



OPEN ACCESS

Edited by:

Nicola Mumoli, ASST Ovest Milanese, Italy

Reviewed by:

Antonia Anna Lukito, University of Pelita Harapan, Indonesia Wenyang Jiang, Chinese Academy of Medical Sciences and Peking Union Medical College, China Efstratios Karagiannidis, Aristotle University of Thessaloniki, Greece Vinod Krishnappa, University of North Carolina Health Southeastern, United States

*Correspondence:

Tao-Hsin Tung ch2876@gmail.com Sizhong Xing xsz7220@163.com

[†]These authors have contributed equally to this work and share first authorship

Specialty section:

This article was submitted to Cardiovascular Epidemiology and Prevention, a section of the journal Frontiers in Cardiovascular Medicine

> Received: 09 December 2021 Accepted: 07 February 2022 Published: 14 March 2022

Citation:

Wang Y, Kang L, Chien C-W, Xu J, You P, Xing S and Tung T-H (2022) Comparison of the Characteristics, Management, and Outcomes of STEMI Patients Presenting With vs. Those of Patients Presenting Without COVID-19 Infection: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:831143. doi: 10.3389/fcvm.2022.831143

Comparison of the Characteristics, Management, and Outcomes of STEMI Patients Presenting With vs. Those of Patients Presenting Without COVID-19 Infection: A Systematic Review and Meta-Analysis

Yanjiao Wang^{1,2†}, Linlin Kang^{1,2†}, Ching-Wen Chien², Jiawen Xu², Peng You², Sizhong Xing^{1*} and Tao-Hsin Tung^{3*}

¹ Shenzhen Bao'an District Traditional Chinese Medicine Hospital, Shenzhen, China, ² Institute for Hospital Management, Tsing Hua University, Shenzhen, China, ³ Evidence-Based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai, China

Objectives: This study aimed to investigate the differences in the characteristics, management, and clinical outcomes of patients with and that of those without coronavirus disease 2019 (COVID-19) infection who had ST-segment elevation myocardial infarction (STEMI).

Methods: Databases including Web of Science, PubMed, Cochrane Library, and Embase were searched up to July 2021. Observational studies that reported on the characteristics, management, or clinical outcomes and those published as full-text articles were included. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of all included studies.

Results: A total of 27,742 patients from 13 studies were included in this meta-analysis. Significant delay in symptom onset to first medical contact (SO-to-FMC) time (mean difference = 23.42 min; 95% CI: 5.85–40.99 min; p = 0.009) and door-to-balloon (D2B) time (mean difference = 12.27 min; 95% CI: 5.77–18.78 min; p = 0.0002) was observed in COVID-19 patients. Compared to COVID-19 negative patients, those who are positive patients had significantly higher levels of C-reactive protein, D-dimer, and thrombus grade (p < 0.05) and showed more frequent use of thrombus aspiration and glycoprotein IbIIIa (Gp2b3a) inhibitor (p < 0.05). COVID-19 positive patients also had higher rates of in-hospital mortality (OR = 5.98, 95% CI: 4.78–7.48, p < 0.0001), cardiogenic shock (OR = 2.75, 95% CI: 2.02–3.76, p < 0.0001), and stent thrombosis (OR = 5.65, 95% CI: 2.41–13.23, p < 0.0001). They were also more likely to be admitted to the intensive care unit (ICU) (OR = 4.26, 95% CI: 2.51–7.22, p < 0.0001) and had a longer length of stay (mean difference = 4.63 days; 95% CI: 2.56–6.69 days; p < 0.0001).

Conclusions: This study revealed that COVID-19 infection had an impact on the time of initial medical intervention for patients with STEMI after symptom onset and showed that COVID-19 patients with STEMI were more likely to have thrombosis and had poorer outcomes.

Keywords: COVID-19, SARS-CoV-2, mortality, ST-segment elevation myocardial infarction, STEMI

INTRODUCTION

An eventual pandemic brought by the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in plenty of deaths and has had a strong impact on the world's healthcare system (1-3). Although the disease is predominantly characterized by respiratory symptoms, including pneumonia, dyspnea, and cough (4), various extrapulmonary features, such as myocardial damage, arrhythmia, thrombotic events, and renal injury have also been observed (5, 6).

A type of heart attack called ST-segment elevation myocardial infarction (STEMI) is usually caused by thrombotic occlusion at the site of a ruptured plaque in the coronary artery (7). Although the survival rates of STEMI patients have improved, it is still associated with high morbidity and mortality worldwide with a 1-year mortality rate of up to 10% (8-10). The COVID-19 pandemic may lead to a decrease in the number of STEMI admissions and could have a significant impact on the reperfusion strategy for patients with STEMI (11, 12). The tendency of patients with COVID-19 to be predisposed to cardiac arrest and coronary thrombosis due to increased inflammation, platelet activation, endothelial dysfunction, and SARS-CoV-2 invasion of cardiomyocytes has been reported (13-15). Moreover, data regarding the characteristics, management strategies, and clinical outcomes including in-hospital mortality and cardiogenic shock in patients presenting with STEMI concurrent with COVID-19 infection are limited (16). Accordingly, we aimed to conduct a systematic review and meta-analysis to compare the characteristics, management, and clinical outcomes between the COVID-19 and non-COVID-19 patients concomitant STEMI.

METHODS

Literature Search

We performed a literature search using databases including Web of Science (Beijing), PubMed (Bethesda), Cochrane Library (UK), and Embase (Amsterdam) for relevant papers without language limitation on July 31, 2021. The search strategy included a mix of MeSH and free-text terms relevant to the critical concept of "STEMI" and "COVID-19" (**Table 1**). The protocol for this meta-analysis was registered at PROSPERO under the number CRD42021283880.

Study Selection

Studies were included if they met the following inclusion criteria: (i) studies involving STEMI patients; (ii) the exposure group included patients diagnosed with COVID-19 using PCR test or had a high index of clinical suspicion, and the control group included patients without COVID-19; (iii) studies that reported at least one of the following information: characteristics, management strategy, or clinical outcomes; (iv) relevant cohort studies, cross-sectional studies, case series, and case-control studies. Two independent authors screened the titles and abstracts of all relevant studies and identified whether they met the inclusion criteria by reviewing the full text of each potential study. Any discrepancy was resolved through consensus with a third author.

Data Extraction and Quality Assessment

Relevant data from all included studies were extracted by two authors independently, and any disagreement was resolved by discussion with a third author. The following data were extracted: authors, publication year, country, study design, study subject, sample size, mean age of patients/subjects, sex, comparison period, participant characteristics, management strategies, and clinical outcomes. The Newcastle–Ottawa Scale (NOS), which includes participant selection, comparability, and outcome, was used to assess the quality of the included studies. Likewise, all included studies were rated by two authors independently, and any discrepancy was adjudicated by consensus.

Statistical Analysis

We used Review Manager 5.4 (The Nordic Cochrane Center, Cochrane Collaboration, 2020, Denmark) to perform the statistical analysis. If studies only reported median values and interquartile ranges (IQR), means and *SD*s were calculated according to the Box-Cox method (17). Categorical variables were presented as odds ratios (ORs), including 95% CIs, and continuous variables were presented as the mean difference (MD) or standardized mean difference (SMD), including 95% CI. Heterogeneity was assessed using the I² statistic and the *p*-value of the chi-square test. The I² statistic > 50% indicates significant heterogeneity. The choice between the fixed and random effects models depended on the comparability among the studies. A two-tailed *p*-value of < 0.05 was interpreted to be statistically significant. The risk of publication bias was evaluated using the funnel plots.

RESULTS

Characteristics of Included Studies

A total of 2,702 articles were retrieved through electronic database searches, of which 1,371 were duplicates. After screening the titles and abstracts, 24 potential articles were assessed for eligibility after a full-text review, and 13 articles (18–30) with a total of 27,742 patients were finally included

TABLE 1 | Search strategy.

Database	Searching	key words
PubMed	(1) "ST Segment Elevation Myocardial Infarction": 9451	(10) SARS-CoV-2: 106826
	(2) "ST Elevated Myocardial Infarction": 317	(11) "Coronavirus disease 19": 1603
	(3) STEMI: 28060	(12) "Severe Acute Respiratory Syndrome Coronavirus 2": 16865
	(4) "Acute myocardial infarction": 61630	(13) "novel coronavirus": 9766
	(5) AMI: 25165	(14) "2019 novel coronavirus": 1550
	(6) "Acute coronary syndromes": 13188	(15) #1 or #2 or #3 or #4 or #5 or #6 or #7: 208085
	(7) ACS: 116546	(16) #8 or #9 or #10 or #11 or #12 or #13 or #14: 169136
	(8) "SARSCoV-2 pandemic": 120(9) COVID-19: 168784	(17) #15 and #16: 1340
Web of science	(1) "ST Segment Elevation Myocardial Infarction": 17531	(10) SARS-CoV-2: 127748
	(2) "ST Elevated Myocardial Infarction": 1899	(11) "Coronavirus disease 19": 3460
	(3) STEMI: 23388	(12) "Severe Acute Respiratory Syndrome Coronavirus 2": 58794
	(4) "Acute myocardial infarction": 145384	(13) "novel coronavirus": 14678
	(5) AMI: 44201	(14) "2019 novel coronavirus": 2224
	(6) "Acute coronary syndromes": 27560	(15) #1 or #2 or #3 or #4 or #5 or #6 or #7: 248982
	(7) ACS: 58425	(16) #8 or #9 or #10 or #11 or #12 or #13 or #14: 262441
	(8) "SARSCoV-2 pandemic": 25 (9) COVID-19: 248069	(17) #15 and #16: 1098
Cochrane library	(1) "ST Segment Elevation Myocardial Infarction": 4031	(10) SARS-CoV-2: 322
2	(2) "ST Elevated Myocardial Infarction": 156	(11) "Coronavirus disease 19": 43
	(3) STEMI: 3616	(12) "Severe Acute Respiratory Syndrome Coronavirus 2": 631
	(4) "Acute myocardial infarction": 9325	(13) "novel coronavirus": 497
	(5) AMI: 3603	(14) "2019 novel coronavirus": 55
	(6) "Acute coronary syndromes": 2562	(15) #1 or #2 or #3 or #4 or #5 or #6 or #7: 19050
	(7) ACS: 4853	(16) #8 or #9 or #10 or #11 or #12 or #13 or #14: 6784
	(8) "SARSCoV-2 pandemic": 52	(17) #15 and #16: 31
	(9) COVID-19: 6666	
Embase	('acute myocardial infarction':ti,ab coronary syndromes':ti,ab,kw OF elevation myocardial infarction':ti, infarction':ti,ab,kw OR stemi:ti,ab pandemicor COVID-19':ti,ab,kw 'coronavirus disease 19':ti,ab,kw OR 'severe acute respiratory sync AND [1-1-1900]/sd NOT [1-8-20'	o,kw OR ami:ti,ab,kw OR 'acute acs:ti,ab,kw OR 'st segment ab,kw OR 'st elevated myocardial ,kw) AND ('sarscov-2 DR 'sars cov 2':ti,ab,kw OR OR 'novel coronavirus':ti,ab, kw prome coronavirus 2':ti,ab,kw) 211/sct: result = 233

(Figure 1). A summary of the main characteristics of these 13 studies and the baseline characteristics of all study subjects is presented in **Tables 2A,B**. One study originated from Poland (19), two each from the United Kingdom (24, 28), France (18, 21), Turkey (20, 30), Italy (25, 26), and Spain (27, 29), and the remaining two studies (22, 23) were international studies. The NOS score for all included studies varied from 5 to 8 points.

Delays

The symptom onset to first medical contact (SO-to-FMC) time among STEMI, which was reported in four studies (19, 20, 27, 30), was significantly different between the COVID-19 group and the non-COVID-19 group (MD = 23.42 min, 95% CI: 5.85 to 40.99 min, p = 0.009; **Figure 2A**). Furthermore, seven studies (18, 22–25, 28, 30) reported the time from door to balloon (D2B) and found that D2B was significantly longer in the COVID-19 group (MD = 12.27 min, 95% CI: 5.77 to 18.78 min, p= 0.0002; **Figure 2B**) than in the non-COVID-19 group. 3.3 *Laboratory values*.

The meta-analysis showed that compared to the non-COVID-19 group, the COVID-19 group had significantly higher levels of C-reactive protein (CRP), white blood cell count (WBC), and D-dimer (SMD = 0.76, 95% CI: 0.38 to 1.13, p < 0.0001; SMD = 0.39, 95% CI: 0.1 to 0.69, p = 0.009; SMD = 0.79, 95% CI: 0.36 to 1.22, p = 0.0003, respectively, **Figures 3A–C**), and had significantly lower level of lymphocyte count (SMD = -0.52, 95% CI: -0.69, -0.36, p < 0.0001, **Figure 3D**).

Management and Procedural Characteristic

There was no significant difference in the rate of primary angioplasty between the two groups (OR = 0.28, 95% CI: 0.08 to 1.01, p = 0.05; Figure 4A). Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) was more frequently observed, and the rate of stent implantation was lower in patients with COVID-19 infection (OR = 9.57, 95% CI: 2.14 to 42.83, p = 0.003; OR = 0.28, 95% CI: 0.11 to 0.71, p = 0.008, respectively, Figures 4B,C). Baseline thrombus grade > 3 and modified thrombus grade > 3 were significantly higher in the COVID-19 group than in the non-COVID-19 group (OR = 3.09, 95% CI: 1.83 to 5.23, *p* < 0.0001; OR = 5.84, 95% CI: 1.36 to 25.06, p = 0.02, respectively; Figures 4D,E). Intracoronary thrombus was angiographically identified and scored in 0-5 grades as previously described (31). In patients initially presenting with grade 5, thrombus grade will be reclassified into one of the other categories after flow achievement (32). After reclassification and based on clinical outcomes, the thrombus burden can be divided into 2 categories: low thrombus grade for thrombus <grade 4, and high thrombus grade for thrombus grade 4 (32). Consistent with this, the COVID-19 group showed a higher use of thrombus aspiration and glycoprotein IIbIIIa (Gp2b3a) inhibitor (OR = 1.68, 95% CI: 1.25 to 2.26, p = 0.0007; OR = 2.86, 95% CI: 1.78 to 4.62, *p* < 0.0001, respectively; **Figures 4F,G**). Moreover, thrombolysis in myocardial infarction (TIMI)-3 flow post-procedure was less common in the COVID-19 group than in the non-COVID-19 group (OR = 0.6, 95% CI: 0.42 to 0.84, p = 0.003, Figure 4H).



