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Review Article

Outcomes of STEMI Patients in COVID-19 Pandemic: A Systematic Review and Meta-Analysis

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Abstract

Background: The global SARS-CoV-2 pandemic has disrupted health systems and put a huge strain on hospitals and healthcare workers. Prioritizing COVID-19 patients in hospitals caused irreversible harm to cardiac patients. Although multiple studies have shown that ST-segment elevation myocardial infarction (STEMI) patients have worse admission circumstances than before the pandemic, the hospital outcomes of these patients have remained limited. This systematic review and meta-analysis examined STEMI patient outcomes during the COVID-19 epidemic.

Methods: We conducted systematic searches of MEDLINE (through PubMed), Web of Science, Scopus, and Embase through Jan 10, 2021. All studies with reporting in-hospital mortality, length of stay, and door-to-balloon time with over twenty participants were included. Articles without clear definitions or results were excluded. The study followed PRISMA guidelines. The outcomes of interest were door-to-balloon time, death, and hospital stay during COVID-19 pandemic compared prior.

Results: Our meta-analysis included 12 studies and 21170 people (115-6609). The pooled analysis showed significantly more pandemic mortality (OR=1.24; 95% CI: 1.07-1.43). Ten studies (13,091) recorded door-to-balloon times. Door-to-balloon time (in minutes) significantly increased during the pandemic (Standardized Mean Difference [SMD]= 0.46; 95% CI: 0.03-0.89). The length of hospital stay was reported by five studies (n=9448). Length of hospital stay (in days) was not significantly longer during the pandemic than before the outbreak (SMD= 0.04; 95% CI: -0.19-0.26).

Conclusion: The COVID-19 pandemic is associated with increased mortality and door-to-balloon delay that might be attributable to the strict infection control measures in outbreak. Studies with a longer follow-up time are needed to investigate the outcomes of STEMI patients.

Keywords: COVID-19; ST elevation myocardial infarction; Door to balloon; Mortality

Introduction

The viral outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected many countries in every corner of the globe, causing health system disruption and an incredibly massive strain on hospitals and healthcare staff (1-3). The healthcare providers adopted prudent strategies and measurements, such as the deferral of unnecessary procedures and calling off any routine checkups (4), to lower the chance of COVID-19 transmission as less as possible and specified a significant part of their capacity, resources, and facilities to provide appropriate care for the massive numbers of patients with COVID-19 infection (4, 5). While the pandemic itself had caused high morbidity and mortality, prioritizing COVID-19 care-seekers in hospitals resulted in irreparable collateral damage in cardiac patients, especially those in need of medical attention and interventional procedures (6). A significant proportion of deaths detected in the first wave of the outbreak could not be explained; COVID-19 might not be accused for all deaths during that hard time, and cardiac-related deaths might be the possible reason (7).

Recently, the importance of cardiac collateral damage has raised investigators' attention(8). A retrospective study from Austria reported a 1.7-fold rise in ischemic time during the pandemic. The most probable cause was patient-related delays like avoiding seeking medical care due to the fear of getting infected or iatrophobia (8, 9). The strict rules of quarantine and stay-at-home regulations are also thought to be responsible for delayed longer durations from cardiac symptoms initiation till presenting at the hospital (10, 11). A report from northern Italy revealed a substantial decline in the rates of acute coronary syndrome (ACS) hospital admissions in the very early period of the coronavirus disease 2019 (COVID-19) pandemic (7).

Furthermore, another multicenter study suggested that ST-segment elevation myocardial infarction (STEMI) case fatality rates had a threefold increase along with the notably elevated rates of complications during the pandemic (12). A striking decrease in the hospitalization of patients with coronary artery diseases, especially STEMI cases, was reported during the outbreak compared to before this global pandemic (13, 14). A 43% reduction in STEMI admissions was observed during the COVID-19 outbreak compared with the previous period (15). In addition, during the early times of the pandemic period, the longer door-to-balloon time has been revealed (16).

Despite the negative trend in the number of patients admitted with STEMI, the in-hospital mortality rates and the duration from symptom onset to first medical contact surged significantly during the COVID-19 outbreak (17). The current optimal treatment of STEMI patients is the primary percutaneous coronary intervention (PCI). This high-risk procedure may threaten the medical staff's health and risk transmission. On the other side, taking the infection control measurements might also cause a delay in the treatment process. This condition resulted in different approaches among countries where the health care system tends to preserve a logical balance between optimal STEMI care and community health. The rates of detainment in PCI treatment differ across the countries (18).

