

The fundamental principle of STEMI therapy is to achieve immediate, complete, and microvascular reperfusion to limit the extent of myocardial damage. Although PPCI remains the recommended reperfusion therapy by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, it must be performed by an experienced team within a specific time frame to achieve the best outcomes. Compared to fibrinolytic therapy, PPCI significantly improves



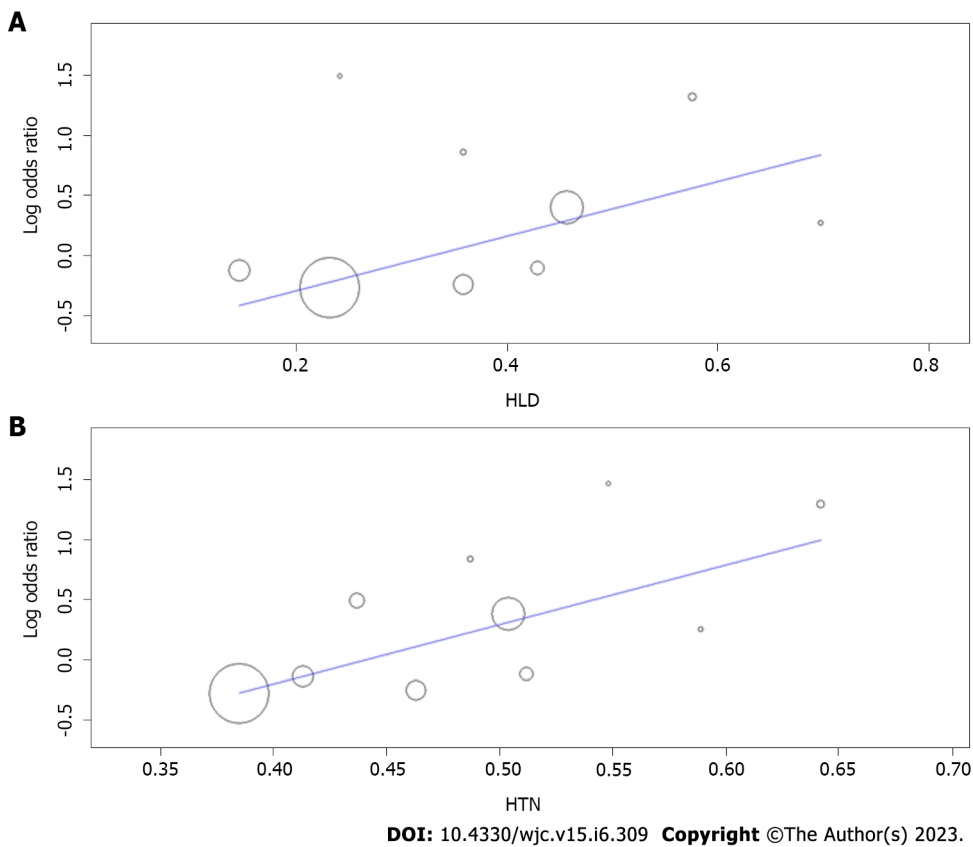
**Figure 4** No association between all-cause mortality rate and the incidence of fibrinolysis.



**Figure 5** Increased all cause-mortality rate in low-and middle-income countries compared to high-income countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

survival and reduces the risk of major adverse cardiovascular events, reinfarction, and intracranial hemorrhage[43]. However, if PPCI cannot be delivered promptly, there is a sharp increase in mortality rates. In response to the pandemic, an interim guideline from China suggested the use of fibrinolytic therapy for STEMI patients presenting to healthcare facilities within 12 h of symptom onset[44]. As the saying goes, 'Time is muscle', emphasizing the importance of prompt treatment to preserve viable myocardium.

Regarding the clinical relevance of our findings, our results suggest that there may have been a decrease in the use of PCI during the COVID-19 pandemic, which could have important implications for patient outcomes. PCI is generally considered the preferred treatment for STEMI, as it has been shown to reduce mortality and the risk of complications compared to fibrinolysis. Therefore, any reduction in the use of PCI should be carefully evaluated to ensure that patient care is not compromised. Overall, the results of our study highlight the impact of the COVID-19 pandemic on the incidence, treatment, and outcomes of STEMI. These findings have important implications for clinical practice, as they underscore the need for continued efforts to promote timely recognition and treatment of STEMI, even in the midst of a pandemic. Strategies such as public education campaigns, telemedicine, and streamlined healthcare delivery systems may help to mitigate the impact of the pandemic on the management of STEMI and improve patient outcomes.