In-Hospital Outcomes

In-hospital mortality among patients with COVID-19 was significantly higher than that in patients without COVID-19 (OR = 5.98, 95% CI: 4.78 to 7.48, p < 0.0001, **Figure 5A**). The rates of cardiogenic shock as well as stent thrombosis were also higher in the COVID-19 group than in the non-COVID-19 group (OR = 2.75, 95% CI: 2.02 to 3.76, p < 0.0001; OR = 5.65, 95% CI: 2.41 to 13.23, p < 0.0001, respectively; **Figures 5B**,C). Although bleeding was more common in STEMI patients with COVID-19, there was no significant difference between the two groups (OR = 2.82, 95% CI: 0.88 to 9.05, p = 0.08, **Figure 5D**). In addition, patients with COVID-19 were more likely to be admitted to the intensive care unit (ICU) and had a longer length of hospital stay (OR = 4.26, 95% CI: 2.51 to 7.22, p < 0.0001; MD =

4.63 days, 95% CI: 2.56 to 6.69 days, p < 0.0001, respectively, **Figures 5E,F**).

Grade Summary of Findings

The GRADE summary of findings tool was used to evaluate the quality of evidence, and the assessment for each outcome is presented in **Table 3**. In addition to in-hospital mortality, which moderates the quality of evidence, other outcomes had low or very low quality of evidence because all included studies were observational.

Sensitivity Analysis and Publication Bias

The leave-one-out approach was applied for sensitivity analysis to evaluate the impact of a single study on

TABLE 2A | Characteristics of included studies.

References	Country	Study design	Study group	Participants characteristics	Comparison period	COVID-19 diagnosis approach/time to diagnosis	Major findings
Popovic et al. France (18)	Monocentric cohort study	COVID-19 STEMI	$n = 11$, age 63.6 \pm 17.4 years, 63.9% males	26/2/2020– 10/5/2020	RT-PCR or typical clinical features plus CT results/NA	D2B time, Laboratory values, Primary angioplasty, MINOCA, Stent implantation, Gp2b3a inhibitor use, TIMI status, In-hospital mortality	
			Non-COVID-19 STEMI	n = 72, age 62.5 ± 12.6 years, 73.6% males	26/2/2020– 10/5/2020		
Siudak et al. (19)	Poland	Multicentric cohort study	COVID-19 STEMI	$n = 145$, age 63.19 \pm 12.55 years, 71.33% males	13/3/2020– 13/5/2020	Swabs for molecular RT-PCR testing/NA	SO-to-FMC time
			Non-COVID-19 STEMI	$n = 2276$, age 65.43 \pm 12.23 years, 67.65% males	13/3/2020– 13/5/2020		
Kiris et al. (20)	Turkey	Multicentric cross-sectional study	COVID-19 STEMI	$n = 65$, age 66.8 \pm 12.0 years, 68% males	11/3/2020– 15/5/2020	Nasal/pharyngeal swabs or semptoms plus radiological imaging/NA	SO-to-FMC time, Laboratory values, Primary angioplasty, Thrombus aspiration, Gp2b3a inhibitor use, Baseline thrombus grade, Modified thrombus grade, TIMI status, In-hospital mortality, Bleeding, Stent thrombosis, Cardiogenic shock
			Non-COVID-19 STEMI	$n = 668$, age 60.0 \pm 12.3 years, 78% males	11/3/2020– 15/5/2020		
Koutsoukis et al. (21)	France	Multicentric cross-sectional study	COVID-19 STEMI	$n = 17$, age 63.4 \pm 13.2 years, 70% males	1/4/2020– 22/4/2020	RT-PCR on nasopharyngeal samples/NA	Laboratory values, Primary angioplasty, Thrombus aspiration, MINOCA, Stent implantation, Gp2b3a inhibitor use, In-hospital mortality
			Non-COVID-19 STEMI	$n = 99$, age 63.8 \pm 13.9 years, 67% males	1/4/2020– 22/4/2020		
Garcia et al. (22)	USA & Canada	Multicentric cohort study	COVID-19 STEMI	n = 230, 71% males	1/1/2020– 6/12/2020	Comfirmed COVID+ by any commercially available test/NA	D2B time, Primary angioplasty, MINOCA, In-hospital mortality, LOS
			Non-COVID-19 STEMI	n = 460, 68% males	1/2015-12/2019		
Kite et al. (23)	Data from 55 international centers	Multicentric corhort study	COVID-19 STEMI	$n = 144$, age 63.1 \pm 12.6 years, 77.8% males	1/3/2020– 31/7/2020	RT-PCR or clinical status plus CXR or CT findings/NA	D2B time, Laboratory values, Thrombus aspiration, In-hospital mortality, Bleeding, Cardiogenic shock, LOS
			Non-COVID-19 STEMI	$n = 24961$, age 65.6 \pm 13.4 years, 72.2% males	2018–2019		
Little et al. (24)	UK	Multicentric cohort study	COVID-19 STEMI	n = 46, age 61.80 ± 7.95 years, 80.4% males	1/3/2020– 30/4/2020	RT-PCR on oro/nasopharyngeal throat swabs or typical symptoms plus radiographic appearances and characteristic blood test/NA	D2B time, Laboratory values, Thrombus aspiration, Gp2b3a inhibitor use, TIMI status, In-hospital mortality, Cardiogenic shock, ICU admission, LOS

Wang et al.

TABLE 2A | Continued

References	Country	Study design	Study group	Participants characteristics	Comparison period	COVID-19 diagnosis approach/time to diagnosis	Major findings
			Non-COVID-19 STEMI	$n = 302$, age 64.18 \pm 13.41 years, 79.8% males	1/3/2020– 30/4/2020		
Marfella et al. (25)	Italy	Multicentric cohort study	COVID-19 STEMI	$n = 46$, age 56.13 \pm 6.21 years, 67.4% males	2/2020–11/2020	RT-PCR on nasal/pharyngeal swabs/NA	D2B time, Laboratory values, Gp2b3a inhibitor use, Modified thrombus grade, TIMI status, In-hospital mortality, LOS, ICU admission, Cardiogenic shock
			Non-COVID-19 STEMI	$n = 130$, age 68.43 \pm 6.46 years, 66.2% males	2/2020-11/2020		
Pellegrini et al. (26)	Italy	Monocentric cohort study	COVID-19 STEMI	$n = 24$, age 69.63 \pm 11.00 years, 83.3% males	8/3/2020– 20/4/2020	RT-PCR on nasal swab or endotracheal aspirate/3–6 h	Thrombus aspiration, MINOCA, Stent implantation, Gp2b3a inhibitor use, In-hospital mortality, Cardiogenic shock, Bleeding
			Non-COVID-19 STEMI	$n = 26$, age 64.65 \pm 13.04 years, 84.6% males	8/3/2020– 20/4/2020		
Rodriguez-Leor et al. (27)	Spain	Multicentric cohort study	COVID-19 STEMI	n = 91, age 64.8 ± 11.8 years, 84.4% males	14/3/2020– 30/4/2020	PCR assay/NA	SO-to-FMC time, Primary angioplasty, Thrombus aspiration, MINOCA, Stent implantation, Gp2b3a inhibitor use, TIMI status, In-hospital mortality, Cardiogenic shock, Stent thrombosis, bleeding
			Non-COVID-19 STEMI	$n = 919$, age 62.5 \pm 13.1 years, 78.4% males	14/3/2020– 30/4/2020		
Choudry et al. (28)	UK	Monocentric cohort study	COVID-19 STEMI	n = 39, age 61.7 ± 11.0 years, 84.6% males	1/3/2020– 20/5/2020	PT-PCR on nasal/ pharyngeal swabs/NA	D2B time, Laboratory values, Primary angioplasty, Thrombus aspiration, Gp2b3a inhibitor use, Baseline thrombus grade, Modified thrombus grade, TIMI status, In-hospital mortality, Stent thrombosis
			Non-COVID-19 STEMI	$n = 76$, age 61.7 \pm 12.6 years, 75% males	1/3/2020– 20/5/2020		
Blasco et al. (29)	Spain	Monocentric cross-sectional study	COVID-19 STEMI	$n = 5$, age 62 \pm 14 years, 80% males	23/3/2020– 11/4/2020	RT-PCR on nasopharyngeal and throat swab samples/NA	Laboratory values
			Non-COVID-19 STEMI	$n=50$, age 58 \pm 12 years, 88% males	7/2015-12/2015		
Güler et al. (30)	Turkey	Monocentric cross-sectional study	COVID-19 STEMI	n = 62, age 60.2 ± 9.5 years, 66.1% males	11/3/2020– 10/1/2021	RT-PCR on nasopharyngeal swabs / NA	SO-to-FMC time, D2B time, Laboratory values, Thrombus aspiration, Gp2b3a inhibitor use, Baseline thrombus grade, TIMI status, In-hospital mortality, ICU admission, LOS
			Non-COVID-19 STEMI	$n = 64$, age 63 ± 8 years, 70.3% males	11/3/2020– 10/1/2021		

UK, United Kingdom; NOS, Newcastle-Ottawa Scale; D2B, door to balloon; MINOCA, myocardial infarction with non-obstructive coronary arteries; TIMI, thrombolysis in myocardial infarction; SO-to-FMC, symptom onset to first medical contact; LOS, length of stay; ICU, intensive care unit; RT-PCR, reverse transcriptase-polymerase chain reaction; CT, computed tomography; CXR, chest x-ray.

TABLE 2B | Baseline characteristics of study subjects.

References	Study group	Total subjects (n)	Age (years) (mean \pm SD)	Male (%)	Body mass index (kg/m ²)	Diabetes mellitus (%)	Hypertension (%)	Dyslipidemia (%)	Smoking (%)	Multivessel desease (%)	Previous myocardial infarction (%)
Popovic et al. (18)	COVID-19 STEMI	11	63.6 ± 17.4	63.9	25.1 ± 8.1	18.2	45.5	27.3	36.4	0	NA
	Non-COVID-19 STEMI	72	62.5 ± 12.6	73.6	27.02 ± 4.8	19.4	43.1	38.9	55.6	12.5	NA
Siudak et al. (19)	COVID-19 STEMI	145	63.19 ± 12.55	71.33	NA	14.48	46.21	NA	37.24	NA	12.41
	Non-COVID-19 STEMI	2,276	65.43 ± 12.23	67.65	NA	16.86	57.55	NA	31.08	NA	15.94
Kiris et al. (20)	COVID-19 STEMI	65	66.8 ± 12.0	68	NA	26	48	NA	34	44	NA
	Non-COVID-19 STEMI	668	60.0 ± 12.3	78	NA	29	42	NA	33	40	NA
Koutsoukis et al. (21)	COVID-19 STEMI	17	63.4 ± 13.2	70	NA	NA	NA	NA	NA	30.7	NA
	Non-COVID-19 STEMI	99	63.8 ± 13.9	67	NA	NA	NA	NA	NA	61.2	NA
Garcia et al. (22)	COVID-19 STEMI	230	18–55 yrs: 23%; 55–65 yrs: 32%; 66–75 yrs: 28%; >75 yrs: 17%	71	29.3 ± 7.6	46	73	46	44	0	13
	Non-COVID-19 STEMI	460	18–55 yrs: 26%; 55–65 yrs: 30%; 66–75 yrs: 27%; >75 yrs: 17%	68	29.5 ± 6.4	28	69	60	59	16	24
Kite et al. (23)	COVID-19 STEMI	144	63.1 ± 12.6	77.8	27.3 ± 4.5	34	64.8	46	31.7	NA	16.4
	Non-COVID-19 STEMI	24,961	65.6 ± 13.4	72.2	27.8 ± 5.5	20.9	44.8	28.9	33.7	NA	13
Little et al. (24)	COVID-19 STEMI	46	61.80 ± 7.95	80.4	NA	32.6	54	52.2	41.3	NA	10.9
	Non-COVID-19 STEMI	302	64.18 ± 13.41	79.8	NA	23.5	50.7	33.1	41.7	NA	12.6
Marfella et al. (25)	COVID-19 STEMI	46	56.13 ± 6.21	67.4	27.09 ± 1.81	17.4	39.1	15.2	6.5	NA	NA
	Non-COVID-19 STEMI	130	68.43 ± 6.46	66.2	29.55 ± 1.97	29.2	55.4	23.7	29.2	NA	NA
Pellegrini et al. (26)	COVID-19 STEMI	24	69.63 ± 11.00	83.3	26.60 ± 3.36	41.7	70.8	62.5	29.2	45.8	29.2
	Non-COVID-19 STEMI	26	64.65 ± 13.04	84.6	26.11 ± 3.43	15.4	53.9	65.4	38.5	28.6	19.2
Rodriguez-Leor et al. (27)	COVID-19 STEMI	91	64.8 ± 11.8	84.4	NA	23.1	51.7	48.4	18.7	37.4	NA
	Non-COVID-19 STEMI	919	62.5 ± 13.1	78.4	NA	20.9	53.3	46.9	45.5	37.1	NA
Choudry et al. (28)	COVID-19 STEMI	39	61.7 ± 11.0	84.6	26.7 (24.8–30.7)	46.2	71.8	61.6	61.6	NA	15.4
	Non-COVID-19 STEMI	76	61.7 ± 12.6	75	26.7 (24.8–30.7)	46.2	42.1	36.8	46.1	NA	3.9
Blasco et al. (29)	COVID-19 STEMI	5	62 ± 14	80	28.0 (27.3–30.1)	0	80	0	40	NA	NA
	Non-COVID-19 STEMI	50	58 ± 12	88	27.6 (24.9–30.3)	8	42	52	78	NA	NA
Güler et al. (30)	COVID-19 STEMI	62	60.2 ± 9.5	66.1	NA	48.4	59.7	43.5	51.6	NA	9.7
	Non-COVID-19 STEMI	64	63 ± 8	70.3	NA	54.7	57.8	34.3	56.3	NA	28.1



outcomes with a high degree of heterogeneity. As shown in **Table 4**, the overall results were relatively robust and not influenced by a single study, except for primary angioplasty, stent implantation, and modified thrombus grade. An asymmetrical plot was observed in some funnel plots, suggesting that publication bias may exist (**Figures 6A-9F**).

DISCUSSION

Clinical Implications

This is the first meta-analysis to compare the characteristics, management, and clinical outcomes of patients with STEMI presenting with COVID-19 infection and that of those patients without COVID-19 infection. Compared to the non-COVID-19 group, the COVID-19 group had significant delays in SOto-FMC and D2B times. Among the two groups, laboratory values, such as CRP, WBC, and D-dimer, were elevated in the COVID-19 group, while lymphocyte count was found to be lower compared to the non-COVID-19 group. In addition, STEMI concomitant with COVID-19 infection was characterized by a higher rate of MINOCA, lower rate of stent implantation, and higher thrombus grade, and associated higher use of thrombus aspiration and Gp2b3a inhibitors. Furthermore, we found that the COVID-19 group had an increased rate of inhospital mortality, cardiogenic shock, stent thrombosis, ICU admission, longer length of hospital stays, and decreased TIMI flow post-procedure.