Although there are several studies regarding the worse conditions at the time of admission among STEMI patients compared to the patients before the pandemic, the specific and apparent Effect on STEMI-related mortality rates has not been much assessed, and the evidence regarding the hospital outcomes of these patients has remained limited (8). Therefore, this systematic review and meta-analysis aimed to address the outcomes of STEMI patients during the COVID-19 pandemic.

Methods

Search strategy

This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards (19). Up to Jan 10th, 2021, we thoroughly searched MEDLINE (via PubMed), Web of Science, Scopus, and Embase. We looked up references in the included research, the reference lists of review papers, and Google Scholar to cover grey literature. Keywords included ST Elevation Myocardial Infarction (STEMI), COVID-19, SARS-CoV-2, SARS virus, coronavirus infection, hospitalization, length of stay, hospital mortality, and door-to-balloon time. Our search was restricted to the English language.

Eligibility criteria

Cohort, case-control, and cross-sectional studies were eligible for inclusion. Case reports, animal studies, letters, and review papers were not included. Only the research with a bigger sample size and more illuminating data was considered when numerous publications from the same population were published. We included all studies with a sample size of over twenty, containing necessary data about the following variables: in-hospital mortality, length of stay, and door-to-balloon time. Every article with no clear definition or report of the aforementioned outcomes was excluded. The following are the applicable definitions for results: Patients with symptoms of ACS with a considerable ST-T segment deviation were considered to have STEMI (V1-V4) (20). In-hospital mortality was defined as any cause of death during the index hospitalization. The definition of hospital length of stay was the number of days between admission and discharge from an inpatient care institution. Door-to-balloon time is from arrival at a PCI-capable hospital to balloon inflation (21). Two authors independently reviewed each record's title and abstract before retrieving and examining any possibly relevant full-text papers. The discrepancy was resolved by inviting a third researcher.

Selection process

Two researchers (SK and MSF) thoroughly reviewed all of the results of the systematic literature search. Each item was first filtered using the titles and abstracts. In the second stage, the entire texts of potentially admissible recordings were further evaluated. In the end, recordings that did not meet the predetermined eligibility criteria were rejected. Disagreements were addressed by agreement among all writers and through group discussion.

Data extraction

Two researchers extracted the data and filled out the predetermined forms separately. Data included the first author's name, publication year, study design, sex, age, the total number of populations, in-hospital mortality before the COVID-19 period (control group), in-hospital mortality in the COVID-19 period, a door-to-balloon time before COVID-19 period, door to balloon in COVID era, duration of hospitalization before COVID-19 period, duration of hospitalization in COVID era and study location. All writers came to a compromise to settle the conflict.

Quality assessment and Critical appraisal

Quality assessment of articles was performed using the National Institutes of Health (NIH) Quality Assessment Tool for observational cohort and cross-sectional studies. The possibility of bias was evaluated by two separate researchers, who also agreed on the evidence and any areas of dispute. Each article received a score to show the level of bias (Good bias studies included, fair and poor bias studies excluded). The mean NIH score for cohorts, cross-sectional, and case controls was 6.25, 6, and 6, respectively. The records' quality and bias risk were evaluated (studies with an overall score > 5 points were considered as good quality) (22). All records included in the meta-analysis had NIH scores > 5. Thirty studies with an overall score of equal or less than 5 points were excluded (Fig. 1). Discrepancies in quality assessments were resolved through discussion with a third researcher.

Data synthesis

The included studies for quantitative synthesis were pooled into three sections. 1) In the first section, twelve studies were evaluated. The odds of mortality of STEMI patients were compared

between patients referred during the COVID-19 pandemic and patients presented before the COVID-19 pandemic, and the odds ratio of mortality was calculated. 2) In the second section, the pooled standardized mean time of door-to-balloon before and during the pandemic is reported in ten studies.
3) In the third section, the pooled standardized mean time of hospital stay before and during the pandemic is reported in five studies.