**Figure 6 Meta-regression plot.** A: The significant direct relationship between hyperlipidemia and the risk for all-cause of mortality; B: Meta-regression plot displaying the direct relationship between hypertension and the risk for all-cause of mortality. HLD: Hyperlipidemia; HTN: Hypertension.

### Limitations

This meta-analysis has some limitations that warrant consideration. Firstly, it is possible that the use of diverse fibrinolytic agents might have had an impact on our findings, thus confounding the results. Secondly, some of the outcomes in our study displayed high heterogeneity and wide confidence intervals, indicating low certainty. This could be due to the fact that the results were based on small sample sizes with varied outcomes. Additionally, the restriction of the review to English-language studies might have resulted in the exclusion of data published in other languages, which could have affected the findings.

## CONCLUSION

Fibrinolysis-based reperfusion was found to be a major reperfusion strategy during the pandemic period, but the hypothesis of an association between overall all-cause mortality and the incidence of fibrinolysis was nullified. The present analysis of non-randomized studies was suggestive of a high casual association in populations living in LMICs. These results should remain an important focus of public health initiatives. The non-randomized selection process in individual studies could have contributed bias to the current meta-analysis.

## ARTICLE HIGHLIGHTS

### Research background

ST-elevation myocardial infarction (STEMI) is a severe form of coronary artery disease with high morbidity and mortality rates. The preferred treatment is primary percutaneous coronary intervention, but the coronavirus disease 2019 (COVID-19) pandemic led to changes in STEMI management, including the use of fibrinolytic therapy as an alternative treatment.

### **Research motivation**

The COVID-19 pandemic placed a significant strain on healthcare resources and providers, leading to changes in STEMI management. However, the impact of fibrinolytic therapy on clinical outcomes during the pandemic remains largely unknown.

### **Research objectives**

The aim of this systematic review is to examine the significance of the increase in fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-COVID-19 era and to assess the impact of this treatment strategy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to patients who received standard-care before or during the pandemic.

### **Research methods**

This study analyzed the incidence of fibrinolytic therapy and all-cause mortality for STEMI patients during the COVID-19 pandemic compared to the pre-pandemic period. Data synthesis and analysis were performed using the DerSimonian and Laird random-effects model, subgrouping studies based on changes in fibrinolysis incidence and economic status of countries. The study used sensitivity analysis, meta-regression analysis, and Begg's funnel plot test to assess publication bias and heterogeneity. Statistical significance was set at  $< 0.05$ .

### **Research results**

This meta-analysis of 14 studies revealed a significantly higher incidence of fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-pandemic era. Patients in low- and middle-income countries (LMICs) were more likely to receive fibrinolytic therapy, and those who received it in LMICs had a higher risk of all-cause mortality. However, overall, there was no significant association between the all-cause mortality rate and the incidence of fibrinolytic therapy. Meta-regression analysis showed that hyperlipidemia and hypertension were significant predictors of all-cause mortality, indicating that managing these conditions may be crucial in reducing mortality risk.

### **Research conclusions**

The incidence of fibrinolytic therapy for STEMI patients increased during the COVID-19 pandemic, particularly in LMICs. However, there was no significant association between fibrinolysis and all-cause mortality. The findings of this study have important implications for public health initiatives.

### **Research perspectives**

Fibrinolytic therapy was more frequently used during the COVID-19 pandemic, particularly in LMICs, but no significant association was found between the incidence of fibrinolysis and overall all-cause mortality.

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## **FOOTNOTES**

**Author contributions:** Khedr A substantial contributions to conception and design of the study, drafting the article, final approval; Hennawi HA acquisition of data, or analysis and interpretation of data, drafting the article, final approval; Khan MK analysis of data, revising and drafting the article, final approval; Elbanna M performed the data analysis, drafting the article, final approval; Jama AB and Proskuriakova E interpretation of data, drafting the article, final approval; Mushtaq H and Jain N contributed to the acquisition of data, revising the article, final approval; Mir M, Boike S, Rauf I, Eissa A, Koritala T, and Khan SA contributed to the interpretation of data, revising the article, final approval; Urtecho M contributed to the interpretation of data, making critical revisions, final approval; Surani S contributed to the acquisition of data, making critical revisions, final approval.

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