The COVID-19 pandemic started in late 2019 and has caused severe delays in the treatment of patients with STEMI compared to the pre-COVID-19 era, and this is mostly explained by the limited access to emergency medical services (EMS) and the lack of effective organization of healthcare systems (33, 34). Several studies reported that the time from SO-to-FMC and D2B was longer in STEMI patients with COVID-19 than in those without COVID-19, which may be related to the following factors: a higher rate of respiratory symptoms without chest pain as a clinical manifestation in COVID-19 patients may result in an unclear diagnosis of heart attack and lead to a delay in seeking medical service (35), Furthermore, interventional procedures may be more complex in COVID-19 patients than in non-COVID-19 patients (24).

The reperfusion strategy for patients with STEMI during the COVID-19 pandemic remains controversial. The Chinese Cardiac Society and the Canadian Association of Interventional Cardiology recommend thrombolysis as the preferred reperfusion strategy for patients with STEMI (36, 37). In contrast, the American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions (SCAI) still suggested the use of primary percutaneous coronary intervention (PPCI) as the main treatment for all patients with STEMI during the COVID-19 crisis (1, 2). Rashid et al. reported that STEMI patients with COVID-19 were less likely to receive PPCI than STEMI patients without COVID-19 (38). However, in this study, we did not find a significant difference in the rate of primary angioplasty between both groups. Moreover, we found that the COVID-19 group had a lower rate of stent implantation, which may be associated with a higher rate of MINOCA.

Previous studies have shown that COVID-19 may lead to a prothrombotic state and that a high thrombus burden is more common in STEMI patients with COVID-19 (39–42). SARS-CoV-2 causes a systemic inflammatory response, resulting **TABLE 3** | GRADE summary of findings.

Effects of COVID-19 in STEMI patients

Patient or population: STEMI Patients Setting: Europe, Asian, North America Intervention: COVID-19 Comparison: Non-COVID-19

Outcomes	Anticipated abs	solute effects* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments	
	Risk with Non-COVID-19	Risk with COVID-19	_				
Symptom-to-FMC time	The mean symptom-to-FMC time was 0	MD 23.42 higher (5.85 higher to 40.99 higher)	_	4,290 (4 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
D2B time	The mean D2B time was 0	MD 12.27 higher (5.77 higher to 18.78 higher)	-	26,643 (7 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
CRP	-	SMD 0.76 higher (0.38 higher to 1.13 higher)	-	1,576 (7 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
WBC	-	SMD 0.39 higher (0.1 higher to 0.69 higher)	-	1,205 (5 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
D–Dimer	-	SMD 0.79 higher (0.36 higher to 1.22 higher)	-	324 (3 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
Lymphocyte count	-	SMD 0.52 lower (0.69 lower to 0.36 lower)	-	848 (5 observational studies)	$\oplus \oplus \bigcirc \bigcirc$ Low	NA	
Primary angioplasty	942 per 1,000	820 per 1,000 (566 to 943)	OR 0.28 (0.08 to 1.01)	2,796 (7 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
MINOCA	55 per 1,000	356 per 1,000 (110 to 712)	OR 9.57 (2.14 to 42.83)	1,949 (5 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
Stent implantation	895 per 1,000	704 per 1,000 (483 to 858)	OR 0.28 (0.11 to 0.71)	1,264 (4 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
Baseline thrombus grade > 3	677 per 1,000	866 per 1,000 (793 to 916)	OR 3.09 (1.83 to 5.23)	974 (3 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
Modified thrombus grade > 3	350 per 1,000	759 per 1,000 (423 to 931)	OR 5.84 (1.36 to 25.06)	1,024 (3 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
Thrombus aspiration	204 per 1,000	301 per 1,000 (243 to 367)	OR 1.68 (1.25 to 2.26)	2,498 (7 observational studies)	$\oplus \oplus \bigcirc \bigcirc$ Low	NA	
Gp2b3a inhibitor	176 per 1,000	379 per 1,000 (275 to 496)	OR 2.86 (1.78 to 4.62)	2,757 (9 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
TIMI-3 Flow	892 per 1,000	832 per 1,000 (776 to 874)	OR 0.60 (0.42 to 0.84)	2,572 (7 observational studies)	$\oplus \oplus \bigcirc \bigcirc$ Low	NA	
In- hospital mortality	57 per 1,000	265 per 1,000 (224 to 311)	OR 5.98 (4.78 to 7.48)	25,266 (11 observational studies)	$\oplus \oplus \oplus \bigcirc$ Moderate	NA	
Cardiogenic shock	84 per 1,000	201 per 1,000 (156 to 256)	OR 2.75 (2.02 to 3.76)	24,085 (5 observational studies)	$\oplus \oplus \bigcirc \bigcirc$ Low	NA	
Stent thrombosis	10 per 1,000	52 per 1,000 (23 to 114)	OR 5.65 (2.41 to 13.23)	1,858 (3 observational studies)	$\oplus \oplus \bigcirc \bigcirc$ Low	NA	
Bleeding	5 per 1,000	13 per 1,000 (4 to 39)	OR 2.82 (0.88 to 9.05)	15,850 (4 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
ICU admission	83 per 1,000	277 per 1,000 (184 to 394)	OR 4.26 (2.51 to 7.22)	650 (3 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	
Length of stay	The mean length of stay was 0	MD 4.63 higher (2.56 higher to 6.69 higher)	-	26,445 (5 observational studies)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low	NA	