Statistical analysis

Quantitative synthesis was planned. All statistical analyses were performed using R version 4.2.1, implementing the R package 'meta' version 5.2-0 (23), using the Mantel-Haenszel method for binary endpoints and the inverse variance method for continuous endpoints (24, 25). For part one, the 'metabin' function was used to pool the binary data on the incidence of mortality. The odds ratio (OR), with the corresponding 95% confidence intervals (CIs), was opted as the measure of Effect. Parts two and three used the 'meta cont' function to measure the standardized mean differences (SMDs) with related 95% CIs. In the included studies where the median and interquartile range [IQR] were reported, the mean and standard deviation [SD] were calculated using the Box-Cox method (26). Continuity will be addressed by replacing zero events with 0.5. Inter-study heterogeneity was determined using Cochran's Q and Higgin's I^2 tests (27, 28). When heterogeneity was considerable ($I^2 > 50\%$), random-effect models were used to combine the estimates; otherwise, fixed-effect models were employed. We did a sensitivity analysis using the Leave-One-Out method to identify the source of heterogeneity. (Supplementary Fig. 1) (Not published).
Publication bias was assessed visually by funnel plots. A two-tailed *P*-value<0.05 was considered statistically significant.
Ethics Committee of Rajaie Cardiovascular, Medical and Research Center approved the study (The ethical code is IR.RHC.REC.1401.018).

Results

Summary of the included studies

According to the planned search strategy, 409 studies were retrieved from four distinct search databases, of which 6 were obtained by hand search. Fig. 1 provides a summary of the database search procedure. In the end, 12 studies with 21170 individuals (range: 115-6609) were analyzed in our meta-analysis (29-40) (Table 1).

Mortality

Twelve studies (29-40) reported in-hospital mortality following primary PCI (n= 20,767). The pooled analysis showed significantly higher mortality during the pandemic than before it (OR= 1.24; 95% CI: 1.07-1.43; Fig. 2). Publication bias is represented in supplementary Fig. 2 through a funnel plot. For the comparison of in-hospital mortality, I^2 was equal to 39%. Thus, we employed a fixed effect model.