Ana Blasco 2020 Arda Giller 2021 Athanasios Kouteoukis 2021			-		oovia	10		Sto. Mean Difference	Std. Mean Difference
Ana Blasco 2020 Arda Giiler 2021 Athanasios Koutsoukis 2021	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% Cl
Arda Giiler 2021 Athanasios Koutsoukis 202	2.9	1.9	5	2.6	4.9	50	8.8%	0.06 [-0.86, 0.98]	
Athanasios Koutsoukis 202	3.67	11.09	62	0.7	0.51	64	16.3%	0.38 [0.03, 0.73]	
Allanasios Routsoukis 202	0 7.2	9.13	17	0.7	1.06	99	13.2%	1.81 [1.25, 2.38]	
Batric Popovic 2020	9.8	9.7	11	2.8	3.9	72	11.8%	1.39 [0.72, 2.06]	
Callum D Little 2020	7.96	11.57	46	2.52	9.27	302	16.8%	0.57 [0.25, 0.88]	
Fizzah A. Choudry 2020	14.69	22.56	39	7.24	37.35	76	15.8%	0.22 [-0.16, 0.61]	
Tuncay Kiris 2021	17.43	56.2	65	2.47	1.92	668	17.4%	0.89 [0.63, 1.15]	
Pooled (95% CI)			245	5		1331	1 100.0%	0.76 [0.38, 1.13]	•
Heterogeneity: Tau ² = 0.19;	Chi ² = 32.	61, df =	6 (P < 0	0.0001);	12 = 829	6			
Test for overall effect: Z = 3	.98 (P < 0.	.0001)							-2 -1 U 1 2 Eavours [Covid 19] Eavours [Non Covid 19]
Total: total study patients									
5	Covid	i-19	No	on-Covi	d-19		Std.	Mean Difference	Std. Mean Difference
Study or Subgroup	Mean S	D Tot	al Mea	n SI) Tota	Wei	ight IV	Random, 95% Cl	IV. Random, 95% Cl
Ana Blasco 2020	16.02 3.9	92	5 12.3	3 4.2	1 50	7	.7%	0.87 [-0.07, 1.80]	*
Arda Guler 2021	11.53 4	37 6	2 11.7	1 4.2	64	22	.5%	-0.04 [-0.39, 0.31]	
Fizzah A. Choudry 2020	13.84 4	94 3	9 12.3	9 4.04	5 76	20	.9%	0.33 [-0.06, 0.72]	
Raffaele Marfella 2021	15.76 1	27 4	6 12 4	9 4 83	130	22	6%	0.78 [0.43, 1.12]	
Tuncav Kiris 2021	13.6 4	8 6	5 1	2 4	5 668	26	3%	0.35 [0.10, 0.61]	
randay rand 2021	10.0 4			- 4.		20		0.00 [0.10, 0.01]	
Pooled (95% CI)		2	17		98	8 10	0.0%	0.39 [0.10, 0.69]	•
	Chi ² = 11	.75, df =	4 (P =	0.02); P	= 66%			+	
Heterogeneity: Tau ² = 0.07;								-2	-1 0 1 2
Heterogeneity: $Tau^2 = 0.07$; Test for overall effect: $Z = 2$.62 (P = 0	.009)							Equation [Could 10] Equation [Non Could 10]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients	.62 (P = 0	.009)							Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients	.62 (P = 0	.009)							Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients	.62 (P = 0	.009) vid-19		Non-C	ovid-19	,	s	td. Mean Difference	Favours [Covid-19] Favours [Non-Covid-19] Std. Mean Difference
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup	.62 (P = 0 Co Mean	.009) vid-19 SD 1	<u>Fotal</u>	Non-C Ilean	ovid-19	otal	S Weight	td. Mean Difference IV. Random. 95% Cl	Favours [Covid-19] Favours [Non-Covid-19] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021	.62 (P = 0 Con <u>Mean</u> 1.38	.009) vid-19 <u>SD</u> 0.6	<u>Fotal N</u> 62	Non-C <u>flean</u> 1.02 (ovid-19 <u>SD T</u>	o <u>tal</u>	S Weight 39.2%	itd. Mean Difference <u>IV. Random, 95% CI</u> 0.74 [0.38, 1.10]	Favours [Covid-19] Favours [Non-Covid-19] Std. Mean Difference IV. Random. 95% Cl
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020	.62 (P = 0 Cov <u>Mean</u> 1.38 3.12	.009) vid-19 <u>SD</u> 0.6 2.5	<u>Fotal N</u> 62 11	Non-C <u>fean</u> 1.02 (0.8	ovid-19 <u>SD T</u> 0.33 1.5	9 0tal 1 64 72	S Weight 39.2% 23.4%	td. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06]	Std. Mean Difference
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020	.62 (P = 0 <u>Mean</u> 1.38 3.12 7.18	.009) vid-19 SD 1 0.6 2.5 23.44	<u>Fotal N</u> 62 11 39	Non-C <u>Mean</u> 1.02 (0.8 0.76 (ovid-19 <u>SD T</u> 0.33 1.5 0.63	0 64 72 76	S Weight 39.2% 23.4% 37.4%	td. Mean Difference <u>IV. Random. 95% CI</u> 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86]	Std. Mean Difference IV. Random. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Güler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI)	.62 (P = 0 Con Mean 1.38 3.12 7.18	.009) vid-19 SD 1 0.6 2.5 23.44	<u>Fotal N</u> 62 11 39 112	Non-C <u>Mean</u> 1.02 (0.8 0.76 (ovid-19 <u>SD T</u> 0.33 1.5 0.63	otal 1 64 72 76 212	S Weight 39.2% 23.4% 37.4%	td. Mean Difference <u>IV. Random. 95% Cl</u> 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22]	Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients <u>Study or Subgroup</u> Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.02	.62 (P = 0 Con Mean 1.38 3.12 7.18 2 9: Chi ² = 5	.009) vid-19 <u>SD</u> 0.6 2.5 23.44	<u>Fotal №</u> 62 11 39 112 = 2 (P =	Non-C <u>Mean</u> 1.02 (0.8 0.76 (0.07)-1	ovid-19 <u>SD T</u> 0.33 1.5 0.63 1 ² = 63%	0 64 72 76 212	S Weight 39.2% 23.4% 37.4% 100.0%	td. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22]	Std. Mean Difference IV. Random. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.07 Test for overall effect: Z =	.62 (P = 0 <u>Cov</u> <u>Mean</u> 1.38 3.12 7.18 2 9; Chi ² = 5 3.60 (P =	vid-19 <u>SD</u> 0.6 2.5 23.44 5.41, df = 0.0003	<u>Fotal №</u> 62 11 39 112 = 2 (P =	Non-C <u>Mean</u> 1.02 (0.8 0.76 (:0.07);	ovid-19 <u>SD T</u> 0.33 1.5 0.63	o <u>tal</u> 64 72 76 212	S Weight 39.2% 23.4% 37.4%	itd. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22]	Std. Mean Difference IV. Random. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Güler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Total: total study patiens	.62 (P = 0 	.009) vid-19 <u>SD</u> 0.6 2.5 23.44 5.41, df = 0.0003)	Fotal M 62 11 39 112 = 2 (P =	Non-C Mean 1.02 (0.8 0.76 (:0.07);	ovid-19 <u>SD T</u> 0.33 1.5 0.63	9 64 72 76 212	S <u>Weight</u> 39.2% 23.4% 37.4%	itd. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22]	Std. Mean Difference IV. Random. 95% Cl -2 -1 0 1 2 Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = Total: total study patiens	.62 (P = 0 Cov Mean 1.38 3.12 7.18 29; Chi ² = 5 3.60 (P =	.009) vid-19 <u>SD</u> 0.6 2.5 23.44 5.41, df = 0.0003)	<u>fotal №</u> 62 11 39 112 = 2 (P =	Non-C <u>Mean</u> 1.02 (0.8 0.76 (:0.07);	ovid-19 <u>SD T</u> 0.33 1.5 0.63	otal 1 64 72 76 212	S <u>Weight</u> 39.2% 23.4% 37.4% : 100.0%	itd. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22]	Std. Mean Difference IV. Random. 95% CI -2 -1 0 1 2 Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = Total: total study patiens	.62 (P = 0 Cov 1.38 3.12 7.18 9; Chi ² = 5 3.60 (P =	vid-19 <u>SD</u> 0.6 2.5 23.44 5.41, df = 0.0003) rid-19	<u>fotal M</u> 62 11 39 112 = 2 (P =	Non-C Mean 1.02 (0.8 0.76 (:0.07); Non-Co	ovid-19 <u>SD Tr</u> 0.33 1.5 0.63 4 ² = 63%	9 64 72 76 212	S Weight 39.2% 23.4% 37.4% 100.0%	 itd. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference 	Std. Mean Difference IV. Random. 95% CI -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference Std. Mean Difference
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = Total: total study patiens	.62 (P = 0 <u>Con</u> 1.38 3.12 7.18 9; Chi ² = 5 3.60 (P = <u>Cov</u> <u>Mean</u>	vid-19 <u>SD 1</u> 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>SD T</u> c	Fotal N 62 11 39 112 = 2 (P =	Non-C <u>Mean</u> 1.02 (0.8 0.76 (0.07); 0.07); Non-Co ean	ovid-19 <u>SD T</u> 0.33 1.5 0.63 ¹² = 63% vid-19 <u>SD To</u>	00000000000000000000000000000000000000	S <u>Weight</u> 39.2% 23.4% 37.4% 100.0% St Veight	 d. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% CI 	Std. Mean Difference IV. Random. 95% CI -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giller 2021	.62 (P = 0 <u>Mean</u> 1.38 3.12 7.18 2 9; Chi ² = 5 3.60 (P = <u>Cov</u> <u>Mean</u> 1.59 (I	.009) vid-19 <u>SD 1</u> 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>SD Te</u> 0.71	Fotal N 62 11 39 112 = 2 (P = 0 0 1 0 0 0 0 0 0	Non-C Mean 1.02 (0.8 0.76 (0.07); Non-Cc ean 2.05 0.	ovid-19 <u>SD</u> Tr 0.33 1.5 0.63 ¹² = 63% wid-19 <u>SD</u> To 68	9 64 72 76 212 6 ********************************	st <u>weight</u> 39.2% 23.4% 37.4% 100.0% <u>st</u> <u>veight</u> 21.8%	 itd. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% CI -0.66 [-1.02, -0.30] 	Std. Mean Difference IV. Random, 95% Cl -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed, 95% Cl
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giller 2021 Batric Popovic 2020	.62 (P = 0 <u>Mean</u> 1.38 3.12 7.18 9; Chi ² = 5 3.60 (P = <u>Cov</u> <u>Mean</u> 1.59 (4.5)	vid-19 <u>SD</u> 1 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>SD</u> Tc 0.71 9.3	Fotal M 62 11 39 112 = 2 (P =) 0 112 0 62 0 62 11 1	Non-C Mean 1.02 (0.8 0.76 (0.07); 1 Non-Co ean 2.05 0 15.9 10	ovid-19 <u>SD</u> Tr 0.33 1.5 0.63 P = 63% vid-19 <u>SD</u> To 68 6.1	9 <u>otal</u> 64 72 76 212 6 tal <u>M</u> 64	\$ weight 39.2% 23.4% 37.4% 100.0% \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	 itd. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% CI -0.66 [-1.02, -0.30] -0.73 [-1.38, -0.09] 	Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giiler 2021 Batric Popovic 2020 Callum D Little 2020	.62 (P = 0 .62 (P = 0 .1.38 .1.288 .1.2	vid-19 <u>SD</u> 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>SD</u> Te 0.71 9.3 0.54	Fotal N 62 11 39 112 = 2 (P = 0 otal Me 62 2 11 1 46 46	Non-C Mean 1.02 (0.8 0.76 (0.07); 0.07); Non-Cc ean 2.05 0. (5.9 1) 1.8 (SD T 3.3 1.5 0.63 1 ² = 63% vvid-19 SD To 68 6.1 0.9 3	otal 1 64 72 76 212 6 4 4 64 72 72	\$ Weight 39.2% 23.4% 37.4% 100.0% \$ Veight 21.8% 6.8%	itd. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22]	Std. Mean Difference IV. Random. 95% CI -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giiler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020	.62 (P = 0 <u>Cov</u> 1.38 3.12 7.18 9; Chi ² = 5 3.60 (P = <u>Cov</u> <u>Mean</u> 1.59 (4.5 1.28 (1.39 (1.3	vid-19 <u>5.41</u> , df = 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>5.0</u> Tr 0.71 9.3 0.54 0.85	Fotal M 62 11 39 112 9 112 10 11 11 1 11 1 11 1 11 1 11 1 46 39 39 1	Non-C Mean 1.02 (0.8 0.76 (0.07); Non-Co ean 2.05 0. 1.5.9 10 1.8 0. .81 0.	ovid-19 <u>SD T</u> 0.33 1.5 0.63 ¹² = 63% vid-19 <u>SD To</u> 68 6.1 0.9 3 75	etal V 64 72 76 212 6 4 76 5 72 72 76 77	S Weight 39.2% 23.4% 37.4% 100.0% St Veight 21.8% 6.8% 28.6% 18.2%	 itd. Mean Difference IV. Random. 95% CI 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% CI -0.66 [-1.02, -0.30] -0.73 [-1.38, -0.09] -0.60 [-0.92, -0.29] -0.53 [-0.92, -0.141] 	Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giller 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Raffaele Marfella 2021	.62 (P = 0 .62 (P = 0 .1.38 3.12 7.18 9; Chi ² = 5 3.60 (P = .00 .00 .00 .00 .00 .00 .00 .0	vid-19 <u>sp</u> 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>sp</u> 1.5 0.71 9.3 0.54 0.54 0.54 0.54 0.54	Fotal M 62 11 39 112 = 2 (P =) 0 1 0 1 0 1 0 1 11 1 46 39 46 46	Non-C Mean 1.02 (0.8 0.76 (0.07); Non-Co ean 2.05 0. (5.9 1) 1.8 0. 1.8 0.	ovid-19 SD Tr. 0.33 1.5 0.63 P = 63% wid-19 SD To 68 6.1 0.9 75 1.4	otal 1 64 72 76 212 64 5 212 6 tal M 5 72 6 72 7 72 02 2 76 30	S Weight 39.2% 23.4% 37.4% 100.0% St Veight 21.8% 6.8% 18.2% 28.6% 18.2% 24.7%	itd. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% Cl -0.66 [-1.02, -0.30] -0.66 [-0.92, -0.29] -0.63 [-0.92, -0.14] -0.25 [-0.59, 0.08]	Std. Mean Difference IV. Random. 95% CI -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed. 95% CI -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.07 Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giiler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Raffaele Marfella 2021 Pooled (95% CI)	.62 (P = 0 .02 (P = 0 .1.38 .1.58 .1.58 .1.58 .1.58 .1.59	vid-19 <u>SD</u> 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 <u>SD</u> To 0.71 9.3 0.54 0.85 0.2	Fotal N 62 11 39 112 11 16 62 2 11 14 46 39 46 204	Non-Co 1.02 (0.8 0.76 (0.07); 0.07); 0.07]; 0.07];	ovid-19 <u>SD T.</u> 0.33 1.5 0.63 1 ² = 63% <u>sD To</u> 68 6.1 0.9 3 7.5 1.4 1 6	otal 1 64 72 76 212 2 2 6 30 1 30 30 30	S Weight 39.2% 23.4% 37.4% 100.0% St Veight 21.8% 6.8% 28.6% 18.2% 24.7% 00.0%	td. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% Cl -0.66 [-1.02, -0.30] -0.73 [-1.38, -0.09] -0.53 [-0.92, -0.14] -0.25 [-0.59, 0.08] -0.52 [-0.69, -0.36]	Favours [Covid-19] Favours [Non-Covid-19]
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% CI) Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giller 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Raffaele Marfella 2021 Pooled (95% CI) Heterogeneity: Chi ² = 3.65	.62 (P = 0 .62 (P = 0 .1.38 3.12 7.18 9; Chi ² = 5 3.60 (P = .0000 .000 .0	vid-19 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 SD T 0.71 9.3 0.54 0.55 0.54 0.55 0.54 0.55 0	Fotal M 62 11 39 112 = 2 (P = 1 0 1 0 1 0 1 0 1 1 1 46 39 204 1	Non-C Mean 1.02 (0.8 0.76 (0.07); Non-Cc ean 2.05 0. 1.5.9 11 1.8 0. 1.8 0. 1.8 0. 2.4	ovid-19 <u>SD</u> Tr. 0.33 1.5 0.63 1 ² = 63% vid-19 <u>SD</u> To 68 6.1 0.9 3.75 1.4 1 6	e contraction of the second se	S Weight 39.2% 23.4% 37.4% 100.0% St Veight 21.8% 6.8% 6.8% 18.2% 24.7% 00.0%	itd. Mean Difference IV. Random. 95% Cl 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference IV. Fixed. 95% Cl -0.66 [-1.02, -0.30] -0.66 [-1.02, -0.30] -0.65 [-0.92, -0.29] -0.53 [-0.92, -0.14] -0.25 [-0.59, 0.08]	Std. Mean Difference IV. Random. 95% CI -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed. 95% CI
Heterogeneity: Tau ² = 0.07; Test for overall effect: Z = 2 Total: total study patients Study or Subgroup Arda Güler 2021 Batric Popovic 2020 Fizzah A. Choudry 2020 Pooled (95% Cl) Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = Total: total study patiens Study or Subgroup Arda Giiler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Raffaele Marfella 2021 Pooled (95% Cl) Heterogeneity: Chi ² = 3.66 Test for overall offect: Z =	.62 (P = 0 .62 (P = 0 	vid-19 vid-19 0.6 2.5 23.44 5.41, df = 0.0003) vid-19 SD Tr 0.71 9.3 0.54 0.25 0.2 2 = 0.45 0 0000	Fotal M 62 11 39 112 e = 2 (P = 11 0 11 0 11 14 14 46 39 204 1; 12 = 0	Non-C Mean 1.02 (0.8 0.76 (0.07); Non-Co ean 2.05 0. 1.5.9 11 1.8 0. .81 0. .81 0. .81 0.	ovid-19 <u>SD T</u> 0.33 1.5 0.63 ¹² = 63% vid-19 <u>SD To</u> 68 6.1 0.9 3 75 14 1 6	212 76 212 6 4 44 1	St Weight 39.2% 23.4% 37.4% 100.0% St Veight 21.8% 6.8% 28.6% 18.2% 00.0%	tid. Mean Difference <u>IV. Random. 95% Cl</u> 0.74 [0.38, 1.10] 1.39 [0.72, 2.06] 0.47 [0.08, 0.86] 0.79 [0.36, 1.22] d. Mean Difference <u>IV. Fixed. 95% Cl</u> -0.66 [-1.02, -0.30] -0.73 [-1.38, -0.09] -0.60 [-0.92, -0.29] -0.53 [-0.92, -0.14] -0.25 [-0.59, 0.08] 2	Std. Mean Difference IV. Random. 95% Cl -2 -1 0 1 2 Favours [Covid-19] Std. Mean Difference IV. Fixed. 95% Cl

in endothelial and hemostatic activation, which involves the activation of platelets and the coagulation cascade (43). In addition, our study found that the time from SO-to-FMC and D2B was longer in STEMI patients with COVID-19 than in those without COVID-19. The studies of Duman et al. (44) and Ge et al. (45) reported that the delay in SO-to-FMC and D2B would prolong the time for opening infarct-related vessels which may account for a higher thrombus burden. Therefore, in the COVID era, it is of great significance that novel technologies should be developed so as to achieve more

efficient thrombus aspiration in patients with very high intracoronary thrombus burden such as patients with STEMI and coexistent COVID-19 infection (46). Furthermore, strategies to reduce reperfusion delay times such as educating the public about the recognition and diversity of coronary symptoms and optimizing interventional procedures are essential. In keeping with the high thrombus burden, the COVID-19 group had elevated CRP, WBC, and D-dimer levels and a lower lymphocyte count compared to the non-COVID-19 group. High thrombus grade, reduced TIMI flow, high rate of MINOCA, and stent