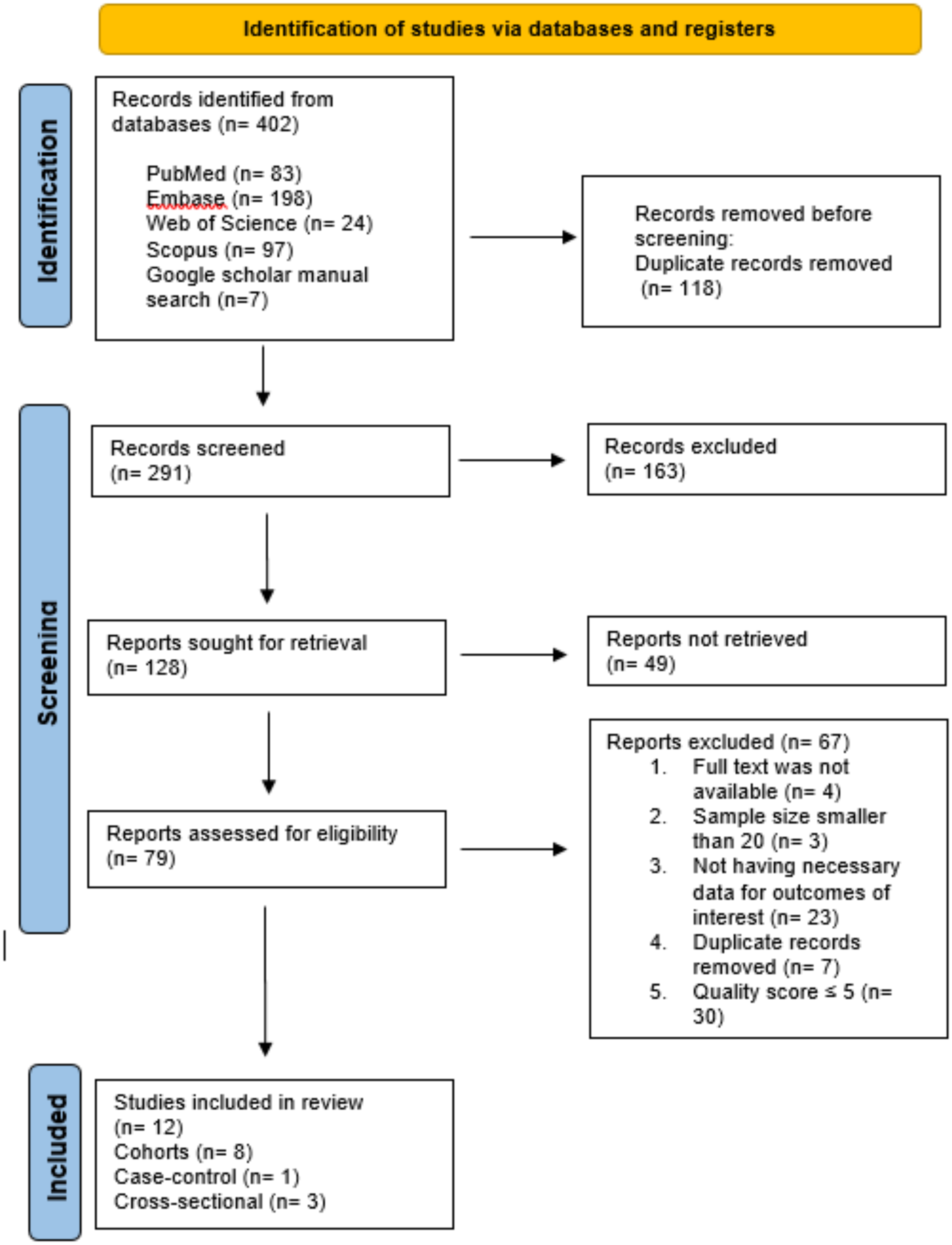

Fig. 1: Flow chart of study selection

Table 1: Summary of the included studies

Ref. No.	No. of patients		Sex, female		Age, years		In-hospital mortality(%)		Door to balloon time		Length of stay	
	Pandemic period	Non-pandemic period	Pandemic period	Non-pandemic period	Pandemic period	Non-pandemic period	Pandemic period	Non-pandemic period	Pandemic period	Non-pandemic period	Pandemic period	Non-pandemic period
29	56	69	16	14	66.6±11.9*	63.2±11.1*	1.4	0	48 (39-70) ᵻ	47(38-63) ᵻ	NR	NR
30	95	208	74	41	57 (49-64) ᵻ	59 (48-69) ᵻ	7.8	6.3	52 (39-74) ᵻ	55 (39-74) ᵻ	4 (4-5) ᵻ	4 (4-6) ᵻ
31	90	174	25	17	63.7±13.3*	59.3±13.4*	3.4	6.7	26.4 (11-40) ᵻ	54.6 (9-55) ᵻ	NR	NR
32	2811	3484	917	716	64 (55-73) ᵻ	64 (55-73) ᵻ	4.8	6.8	34 (21-36) ᵻ	36 (24-60) ᵻ	NR	NR
33	485	710	159	98	60 (51-70) ᵻ	58 (49-66) ᵻ	5.3	4.7	37 (25-65) ᵻ	40 (25-68) ᵻ	NR	NR
34	284	4320	1207	73	66±13*	64±12*	7.8	8	NR	NR	55 (42-96) ᵻ h	53 (43-100) ᵻ h
35	187	3411	820	44	63.3±12.6*	61.1±11.9*	5	5.3	66 (49-85) ᵻ	65 (52-96) ᵻ	6.23±11.92*	3.72±2.29*
36	107	136	25	17	61 (51-68) ᵻ	63 (52-70) ᵻ	5.1	8.4	49 (31-75) ᵻ	56 (30-89) ᵻ	4 (3-6) ᵻ	5 (4-6) ᵻ
37	348	440	97	70	63 (55-73) ᵻ	63 (55–71) ᵻ	8.6	11	48 (35-70) ᵻ	48 (34-65) ᵻ	3 (2-5) ᵻ	3 (2-4) ᵻ
38	1535	1536	350	332	52.72±13.8*	55.98±12.05*	3.1	4.1	NR	NR	NR	NR
39	52	158	58	20	66.5 (57-76) ᵻ	71.5 (56.75-77.75) ᵻ	15.3	2.5	50 (42.75-64.25) ᵻ	77 (70-86.5) ᵻ	NR	NR
40	73	95	27	14	60.6±13.9*	61.6±13.1*	2.7	2.1	106 (80-138) ᵻ	122.5 (78.5-187.5) ᵻ	NR	NR

NR: not reported *Data are represented as mean± standard deviation ᵻ Data are represented as median (interquartile range)