	Covid	-19	Non-Co	vid-19		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95%	CI M-H. Random. 95% CI
Athanasios Koutsoukis 2020	11	17	86	99	17.5%	0.28 [0.09, 0.88	B]
Batric Popovic 2020	10	11	70	72	11.5%	0.29 [0.02, 3.45	5]
Dario Pellegrini 2021	21	24	26	26	9.6%	0.12 [0.01, 2.37	7]
Fizzah A. Choudry 2020	38	39	74	76	11.8%	1.03 [0.09, 11.69	Ð]
Oriol Rodriguez-Leor 2020	87	90	838	919	17.4%	2.80 [0.87, 9.06	5]
Santiago Garcia 2021	127	230	425	460	19.9%	0.10 [0.07, 0.16	5]
Tuncay Kiris 2021	62	65	667	668	12.4%	0.03 [0.00, 0.30	
Pooled (95% CI)		476		2320	100.0%	0.28 [0.08, 1.01	
Total events	356		2186				
Heterogeneity: Tau ² = 2.12; Cl	hi ² = 34.23	, df = 6	6 (P < 0.00	0001); I ²	= 82%		0.005 0.1 1 10 200
Total: total study patients) (F = 0.05	,					Favours [Covid-19] Favours [Non-Covid-19]
В							
	Covid	-19	Non-Cov	vid-19		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	M-H. Random, 95% Cl
Athanasios Koutsoukis 2020	4	17	1	99	16.6%	30.15 [3.13, 290.82]	
Batric Popovic 2020	6	11	5	72	21.1%	16.08 [3.61, 71.69]	
Dario Pellegrini 2021	3	24	0	26	12.8%	8.63 [0.42, 176.32]	
Oriol Rodriguez-Leor 2020	11	91	75	919	25.3%	1.55 [0.79, 3.03]	
Santiago Garcia 2021	41	230	5	460	24.1%	19.74 [7.68, 50.73]	
Pooled (95% CI)		373		1576	100.0%	9.57 [2.14, 42.83]	-
Total events	65		86				
Heterogeneity: Tau ² = 2.19; C	chi ² = 25.19	, df = 4	(P < 0.000	01); l ² = 8	34%		
Test for overall effect: Z = 2.9	5 (P = 0.00	3)					Eavoure [Covid-19] Eavoure [Non-Covid-19]
Total: total study patients							
Study or Subgroup	Covid- Events	19 Total	Non-Covi Events	d-19 Total	Weight	Odds Ratio M-H. Random. 95% CI	Odds Ratio M-H, Random, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI)	Covid- Events 1 10 7 77	19 <u>Total</u> 5 17 11 91 124	Non-Covi Events 45 84 62 829	d-19 <u>Total</u> 50 99 72 919 1140	Weight 11.6% 27.7% 22.6% 38.0% 100.0%	Odds Ratio M.H. Random. 95% Cl 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71]	Odds Ratio M-H, Random, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; CH Test for overall effect: Z = 2.66 Total: total study patients	Covid- Events 1 10 7 77 95 ni ² = 7.36, c 6 (P = 0.008	19 <u>Total</u> 5 17 11 91 124 3)	Non-Covi <u>Events</u> 45 84 62 829 1020 P = 0.06); I	d-19 <u>Total</u> 50 99 72 919 1140 ² = 59%	Weight 11.6% 27.7% 22.6% 38.0%	Odds Ratio <u>M-H. Random. 95% Cl</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.77, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71]	Odds Ratio M-H. Random. 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19]
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Ch Test for overall effect: Z = 2.66 Total: total study patients	Covid- <u>Events</u> 1 10 7 77 95 95 95 (P = 0.008 Covid-1	19 <u>Total</u> 5 17 11 91 124 3) 9 9	Non-Covi <u>Events</u> 45 84 62 829 1020 P = 0.06); I Non-Cov	d-19 Total 9 99 72 919 1140 2 = 59% <i>r</i> id-19	Weight 11.6% 27.7% 22.6% 38.0%	Odds Ratio <u>M-H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.77, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] Odds Ratio	Odds Ratio M-H. Random. 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Odds Ratio
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; Ch Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup	Covid-1 Events 1 10 7 77 95 6 (P = 0.008 Covid-1 Events	19 <u>Total</u> 5 17 11 91 124 if = 3 (F 3) 9 <u>7</u> Total	Non-Covi Events 45 84 62 829 1020 P = 0.06); 1 Non-Cov Events	d-19 <u>Total</u> 99 72 919 1140 ² = 59% /id-19 <u>Total</u>	Weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] Odds Ratio <u>M-H. Fixed. 95% CI</u>	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021	Covid-1 Events 1 10 7 77 95 6 (P = 0.008 Covid-1 Events 54	19 Total 5 17 11 91 124 if = 3 (f 3) 9 Total 62	Non-Covi Events 45 84 62 829 1020 P = 0.06); I Non-Cov Events 48	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64	Weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] Odds Ratio <u>M.H. Fixed. 95% CI</u> 2.25 [0.88, 5.72]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; Ct Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020	Covid-1 Events 1 10 7 77 95 6 (P = 0.008 Covid-1 Events 54 33 	19 <u>Total</u> 5 17 11 91 124 4f = 3 (1 3) 9 <u>Total</u> 62 39 <u>5</u>	Non-Covi Events 45 84 62 829 1020 P = 0.06); 1 Non-Cov Events 48 59	d-19 <u>Total</u> 50 99 72 919 1140 ² = 59% ⁴ ⁴ ⁶ ⁶ ⁴ ⁷ ⁶ ⁴ ⁷ ⁷ ⁸ ⁹ ⁹ ⁹ ⁹ ⁷ ⁹ ⁹ ⁷ ⁹ ⁹ ⁹ ¹⁰ ¹¹ ¹⁰ ¹¹ ¹⁰ ¹⁰ ¹⁰ ¹⁰ ¹¹ ¹⁰	weight 11.6% 27.7% 22.6% 38.0% 100.0% weight 31.3% 31.6%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] Odds Ratio <u>M.H. Fixed, 95% CI</u> 2.25 [0.88, 5.72] 1.58 [0.57, 4.41]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Ch Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021	Covid-1 Events 1 10 7 77 95 6 (P = 0.006 Covid-1 Events 54 33 59	Total 5 17 11 91 124 ff = 3 (f 3) 9 Total 62 39 65	Non-Covi Events 45 84 62 829 1020 P = 0.06); Non-Cov Events 48 59 440	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64 76 668	weight 11.6% 27.7% 22.6% 38.0% 100.0% weight 31.3% 31.6% 37.0%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl)	Covid-1 1 10 7 77 95 $n^2 = 7.36$, c 6 (P = 0.006 Covid-1 Events 54 33 59	19 Total 5 17 11 91 124 if = 3 (f 3) 9 Total 62 39 65 166	Non-Covi Events 45 84 62 829 1020 P = 0.06); Non-Cov Events 48 59 440	d-19 <u>Total</u> 99 72 919 1140 2 = 59% /id-19 <u>Total</u> 64 76 668 808	Weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; CH Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% CI) Total events	Covid- 1 1 1 7 77 95 95 (P = 0.005 Covid-1 Events 54 33 59 146	19 Total 5 17 11 91 124 if = 3 (f 3) 19 Total 62 39 65 166	Non-Covi Events 45 84 62 829 1020 = 0.06); 1 Non-Cov Events 48 59 440 547	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64 76 668 808	weight 11.6% 27.7% 22.6% 38.0% 100.0% weight 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; CH Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% CI) Total events Heterogeneity: Chi ² = 3.40,	Covid-1 Fvents 1 10 7 77 95 6 (P = 0.006 Covid-1 Events 54 33 59 146 df = 2 (P =	19 Total 5 17 11 91 124 if = 3 (f 62 39 65 166 = 0.18]	Non-Covi Events 45 84 62 829 1020 P = 0.06); I Non-Cov Events 48 59 440 547); I ² = 41%	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64 76 668 808	weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% Cl</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl 400 0.01 0.1 1 0 10 100
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Ch Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect; Z = 4 Total: total study patients	Covid-1 95 17 77 95 6 (P = 0.006 Covid-1 Events 54 33 59 146 df = 2 (P = 0 0.22 (P < 0	19 Total 5 17 19 124 if = 3 (li) if = 3 (li) 62 39 65 166 = 0.18% .0001)	Non-Covi Events 45 84 62 829 1020 P = 0.06); Non-Cov Events 48 59 440 547 ; ² = 41%	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% 7 7 7 7 2 = 59% 7 7 7 7 9 72 72 9 72 72 9 72 72 9 72 72 72 9 72 72 72 72 72 72 72 72 72 72	Weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 0.1 1 10 100 Favours [Covid-19] Favours [Non-Covid-19]
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% CI) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients	Covid-1 1 1 1 7 7 95 6 (P = 0.008 Covid-1 Events 54 33 59 146 df = 2 (P = 0 22 (P < 0	19 Total 5 17 11 91 124 if = 3 (f 5 162 39 65 166 = 0.18 .0001)	Non-Covi Events 45 84 62 829 1020 P = 0.06); I Non-Cov Events 48 59 440 547 ; I ² = 41%	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64 76 668 808	Weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% Cl</u> 0.03 [0.00, 0.30] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23]	Odds Ratio M.H. Random, 95% Cl 0.005 0.1 1 0 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl 0.01 0.1 1 0 100 Favours [Covid-19] Favours [Non-Covid-19]
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 20200 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cf Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect; Z = 4 Total: total study patients	Covid-1 24 Covid-1 25 36 (P = 0.008 Covid-1 54 33 59 146 df = 2 (P = 0 22 (P < 0 Covid-1	19 Total 5 17 11 91 124 if = 3 (f 5 166 62 39 65 166 = 0.18 .0001)	Non-Covid	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64 76 668 808 808	weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% Cl</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23]	Odds Ratio M.H. Random, 95% CI 0.005 0.1 1 0 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed, 95% CI 0.01 0.1 1 0 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cł Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients	Covid-1 Events 1 10 7 77 95 95 95 95 95 95 95 95 95 95	19 Total 5 17 11 91 124 if = 3 (f 162 39 65 166 = 0.18 .0001) N Natal E	Non-Covi <u>Events</u> 45 84 62 829 1020 P = 0.06); I Non-Cov <u>Events</u> 48 59 440 547); I ² = 41% on-Covid vents	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% rid-19 <u>Total</u> 64 76 668 808 808	Weight 11.6% 27.7% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0% (weight N	Odds Ratio <u>M-H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.7, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] Odds Ratio <u>Codds Ratio</u> Codds Ratio	Odds Ratio M-H. Random. 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed. 95% Cl 0.01 0.1 10 100 Favours [Non-Covid-19] Odds Ratio M-H. Random. 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients	Covid-1 54 33 59 146 6 (P = 0.005 Covid-1 54 33 59 146 122 (P < 0 Covid-19 21	19 Total 5 17 91 124 if = 3 (f 62 39 65 166 = 0.18 .00001) N xtal E 39	Non-Covi <u>Events</u> 45 84 62 829 1020 P = 0.06); Non-Cov <u>Events</u> 48 59 440 547 ; ² = 41% 00n-Covid <u>vents</u> 16	d-19 <u>Total</u> 50 99 72 919 1140 2 = 59% 76 64 76 668 808 808 -19 <u>Total</u> 64 76 668 808	Weight 11.6% 27.7% 22.6% 38.0% 100.0% 100.0% 31.3% 31.6% 37.0% 100.0%	Odds Ratio <u>M.H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] Odds Ratio <u>I.H. Random. 95% CI</u> 4.38 [1.89, 10.10]	Odds Ratio M.H. Random. 95% CI 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed. 95% CI 0.01 0.1 0.1 1 10 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Random. 95% CI
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cł Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients	Covid-1 1 10 7 77 95 $0^{12} = 7.36$, cs 5 (P = 0.006 Covid-1 Events 54 33 59 1466 df = 2 (P = 0.0000000000000000000000000000000000	19 Total 5 17 91 124 if = 3 (l if = 3 (l 0 Total 62 39 65 166 = 0.18 (l .0001) N value 39 46 65	Non-Covi 45 45 82 829 1020 P = 0.06); 1 Non-Cov Events 48 59 440 547); 1 ² = 41% on-Covid vents 16 300 260	d-19 Total V 50 99 72 919 1140 2 = 59% rid-19 Total 64 76 668 808 808 -19 Total V 76 130 2 50 0 10 10 10 10 10 10 10 10 10	Weight 11.6% 27.7% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0% (eight N 33.1% 31.5%	Odds Ratio <u>M-H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.7, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.20, 0.7] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71]	Odds Ratio M.H. Random. 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed. 95% Cl 0.01 0.1 10 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M.H. Random. 95% Cl
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect; Z = 4 Total: total study patients E Study or Subgroup E Fizzah A. Choudry 2020 Raffaele Marfella 2021 Tuncay Kiris 2021	Covid-1 54 33 59 146 6 (P = 0.006 Covid-1 Events 1 41 36	19 Total 5 17 11 91 124 if = 3 (l 62 39 65 166 = 0.18 ³ , .0001) N N tal E 39 65 	Non-Covi 45 84 62 829 1020 P = 0.06); 1 Non-Covi Events 48 59 440 547); 1 ² = 41% 0 0 0 0 260	d-19 Total 1 50 99 72 919 1140 2 = 59% rid-19 Total 64 76 668 808 808 5 5 6 6 8 8 8 8 8 8 8 8 8 8 8 8 8	weight 11.6% 27.7% 38.0% 100.0% weight 31.6% 37.0% 100.0% ////////////////////////////////////	Odds Ratio <u>M-H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.7, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] Odds Ratio <u>I-H. Random. 95% CI</u> 4.38 [1.89, 10.10] 27.33 [9.91, 75.36] 1.95 [1.17, 3.25]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M-H, Random, 95% Cl 0 0 0 Favours [Non-Covid-19]
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% CI) Total: total study patients E Study or Subgroup Fizzah A. Choudry 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI) Total: total study patients	Covid-1 1 1 7 77 95 95 95 95 95 95 95 95 95 95	19 Total 5 17 11 91 124 if = 3 (l 62 39 65 166 = 0.18 ,0001) N tal E 39 65 166 50	Non-Covi 45 45 84 62 829 1020 P = 0.06); I Non-Cov Events 48 59 440 547 ; I ² = 41% on-Covid vents 16 30 260 200 200 200 200 200 200 20	d-19 Total 1 50 99 72 919 1140 2 = 59% rid-19 Total 64 76 668 808 808 5 5 6 8 8 8 8 8 8 8 8 8 8 8 8 8	Weight 11.6% 27.7% 38.0% 100.0% Weight 31.3% 31.3% 37.0% 100.0% Keight N 33.1% 31.5% 35.5% 00.0%	Odds Ratio <u>M-H. Random. 95% CI</u> 0.03 [0.00, 0.30] 0.28 [0.07, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] Odds Ratio <u>H.H. Random. 95% CI</u> 4.38 [1.89, 10.10] 27.33 [9.91, 75.36] 1.95 [1.17, 3.25] 5.84 [1.36, 25.06]	Odds Ratio M-H, Random, 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H, Fixed, 95% Cl 0.01 0.1 1 10 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M-H, Random, 95% Cl 0 0 0 Favours [Non-Covid-19]
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients	Covid-1 1 10 7 77 95 $n^2 = 7.36$, c 6 (P = 0.006 Covid-1 Events 54 33 59 146 df = 2 (P = 0 6.22 (P < 0	19 Total 5 17 91 124 if = 3 (f 16 62 39 65 166 = 0.18% .0001) N vetal E 39 46 50 65	Non-Covi Events 45 84 82 829 1020 P = 0.06); 1 Non-Covi Events 48 59 440 547); 1 ² = 41% 0n-Covid vents 16 30 260 306	d-19 Total 1 50 99 72 919 1140 2 = 59% 76 668 808 808 -19 Total W 76 330 3668 3 874 10 0010 5	Weight 11.6% 27.7% 22.6% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0% 100.0%	Odds Ratio M.H. Random. 95% CI 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.7, 1.14] 0.60 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] Odds Ratio H.H. Random. 95% CI 4.38 [1.89, 10.10] 27.33 [9.91, 75.36] 1.95 [1.17, 3.25] 5.84 [1.36, 25.06]	Odds Ratio M.H. Random. 95% CI 0.005 0.1 1 0 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed. 95% CI 0.01 0.1 1 0 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Random. 95% CI
Study or Subgroup Ana Blasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients E Study or Subgroup Fizzah A. Choudry 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% Cl) Total events Heterogeneity: Tau ² = 1.49; CD	Covid-1 1 10 7 77 95 $G(P = 0.006)$ Covid-1 Events 54 33 59 146 df = 2 (P = 0.006) Covid-19 Events 21 41 36 1 98 chi ² = 21.3	19 Total 5 17 91 124 if = 3 (f 62 39 65 166 = 0.18 .00001) N vtal E 39 46 65 50 6, df =	Non-Covi 45 84 62 829 1020 P = 0.06); 1 Non-Covi Events 48 59 440 547 ; 1 ² = 41% 00n-Covid vents 16 30 260 306 2 (P < 0.0	d-19 Total 1 50 99 72 919 1140 2 = 59% 76 64 76 668 808 808 808 808 808 808 80	Weight Ill.6% 27.7% 22.6% 38.0% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0% Veight N 33.1% 31.5% 35.5% 00.0% = 91% 21%	Odds Ratio M.H. Random. 95% CI 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] Odds Ratio I-H. Random. 95% CI 4.38 [1.89, 10.10] 27.33 [9.91, 75.36] 1.95 [1.17, 3.25] 5.84 [1.36, 25.06]	Odds Ratio M.H. Random. 95% Cl 0.005 0.1 1 10 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed. 95% Cl 0.01 0.1 1 10 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Random. 95% Cl 0.01 0.1 1 10 100
Study or Subgroup Ana Biasco 2020 Athanasios Koutsoukis 2020 Batric Popovic 2020 Oriol Rodriguez-Leor 2020 Pooled (95% CI) Total events Heterogeneity: Tau ² = 0.51; Cf Test for overall effect: Z = 2.66 Total: total study patients D Study or Subgroup Arda Guler 2021 Fizzah A. Choudry 2020 Tuncay Kiris 2021 Pooled (95% CI) Total events Heterogeneity: Chi ² = 3.40, Test for overall effect: Z = 4 Total: total study patients E Study or Subgroup E Fizzah A. Choudry 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI) Total: vents Hizzah A. Choudry 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI) Total events Heterogeneity: Tau ² = 1.49; C Test for overall effect: Z = 2.3	Covid-1 1 1 1 1 7 7 95 6 (P = 0.006 Covid-1 Events To 21 41 36 1 98 Chi ² = 21.3 38 (P = 0.0	19 Total 5 17 91 124 if = 3 (l 62 39 65 166 = 0.18() .00001) N 839 46 65 50 6, df = 2)	Non-Covi 45 84 62 829 1020 P = 0.06); 1 Non-Cov Events 48 59 440 547 ; 1 ² = 41% 0n-Covid vents 16 30 260 306 2 (P < 0.0	d-19 Total 1 50 99 72 919 1140 2 = 59% rid-19 Total 64 76 668 808 808 5 64 76 668 808 808 5 7 7 7 7 7 7 7 7 7 7 7 7 7	weight 11.6% 27.7% 38.0% 100.0% Weight 31.3% 31.6% 37.0% 100.0% (eight) 33.1% 33.1% 33.5% 00.0% = 91%	Odds Ratio M.H. Random. 95% Cl 0.03 [0.00, 0.30] 0.26 [0.08, 0.77] 0.28 [0.07, 1.14] 0.00 [0.32, 1.10] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 0.28 [0.11, 0.71] 2.25 [0.88, 5.72] 1.58 [0.57, 4.41] 5.10 [2.17, 11.98] 3.09 [1.83, 5.23] 00dds Ratio Codds Ratio 1.48 [1.89, 10.10] 27.33 [9.91, 75.36] 1.95 [1.17, 3.25] 5.84 [1.36, 25.06]	Odds Ratio M.H. Random, 95% Cl 0.005 0.1 1 0 200 Favours [Covid-19] Favour[Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl 0.01 0.1 1 0 100 Favours [Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Random, 95% Cl 0.01 0.1 1 0 100 Favours [Covid-19] Favours [Non-Covid-19]

F							
	Covid-	-19	Non-Covi	id-19		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed. 95% Cl	M-H, Fixed, 95% Cl
Arda Guler 2021	4	62	3	64	4.4%	1.40 [0.30, 6.54]	
Athanasios Koutsoukis 2020	3	17	15	99	5.8%	1.20 [0.31, 4.69]	
Callum D Little 2020	14	46	54	302	15.8%	2.01 [1.00, 4.02]	-
Dario Pellegrini 2021	8	24	12	26	12.2%	0.58 [0.19, 1.84]	
Fizzah A. Choudry 2020	7	39	1	76	0.9%	16.41 [1.94, 138.85]	
Oriol Rodriguez-Leor 2020	40	91	308	919	49.5%	1.56 [1.01, 2.41]	
Tuncay Kiris 2021	9	65	47	668	11.4%	2.12 [0.99, 4.56]	-
Pooled (95% CI)		34	4	2154	100.0%	1.68 [1.25, 2.26]	•
Total events	85		440				
Heterogeneity: Chi ² = 8.66, df	= 6 (P = 0.	.19); l ² =	= 31%			0.01	
Test for overall effect: Z = 3.40	(P = 0.00)	07)				0.01	Favours [Covid-19] Favours [Non-Covid-19]
Total: total study patients							
G							
	Covid-	19	Non-Covi	id-19		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% Cl	M-H. Random. 95% Cl
Arda Guler 2021	13	62	6	64	10.3%	2.56 [0.91, 7.25]	
Athanasios Koutsoukis 2020	3	17	9	99	7.2%	2.14 [0.52, 8.89]	
Batric Popovic 2020	1	11	9	72	3.9%	0.70 [0.08, 6.14]	
Callum D Little 2020	26	46	117	302	14.9%	2.06 [1.10, 3.85]	
Dario Pellegrini 2021	7	24	5	26	8.0%	1.73 [0.46, 6.43]	
Fizzah A. Choudry 2020	23	39	7	76	10.6%	14.17 [5.18, 38.74]	
Oriol Rodriguez-Leor 2020	19	91	103	919	15.9%	2.09 [1.21, 3.61]	
Raffaele Marfella 2021	25	46	19	130	13.3%	6.95 [3.26, 14.83]	
Tuncay Kiris 2021	22	65	139	668	15.9%	1.95 [1.13, 3.36]	
Pooled (95% CI)		401		2356	100.0%	2.86 [1.78, 4.62]	•
Total events	139		414				
Total events Heterogeneity: Tau² = 0.30; Ch	139 1 ² = 21.43,	df = 8	414 (P = 0.006); I ² = 63	3%	+	
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31	139 ni² = 21.43, (P < 0.000	df = 8 01)	414 (P = 0.006); I² = 63	3%	+	0.005 0.1 1 10 200 Eavours[Covid-19] Eavours [Non-Covid-19]
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients	139 ai ² = 21.43, (P < 0.000	, df = 8 01)	414 (P = 0.006); I ² = 63	3%	+ 0	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19]
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect: Z = 4.31 Total: total study patients	139 ni² = 21.43, (P < 0.000	, df = 8 01)	414 (P = 0.006); I² = 63	3%	ċ	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19]
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients	139 i ² = 21.43, (P < 0.000 Covid	, df = 8 01) - 19	414 (P = 0.006 Non-Co); I ² = 63	3%	+ 0 Odds Ratio	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19]
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect: Z = 4.31 Total: total study patients	139 ii ² = 21.43, (P < 0.00) Covid <u>Events</u>	. df = 8 01) -19 	414 (P = 0.006 Non-Co); ² = 6; ovid-19 Tot	3% al Weigt	+ 0 Odds Ratio 14 <u>M-H. Fixed, 95% Cl</u>	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Güler 2021	139 ii ² = 21.43, (P < 0.000 Covid <u>Events</u> 51	, df = 8 01) -19 <u>Total</u> 62	414 (P = 0.006 Non-Co Events 57); I ² = 63 ovid-19 <u>Tota</u> 6	3% <u>al Weig</u> t 4 12.99	+ 0 Odds Ratio <u>M-H. Fixed. 95% CI</u> 6 0.57 (0.21. 1.58)	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect: Z = 4.31 Total: total study patients Study or Subgroup Arda Guler 2021 Batric Popovic 2020	139 ai ² = 21.43, (P < 0.000 Covid <u>Events</u> 51	, df = 8 01) - 19 <u>Total</u> 62 11	414 (P = 0.006 Non-Co Events 57 65); ² = 6; ovid-19 <u>Tot</u> 6 7	3% al Weigh 4 12.9% 2 10.2%	Odds Ratio <u>M.H. Fixed. 95% CI</u> 6 0.57 [0.21, 1.58] 0 13 [0.03, 0.53]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect: Z = 4.31 Total: total study patients Study or Subgroup Arda Güler 2021 Batric Popovic 2020 Callum D Little 2020	139 ai ² = 21.43, (P < 0.000 Covid <u>Events</u> 51 6 37	, df = 8 01) - 19 <u>Total</u> 62 11	414 (P = 0.006 Non-Cc Events 57 65 278); ² = 6; ovid-19 <u>Tot</u> 6 7 30	al Weigh 4 12.99 2 10.29 2 18.70	Odds Ratio M-H, Fixed, 95% Cl 0.57 [0.21, 1.58] 0.13 [0.03, 0.53] 0.35 [0.15, 0.82]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Güler 2021 Batric Popovic 2020 Callum D Little 2020 Eizzab A. Chourtor 2020	139 i ² = 21.43, (P < 0.00) Covid <u>Events</u> 51 6 37 35	. df = 8 01) - 19 <u>Total</u> 62 11 46 30	414 (P = 0.006 Non-Co Events 57 65 278 70); ² = 6; bvid-19 <u>Tot</u> 6 7 30 7	al Weigh 4 12.99 2 10.29 6 6.39	Odds Ratio M-H, Fixed, 95% Cl 0.57 [0.21, 1.58] 0.13 [0.03, 0.53] 0.35 [0.15, 0.82] 0.035 [0.20, 2.83]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriel Pachicies J. Leer 2020	139 i ² = 21.43, (P < 0.00i Covid Events 51 6 37 35 80 90 90 90 90 90 90 90 90 90 9	, df = 8 01) - 19 <u>Total</u> 62 11 46 39	414 (P = 0.006 Events 57 65 278 70 827); l ² = 6: ovid-19 <u>Tot</u> 6 7 30 7 20	al Weigh 4 12.9% 2 10.2% 2 18.7% 6 6.3% 2 17 5%	Odds Ratio M.H., Fixed, 95% Cl 6 0.57 [0.21, 1.58] 6 0.13 [0.03, 0.53] 6 0.35 [0.15, 0.82] 6 0.75 [0.20, 2.83] 6 0.07 [0.02, 1.42]	Odds Ratio
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020	139 i ² = 21.43, (P < 0.00) Covid Events 51 6 37 35 80 42	df = 8 01) - 19 <u>Total</u> 62 11 46 39 88	Non-Cc Events 57 65 278 70 837); ² = 6; ovid-19 <u>Tot</u> 6 7 30 7 90	al Weigh 4 12.99 2 10.29 2 18.79 6 6.39 3 17.59	Odds Ratio t M-H. Fixed, 95% Cl 6 0.57 [0.21, 1.58] 6 0.13 [0.03, 0.53] 6 0.35 [0.15, 0.82] 6 0.75 [0.20, 2.83] 6 0.79 [0.37, 1.70] 6 0.61 [0.12, 2.62]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed. 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H <u>Study or Subgroup</u> Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020 Raffaele Marfella 2021	139 i ² = 21.43, (P < 0.00) Covid Events 51 6 37 35 80 43 73	df = 8 01) - 19 <u>Total</u> 62 11 46 39 88 46	414 (P = 0.006 Events 57 65 278 70 837 124); I ² = 6; ovid-19 <u>Tot</u> 6 7 30 7 90 13 23	al Weigh 4 12.9° 2 10.2° 2 18.7° 6 6.3° 3 17.5° 0 5.5°	Odds Ratio M-H. Fixed. 95% Cl M-H. Fixed. 95% Cl 0.57 [0.21, 1.58] 0.13 [0.03, 0.53] 0.35 [0.15, 0.82] 0.75 [0.20, 2.83] 0.79 [0.37, 1.70] 0.69 [0.17, 2.89]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed. 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020 Raffaele Marfella 2021 Tuncay Kiris 2021	139 i ² = 21.43, (P < 0.000 Covid Events 51 6 37 35 80 43 50	df = 8 01) - 19 <u>Total</u> 62 11 46 39 88 46 65	414 (P = 0.006 Events 57 65 278 70 837 124 544); I ² = 6 ovid-19 <u>Tot</u> 6 7 30 7 90 13 66	al weigt 4 12.99 2 10.29 2 18.79 6 6.39 3 17.59 0 5.59 8 28.99	Odds Ratio M-H. Fixed, 95% Cl 6 0.57 [0.21, 1.58] 6 0.13 [0.03, 0.53] 6 0.35 [0.15, 0.82] 6 0.75 [0.20, 2.83] 6 0.79 [0.37, 1.70] 6 0.69 [0.17, 2.89] 6 0.76 [0.41, 1.40]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Güler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI)	139 i ² = 21.43, (P < 0.000 Covid <u>Events</u> 51 6 37 35 80 43 50	df = 8 01) - 19 62 11 46 39 88 46 65 35	Non-Cc Events 57 65 278 70 837 124 544); I ² = 63 ovid-19 Tot 6 7 30 7 90 13 66 221	al Weigh 4 12.99 2 18.79 6 6.39 3 17.59 8 28.99 5 100.09	Odds Ratio M-H. Fixed. 95% Cl 6 0.57 [0.21, 1.58] 6 0.57 [0.20, 2.83] 6 0.35 [0.15, 0.82] 6 0.75 [0.20, 2.83] 6 0.79 [0.37, 1.70] 6 0.69 [0.17, 2.89] 6 0.76 [0.41, 1.40] % 0.60 [0.42, 0.84]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI) Total events	139 i ² = 21.43, (P < 0.00i Events 51 6 37 35 80 43 50 302	df = 8 01) -19 62 11 46 39 88 46 65 35	414 (P = 0.006 Events 57 65 278 70 837 124 544 54 57 1975); I ² = 63 ovid-19 <u>Tota</u> 6 7 90 13 66 221	al weigt 4 12.99 2 10.29 2 18.79 6 6.39 3 17.59 0 5.59 8 28.99 5 100.09	Odds Ratio M-H. Fixed, 95% Cl 6 0.57 [0.21, 1.58] 6 0.57 [0.21, 1.58] 6 0.57 [0.20, 2.83] 6 0.75 [0.20, 2.83] 6 0.79 [0.37, 1.70] 6 0.69 [0.17, 2.89] 6 0.76 [0.41, 1.40] % 0.60 [0.42, 0.84]	Odds Ratio M-H. Fixed. 95% Cl
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI) Total events Heterogeneity: Chi ² = 7.20, d	139 iP = 21.43, (P < 0.00i Events 51 6 37 35 80 43 50 302 if = 6 (P =	df = 8 01) - 19 Total 62 11 46 39 88 46 65 35 0.30);	414 (P = 0.006 Events 57 7 124 544 54 1975 1 ² = 17%); I ² = 6 ovid-19 <u>Tota</u> 6 7 90 13 66 221	al Weigh 4 12.9 2 10.29 2 18.79 6 6.39 3 17.59 0 5.59 8 28.99 5 100.09	Odds Ratio M-H. Fixed. 95% Cl 6 0.57 [0.21, 1.58] 6 0.13 [0.03, 0.53] 6 0.35 [0.15, 0.82] 6 0.75 [0.20, 2.83] 6 0.79 [0.37, 1.70] 6 0.69 [0.17, 2.89] 6 0.76 [0.41, 1.40] % 0.60 [0.42, 0.84]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19]
Total events Heterogeneity: Tau ² = 0.30; Ch Test for overall effect; Z = 4.31 Total: total study patients H Study or Subgroup Arda Guler 2021 Batric Popovic 2020 Callum D Little 2020 Fizzah A. Choudry 2020 Oriol Rodriguez-Leor 2020 Raffaele Marfella 2021 Tuncay Kiris 2021 Pooled (95% CI) Total events Heterogeneity: Chi ² = 7.20, d Test for overall effect; Z = 2.5	139 iP = 21.43, (P < 0.000 Events 51 6 37 35 80 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 43 50 50 43 50 50 50 43 50 50 50 50 50 50 50 50 50 50 50 50 50	, df = 8 01) Total 62 11 46 39 88 46 65 38 (0.30); 003)	414 (P = 0.006) Events 57 65 278 70 837 124 54 57 1975 12 = 17%); I ² = 63 ovid-19 Tot 7 300 7 90 13 66 221	al Weigh 4 12.99 2 10.29 2 18.79 6 6.39 3 17.59 0 5.59 8 28.99 5 100.09	Odds Ratio M-H. Fixed. 95% CI 6 0.57 [0.21, 1.58] 6 0.13 [0.03, 0.53] 6 0.35 [0.15, 0.82] 6 0.75 [0.20, 2.83] 6 0.79 [0.37, 1.70] 6 0.66 [0.17, 2.89] 6 0.76 [0.41, 1.40] % 0.60 [0.42, 0.84]	0.005 0.1 1 10 200 Favours[Covid-19] Favours [Non-Covid-19] Odds Ratio M-H. Fixed, 95% Cl

thrombosis may be the result of the intense inflammatory and heightened thrombus burden observed in COVID-19 patients (18, 27, 28, 34). Consistently, the data presented here demonstrated a more aggressive use of thrombus aspiration and a Gp2b3a inhibitor in STEMI patients with concomitant SARS-CoV-2 infection. The use of a Gp2b3a inhibitor may also increase the risk of bleeding (47), but this study showed no significant difference between the two groups in terms of bleeding. Hospital-mortality was dramatically higher in STEMI patients who presented with COVID-19 than in those without COVID-19. Longer ischemia time, higher thrombus burden, and increased rate of adverse cardiovascular events, including cardiogenic shock, may also be contributory (48, 49). Current studies (50, 51) have reported that STEMI patients with concomitant COVID-19 have higher ICU admission rates and longer lengths of stay, and the results of this meta-analysis support this finding. An

А	Covi	d-19	Non-C	ovid-19		Odds Ratio		Odds Ratio
Study or Subgroup	Event	s Tota	Events	Tota	Weight	M-H. Fixed. 95% C		M-H. Fixed, 95% Cl
Arda Guler 2021	1(0 62	3	64	5.1%	3.91 [1.02, 14.97]		
Athanasios Koutsoukis 2020		7 17	. 8	9	2.9%	7 96 [2 38 26 61]		
Batric Popovic 2020		3 11	4	7	2.6%	6 38 [1 20, 33 75]		
Callum D Little 2020	10	0 46	28	30	12.0%	2 72 [1 22 6 06]		
Dario Bellegrini 2021	1/	0 24	1	20	1 2.0%	17 96 12 07 154 41		
Eizzeh A. Cheudry 2020		U 24		20	E E E E E E E E E E E E E E E E E E E	2 11 10 02 10 521		
Pizzan A. Choudry 2020	-	1 38	5	0.1	5.0%	5.11[0.92, 10.55]		
Oriol Rodriguez-Leor 2020	2	1 91	52	91	15.0%	5.00 [2.85, 8.78]		
Raffaele Marfella 2021	-	4 46	2	130	2.0%	6.10 [1.08, 34.48]		
Santiago Garcia 2021	73	3 230	18	460	0 17.0%	11.42 [6.61, 19.73]		
Thomas A. Kite 2021	33	3 144	1232	2167	5 26.0%	4.93 [3.33, 7.31]		
Tuncay Kiris 2021	18	8 65	5 43	66	3 11.4%	5.57 [2.98, 10.40]		
Pooled (95% CI)		775		24491	100.0%	5.98 [4.78, 7.48]		•
Total events	196	6	1396					
Heterogeneity: Chi ² = 13.15,	df = 10 (P	= 0.22)	; l ² = 24%	,			-+	
Test for overall effect: Z = 15	.67 (P < 0	.00001)					0.01	0.1 1 10 100
Total: total study patients		,						Favours [Covid-19] Favours [Non-Covid-19]
В	Covid	1.10	Non-Co	PL-biv		Odde Patio		Odds Patio
Study or Subgroup	Evente	Total	Evente	Tota	Weight	M H Eived 95% C		M H Eixed 85% Cl
Study of Subgroup	Events	Total	Events	Tota	weight	MI-H, FIXed, 95% C		M-H. FIXed, 95% CI
Dario Pellegrini 2021	1	24	1	26	2.6%	1.09 [0.06, 18.40]		S
Oriol Rodriguez-Leor 2020	9	91	35	919	16.3%	2.77 [1.29, 5.97]		
Raffaele Marfella 2021	3	46	3	130	4.2%	2.95 [0.57, 15.18]		
Thomas A. Kite 2021	29	144	1898	21972	56.8%	2.67 [1.77, 4.02]		
Tuncay Kiris 2021	13	65	49	668	20.0%	3.16 [1.61, 6.20]		1.0
Pooled (95% CI)		37	0	23715	100.0%	2.75 [2.02, 3.76]		•
Total events	55		1986					
Heterogeneity: Chi ² = 0.60,	df = 4 (P =	= 0.96);	$ ^2 = 0\%$				0.05	0.2 1 5 20
Test for overall effect: Z = 6.	37 (P < 0	.00001)					0.05	Eavours [Covid-19] Eavours [Non-Covid-19]
Total: total study patients								Pavous [Covid-13] Pavous [Noil-Covid-13]
-								
С						ALL BUT		OLL D.C.
	Covid	-19	Non-Co	vid-19		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% Cl		M-H. Fixed, 95% Cl
Fizzah A. Choudry 2020	4	39	1	76	19.3%	8.57 [0.92, 79.53]		
Oriol Rodriguez-Leor 2020	3	91	7	919	38.6%	4.44 [1.13, 17.48]		
Tuncay Kiris 2021	4	65	8	668	42.1%	5.41 [1.58, 18.48]		
Pooled (95% CI)		19	5	1663	100.0%	5.65 [2.41, 13.23]		-
Total events	11		16					
Heterogeneity: $Chi^2 = 0.26$	f = 2 (P =	0.88).1	2 = 0%				-+	+ + +
Test for overall effect: $7 = 3$	08 (P < 0)	0001)	- 070				0.02	0.1 1 10 50
Total: total study nationts	50 (F < 0.	0001)						Favours [Covid-19] Favours [Non-Covid-19]
Total, total study patients								
D								
	Covid-1	19 1	Non-Covi	d-19		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total I	Events	Total V	Veight	M-H. Random. 95% Cl		M-H. Random. 95% Cl
Dario Pellegrini 2021	4	24	3	26	21.9%	1.53 [0.31, 7.69]		
Oriol Rodriguez-Leor 2020	3	91	14	919	26.0%	2.20 [0.62, 7.82]		
Thomas A. Kite 2021	4	144	36	13913	28.8%	11.01 [3.87, 31.36]		
Tuncay Kiris 2021	2	65	17	668	23.3%	1.22 [0.27, 5.38]		
Pooled (95% CI)		324		15526	00 0%	2 92 10 99 9 051		
Total events	40	324	70	3320	00.070	2.02 [0.00, 9.05]		
I otal events	13		70	12 - 070			-+	++++++
Heterogeneity: Tau" = 0.95; C	mr = 9.21,	, ar = 3 (P = 0.03	1-= 679	D		0.005	0.1 1 10 200
lest for overall effect $Z = 1.7$	1/0 - 0 0	0\						
Total: total study actions	4 (P = 0.0)	8)						Favours [Covid-19] Favours [Non-Covid-19]
Total: total study patients	4 (P = 0.0	8)						Favours [Covid-19] Favours [Non-Covid-19]
Total: total study patients	4 (P = 0.0	8)						Favours [Covid-19] Favours [Non-Covid-19]
Total: total study patients	4 (P = 0.0	8)						Favours [Covid-19] Favours [Non-Covid-19]



(ICU) admission rate forest plot. (F) Length of stay forest plot (days).



increased ICU admission rate and length of stay may have a significant impact on hospital resources. Taken

together, COVID-19 status may have great implications on the characteristics, management, and outcomes of patients with STEMI.

Heterogeneity of Meta-Analysis

In a meta-analysis, heterogeneity may exist while the sample estimates for the population risk were of different magnitudes (52). The I^2 statistic means the percentage of total variation across effect size estimates that is due to heterogeneity rather than chance. In our study, there are significant and high degrees of heterogeneity for some outcomes. The existing heterogeneity can partly result from different sample sizes, study designs, study times, study scope (nation and region), diagnostic methods, the severity of the disease. We aggregate studies that are different methodologies, but the heterogeneity in the results is still inevitable.

Methodological Considerations

To our knowledge, this is the first meta-analysis that summarizes the comparison of clinical information on STEMI patients presenting with vs. those presenting without COVID-19 infection. We included multiple studies that were conducted in Asia, Europe, and North America, so that our findings can provide a broad overview of COVID-19 infection in patients with STEMI. However, our study has several limitations. First, the delay time, laboratory values, and length of stay were reported in terms of median values and IQR in many studies, which have been adjusted to means and SDs using the Box-Cox method. Nevertheless, using this method to calculate SDs may entail inaccuracy and make the SDs greater than the mean in some cases, which is an inherent feature of the method (17). Second, the disparity in study size may affect the weighting of the



studies and the pooled effect size, which is innate to metaanalyses (53, 54). Third, a high degree of heterogeneity was observed in some outcomes. Due to inadequate information for the included studies, it is difficult to conduct a subgroup analysis to explain the heterogeneity. We performed a sensitivity analysis to assess the reliability of our findings and used the randomeffects model when I^2 statistics were more than 50%. Fourth, we were unable to compare the rate of thrombosis and elective PCI, and the revascularization rate of patients undergoing primary angioplasty between the two groups due to a lack of sufficient data. Future studies are needed to further investigate these outcomes. Finally, our data were limited to in-hospital outcomes. Long-term follow-up is required to explore the association between SARS-CoV-2 infection and poor outcomes in patients with STEMI.

CONCLUSION

In patients with STEMI, COVID-19 has had a deep impact on their therapeutic management and clinical outcomes. A longer time from SO-to-FMC and D2B was observed in STEMI patients with COVID-19 in our study. Moreover, patients with STEMI who also had COVID-19 had more severe thrombotic events adverse outcomes. Further studies are required to explore the mechanism of coronary thrombus burden and the optimal treatment for patients with STEMI and COVID-19.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YW, LK, C-WC, SX, and T-HT: conception. YW, LK, C-WC, JX, PY, SX, and T-HT: methodology. YW, LK, JX, PY, and T-HT: analysis. YW, LK, JX, and PY: interpretation and writing. C-WC, SX, and T-HT: supervision. All authors have read and agreed to the published version of the manuscript.







funnel plot. (F) Length of stay funnel plot.

TABLE 4 | Leave-one-out analysis.

Study name	Statistics with study excluded							
	Odds ratio or SMD	95% CI	P-value					
D2B time								
Güler et al. (30)	12.66	2.96 to 22.35	0.01					
Popovic et al. (18)	13.06	7.13 to 18.99	<0.0001					
Little et al. (24)	12.01	4.16 to 19.86	0.003					
Choudry et al. (28)	12.52	4.35 to 20.68	0.003					
Marfella et al. (25)	13.1	4.66 to 21.54	0.002					
Garcia et al. (22)	9.92	4.47 to 15.35	0.0004					
Kite et al. (23)	12.15	6.47 to 17.82	<0.0001					
CRP								
Blasco et al. (29)	0.82	0.43 to 1.21	<0.0001					
Güler et al. (30)	0.83	0.40 to 1.26	0.0002					
Koutsoukis et al. (21)	0.59	0.29 to 0.90	0.0001					
Popovic et al. (18)	0.67	0.28 to 1.06	0.0007					
Little et al. (24)	0.8	0.33 to 1.26	0.0007					
Choudry et al. (28)	0.86	0.45 to 1.26	<0.0001					
Kiris et al. (20)	0.73	0.27 to 1.20	0.002					
WBC								
Blasco et al. (29)	0.35	0.04 to 0.67	0.03					
Güler et al. (30)	0.5	0.25 to 0.76	<0.0001					
Choudry et al. (28)	0.42	0.04 to 0.81	0.03					
Marfella et al. (25)	0.26	0.08 to 0.44	0.004					
Kiris et al. (20)	0.038	0.18 to 0.59	0.0002					
D-Dimer								
Güler et al. (30)	0.89	0.01 to 1.78	0.05					
Popovic et al. (18)	0.62	0.35 to 0.88	<0.0001					
Choudry et al. (28)	1.00	0.38 to 1.62	0.002					
Primary Angioplasty								
Koutsoukis et al. (21)	0.27	0.05 to 1.43	0.12					
Popovic et al. (18)	0.28	0.07 to 1.15	0.08					
Pellegrini et al. (26)	0.31	0.01 to 1.24	0.10					
Choudry et al. (28)	0.23	0.06 to 0.94	0.04					
Rodriguez-Leor et al. (27)	0.12	0.08 to 0.17	<0.0001					
Garcia et al. (22)	0.36	0.09 to 1.49	0.16					
Kiris et al. (20)	0.21	0.16 to 0.29	<0.0001					
MINOCA								
Koutsoukis et al. (21)	7.63	1.44 to 40.43	0.02					
Popovic et al. (18)	8.49	1.37 to 52.74	0.02					
Pellegrini et al. (26)	9.81	1.84 to 52.38	0.01					
			(0					

TABLE 4 | Continued

Study name	Statistics with study excluded							
	Odds ratio or SMD	95% CI	P-value					
Rodriguez-Leor (27)	18.62	8.73 to 39.72	<0.0001					
Garcia et al. (22)	7.56	1.38 to 41.37	0.02					
Stent Implantation								
Blasco et al. (29)	0.46	0.28 to 0.75	0.002					
Koutsoukis et al. (21)	0.25	0.06 to 1.01	0.05					
Popovic et al. (18)	0.25	0.07 to 0.90	0.03					
Rodriguez-Leor et al. (27)	0.20	0.09 to 0.43	<0.0001					
Modified Thrombus Grade								
Choudry et al. (28)	7.03	0.52 to 96.03	0.14					
Marfella et al. (25)	2.72	1.25 to 5.94	0.01					
Kiris et al. (20)	10.69	1.75 to 65.11	0.01					
Gp2b3a inhibitor use								
Güler et al. (30)	2.90	1.70 to 4.93	<0.0001					
Koutsoukis et al. (21)	2.93	1.75 to 4.90	<0.0001					
Popovic et al. (18)	3.03	1.87 to 4.93	<0.0001					
Little et al. (24)	3.02	1.72 to 5.30	0.0001					
Pellegrini et al. (26)	2.99	1.79 to 5.01	<0.0001					
Choudry et al. (28)	2.37	1.81 to 3.11	<0.0001					
Rodriguez-Leor et al. (27)	2.93	2.19 to 3.92	<0.0001					
Marfella et al. (25)	2.41	1.83 to 3.17	< 0.0001					
Kiris et al. (20)	3.01	2.25 to 4.03	<0.0001					
Bleeding								
Pellegrini et al. (26)	3.30	0.77 to 14.07	0.11					
Rodriguez-Leor et al. (27)	2.95	0.55 to 15.73	0.21					
Kite et al. (23)	1.62	0.71 to 3.73	0.25					
Kiris et al. (20)	3.62	0.92 to 14.23	0.07					
Length of Stay								
Güler et al. (30)	5.11	2.17 to 8.06	0.0007					
Little et al. (24)	4.84	2.41 to 7.27	< 0.0001					
Marfella et al. (25)	5.42	3.24 to 7.26	< 0.0001					
Garcia et al. (22)	3.56	1.85 to 5.27	< 0.0001					
Kite et al. (23)	4.41	2.14 to 6.69	0.0001					

(Continued)

REFERENCES

Wang et al.

- 1. Mahmud E, Dauerman HL, Welt FGP, Messenger JC, Rao SV, Grines C, et al. Management of Acute myocardial infarction during the COVID-19 pandemic: a position statement from the society for cardiovascular angiography and interventions (SCAI), the American college of cardiology (acc), and the American college of emergency physicians (ACEP). J Am Coll Cardiol. (2020) 76:1375–84. doi: 10.1016/j.jacc.2020.04.039
- Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet.* (2017) 389:197–210. doi: 10.1016/S0140-6736(16)30677-8
- Gulati A, Pomeranz C, Qamar Z, Thomas S, Frisch D, George G, et al. A comprehensive review of manifestations of novel coronaviruses in the context of deadly COVID-19 global pandemic. *Am J Med Sci.* (2020) 360:5– 34. doi: 10.1016/j.amjms.2020.05.006
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019. Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama*. (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
- Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* (2020) 26:1017– 32. doi: 10.1038/s41591-020-0968-3
- Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview. *Clin Imaging.* (2020) 66:35–41. doi: 10.1016/j.clinimag.2020.05.013
- Choudhury T, West NE, El-Omar M. ST elevation myocardial infarction. *Clin Med* (Lond). (2016) 16:277–82. doi: 10.7861/clinmedicine.16-3-277
- Gale CP, Allan V, Cattle BA, Hall AS, West RM, Timmis A, et al. Trends in hospital treatments, including revascularisation, following acute myocardial infarction, 2003-2010: a multilevel and relative survival analysis for the National Institute for Cardiovascular Outcomes Research (NICOR). *Heart.* (2014) 100:582–9. doi: 10.1136/heartjnl-2013-304517
- Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J.* (2016) 37:3232–45. doi: 10.1093/eurheartj/ehw334
- Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol. (2014) 64:2101–8. doi: 10.1016/j.jacc.2014.08.037
- Baumhardt M, Dreyhaupt J, Winsauer C, Stuhler L, Thiessen K, Stephan T, et al. The effect of the lockdown on patients with myocardial infarction during the COVID-19 pandemic. *Dtsch Arztebl Int.* (2021) 118:447– 53. doi: 10.3238/arztebl.m2021.0253
- Xiang D, Xiang X, Zhang W, Yi S, Zhang J, Gu X, et al. Management and outcomes of patients with STEMI during the COVID-19 pandemic in China. *J Am Coll Cardiol.* (2020) 76:1318–24. doi: 10.1016/j.jacc.2020.06.039
- Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. (2020) 75:2950–73. doi: 10.1016/j.jacc.2020.04.031
- Pérez-Bermejo JA, Kang S, Rockwood SJ, Simoneau CR, Joy DA, Ramadoss GN, et al. SARS-CoV-2 infection of human iPSC-derived cardiac cells predicts novel cytopathic features in hearts of COVID-19 patients. *bioRxiv*. (2020) doi: 10.1101/2020.08.25.265561
- Hayek SS, Brenner SK, Azam TU, Shadid HR, Anderson E, Berlin H, et al. In-hospital cardiac arrest in critically ill patients with covid-19: multicenter cohort study. *Bmj.* (2020) 371:m3513. doi: 10.1136/bmj.m3513
- Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease (2019). (COVID-19) with myocardial injury and mortality. *JAMA Cardiol.* (2020) 5:751–3. doi: 10.1001/jamacardio.2020.1105
- McGrath S, Zhao XF, Steele R, Thombs BD, Benedetti A, Levis B, et al. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Statistic Methods Med Res.* (2020) 29:2520– 37. doi: 10.1177/0962280219889080
- Popovic B, Varlot J, Metzdorf PA, Jeulin H, Goehringer F, Camenzind E. Changes in characteristics and management among patients with ST-elevation myocardial infarction due to COVID-19 infection. *Catheter Cardiovasc Interv.* (2021) 97:E319–e26. doi: 10.1002/ccd.29114
- Siudak Z, Grygier M, Wojakowski W, Malinowski KP, Witkowski A, Gasior M, et al. Clinical and procedural characteristics of COVID-19 patients treated

with percutaneous coronary interventions. *Catheter Cardiovasc Interv.* (2020) 96:E568–e75. doi: 10.1002/ccd.29134

- Kiris T, Avci E, Ekin T, Akgün DE, Tiryaki M, Yidirim A, et al. Impact of COVID-19 outbreak on patients with ST-segment elevation myocardial infarction (STEMI) in Turkey: results from TURSER study (TURKISH Stsegment elevation myocardial infarction registry). *J Thromb Thrombolysis*. (2021) 2021:1–14. doi: 10.1007/s11239-021-02487-3
- Koutsoukis A, Delmas C, Roubille F, Bonello L, Schurtz G, Manzo-Silberman S, et al. Acute coronary syndrome in the era of sars-cov-2 infection: a registry of the french group of acute cardiac care. *CJC Open.* (2021) 3:311– 7. doi: 10.1016/j.cjco.2020.11.003
- 22. Garcia S, Dehghani P, Grines C, Davidson L, Nayak KR, Saw J, et al. Initial findings from the North American COVID-19 myocardial infarction registry. *J Am Coll Cardiol.* (2021) 77:1994–2003. doi: 10.1016/j.jacc.2021.02.055
- Kite TA, Ludman PF, Gale CP, Wu J, Caixeta A, Mansourati J, et al. International prospective registry of acute coronary syndromes in patients with COVID-19. J Am Coll Cardiol. (2021) 77:2466–76. doi: 10.1016/j.jacc.2021.03.309
- 24. Little CD, Kotecha T, Candilio L, Jabbour RJ, Collins GB, Ahmed A, et al. COVID-19 pandemic and STEMI: pathway activation and outcomes from the pan-London heart attack group. *Open Heart.* (2020) 7:2. doi: 10.1136/openhrt-2020-001432
- 25. Marfella R, Paolisso P, Sardu C, Palomba L, D'Onofrio N, Cesaro A, et al. SARS-COV-2 colonizes coronary thrombus and impairs heart microcirculation bed in asymptomatic SARS-CoV-2 positive subjects with acute myocardial infarction. *Crit Care.* (2021) 25:217. doi: 10.1186/s13054-021-03643-0
- 26. Pellegrini D, Fiocca L, Pescetelli I, Canova P, Vassileva A, Faggi L, et al. Effect of respiratory impairment on the outcomes of primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction and coronavirus disease-2019 (COVID-19). *Circ J*. (2021) 85:1701– 7. doi: 10.1253/circj.CJ-20-1166
- Rodriguez-Leor O, Cid Alvarez AB, Pérez de Prado A, Rossello X, Ojeda S, Serrador A, et al. In-hospital outcomes of COVID-19 STelevation myocardial infarction patients. *EuroIntervention*. (2021) 16:1426– 33. doi: 10.4244/EIJ-D-20-00935
- Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, et al. High thrombus burden in patients with COVID-19 presenting with st-segment elevation myocardial infarction. J Am Coll Cardiol. (2020) 76:1168–76. doi: 10.1016/j.jacc.2020.07.022
- Blasco A, Coronado MJ, Hernández-Terciado F, Martín P, Royuela A, Ramil E, et al. Assessment of neutrophil extracellular traps in coronary thrombus of a case series of patients with COVID-19 and myocardial infarction. *JAMA Cardiol.* (2020) 6:1–6. doi: 10.1001/jamacardio.2020.7308
- Güler A, Gürbak I, Panç C, Güner A, Ertürk M. Frequency and predictors of no-reflow phenomenon in patients with COVID-19 presenting with ST-segment elevation myocardial infarction. *Acta Cardiol.* (2021) 2021:1– 9. doi: 10.1080/00015385.2021.1931638
- Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation*. (2001) 103:2550–4. doi: 10.1161/01.CIR.103.21.2550
- 32. Sianos G, Papafakli MI, Daemen J, Vaina S, van Mieghem CA, van Domburg RT, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol. (2007) 50:573– 83. doi: 10.1016/j.jacc.2007.04.059
- 33. Ferlini M, Andreassi A, Carugo S, Cuccia C, Bianchini B, Castiglioni B, et al. Centralization of the ST elevation myocardial infarction care network in the Lombardy region during the COVID-19 outbreak. *Int J Cardiol.* (2020) 312:24–6. doi: 10.1016/j.ijcard.2020.04.062
- 34. Tam CF, Cheung KS, Lam S, Wong A, Yung A, Sze M, et al. Impact of coronavirus disease (COVID-19) outbreak on st-segment-elevation myocardial infarction care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes.* (2020) 13:e006631. doi: 10.1161/CIRCOUTCOMES.120.006631
- 35. Carugo S, Ferlini M, Castini D, Andreassi A, Guagliumi G, Metra M, et al. Management of acute coronary syndromes during the COVID-19 outbreak

in Lombardy: The "macro-hub" experience. Int J Cardiol Heart Vasc. (2020) 31:100662. doi: 10.1016/j.ijcha.2020.100662

- 36. Han Y, Zeng H, Jiang H, Yang Y, Yuan Z, Cheng X, et al. CSC Expert consensus on principles of clinical management of patients with severe emergent cardiovascular diseases during the COVID-19 epidemic. *Circulation.* (2020) 141:e810–e6. doi: 10.1161/CIRCULATIONAHA.120.047011
- 37. Wood DA, Sathananthan J, Gin K, Mansour S, Ly HQ, Quraishi AU, et al. Precautions and procedures for coronary and structural cardiac interventions during the COVID-19 pandemic: guidance from canadian association of interventional cardiology. *Can J Cardiol.* (2020) 36:780–3. doi: 10.1016/j.cjca.2020.03.027
- Rashid M, Wu J, Timmis A, Curzen N, Clarke S, Zaman A, et al. Outcomes of COVID-19-positive acute coronary syndrome patients: a multisource electronic healthcare records study from England. *J Intern Med.* (2021) 290:88–100. doi: 10.1111/joim.13246
- Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol.* (2020) 95:E131–e4. doi: 10.1002/ajh.25774
- Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013
- Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
- 42. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* (2020) 46:846–8. doi: 10.1007/s00134-020-05991-x
- 43. Masi P, Hékimian G, Lejeune M, Chommeloux J, Desnos C, Pineton De Chambrun M, et al. Systemic inflammatory response syndrome is a major contributor to COVID-19-associated coagulopathy: insights from a prospective, single-center cohort study. *Circulation.* (2020) 142:611–4. doi: 10.1161/CIRCULATIONAHA.120.048925
- 44. Duman H, Çetin M, Durakoglugil ME, Degirmenci H, Hamur H, Bostan M, et al. Relation of angiographic thrombus burden with severity of coronary artery disease in patients with ST segment elevation myocardial infarction. *Med Sci Monit.* (2015) 21:3540–6. doi: 10.12659/MSM.895157
- Ge J, Li J, Dong B, Ning X, Hou B. Determinants of angiographic thrombus burden and impact of thrombus aspiration on outcome in young patients with ST-segment elevation myocardial infarction. *Catheter Cardiovasc Interv.* (2019) 93:E269–e76. doi: 10.1002/ccd.27944
- 46. Karagiannidis E, Papazoglou AS, Sofidis G, Chatzinikolaou E, Keklikoglou K, Panteris E, et al. Micro-CT-Based quantification of extracted thrombus burden characteristics and association with angiographic outcomes in patients with ST-elevation myocardial infarction: the QUEST-STEMI study. *Front Cardiovasc Med.* (2021) 8:646064. doi: 10.3389/fcvm.2021.646064
- Elian D, Guetta V. Glycoprotein 2b3a inhibitors for acute coronary syndromes: what the trials tell us. *Harefuah*. (2003) 142:350–498.

- 48. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. *Eur Heart J.* (2018) 39:1065–74. doi: 10.1093/eurheartj/ehy004
- Singh M, Berger PB, Ting HH, Rihal CS, Wilson SH, Lennon RJ, et al. Influence of coronary thrombus on outcome of percutaneous coronary angioplasty in the current era (the Mayo Clinic experience). *Am J Cardiol.* (2001) 88:1091–6. doi: 10.1016/S0002-9149(01)0 2040-9
- Solano-López J, Zamorano JL, Pardo Sanz A, Amat-Santos I, Sarnago F, Gutiérrez Ibañes E, et al. Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak. *Rev Esp Cardiol (Engl Ed).* (2020) 73:985–93. doi: 10.1016/j.recesp.2020. 07.023
- Matsushita K, Hess S, Marchandot B, Sato C, Truong DP, Kim NT, et al. Clinical features of patients with acute coronary syndrome during the COVID-19 pandemic. J Thromb Thrombolysis. (2021) 52:95–104. doi: 10.1007/s11239-020-02340-z
- 52. Sedgwick P. Meta-analyses: what is heterogeneity? *Bmj-Br Med J.* (2015) 15:350. doi: 10.1136/bmj.h1435
- Rattka M, Dreyhaupt J, Winsauer C, Stuhler L, Baumhardt M, Thiessen K, et al. Effect of the COVID-19 pandemic on mortality of patients with STEMI: a systematic review and meta-analysis. *Heart.* (2020) 20:360. doi: 10.1136/heartjnl-2020-318360
- Kamarullah W, Sabrina AP, Rocky MA, Gozali DR. Investigating the implications of COVID-19 outbreak on systems of care and outcomes of STEMI patients: a systematic review and meta-analysis. *Indian Heart J.* (2021) 73:404–12. doi: 10.1016/j.ihj.2021.06.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Kang, Chien, Xu, You, Xing and Tung. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.