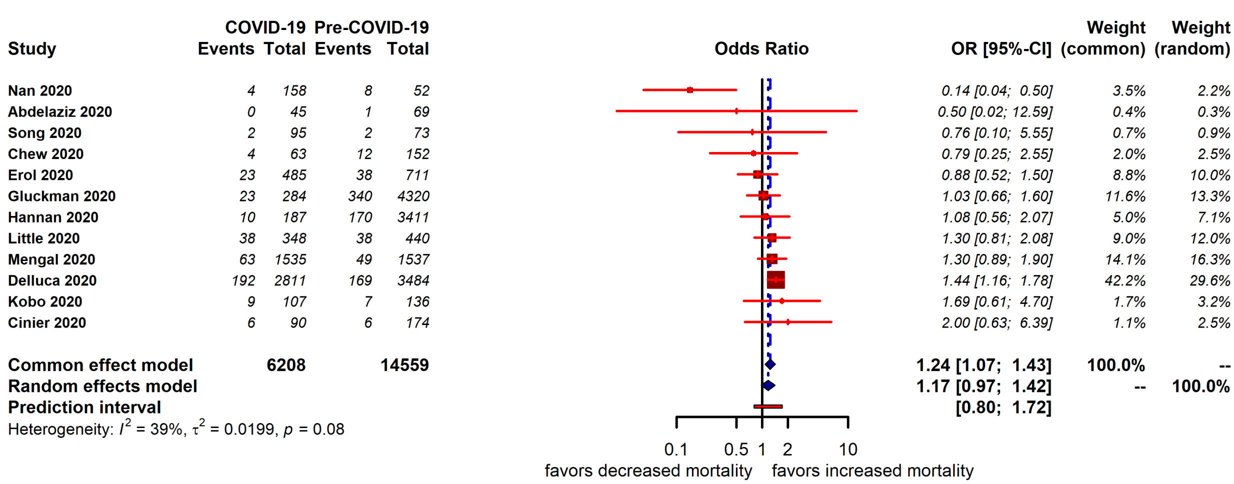

Fig. 2: Forest plot representing mortality odds ratio before COVID-19 pandemic versus during COVID-19 pandemic

Door to Balloon time

Door-to-balloon times were reported by ten studies (n= 13,091). Door-to-balloon time (in minutes) was longer during the pandemic than prior to it (SMD= 0.46; 95% CI: 0.03-0.89; Fig. 3). Supplementary Fig. 3 represents publication bias using a funnel plot. We employed a random-effect model since the entire door-to-balloon time comparison exhibited substantial variability (I^2=98%). In addition, a subgroup analysis based on region was performed to investigate the sources of heterogeneity.

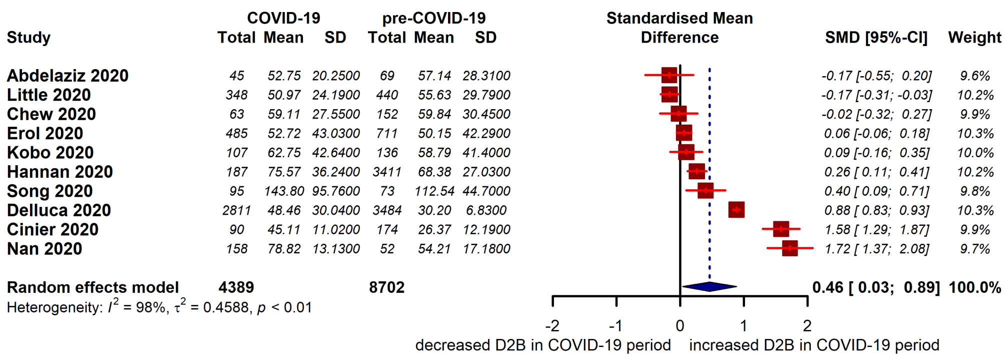

Fig. 3: Forest plot representing estimates of Standardized Mean Difference (SMD) of door-to-balloon time before versus during COVID-19 pandemic

Door-to-balloon time based on region

Subgroup analysis of door-to-balloon times were performed based on the continents of the studies in Fig. 4. Door-to-balloon time in the Europe region was SMD=0.19; 95% CI: -0.51-0.89, this outcome for Asian studies and the only study from North America was SMD=0.63; 95% CI= -0.00- 1.27 and SMD=0.26; 95% CI= -0.11- 0.41, respectively, which has been longer in European region than in other continents. We employed a random-effect model for all regions since the entire door-to-balloon time comparison showed considerable variability (I^2 for Europe, Asia, and North America were 99%, 97%, and 98%, respectively).

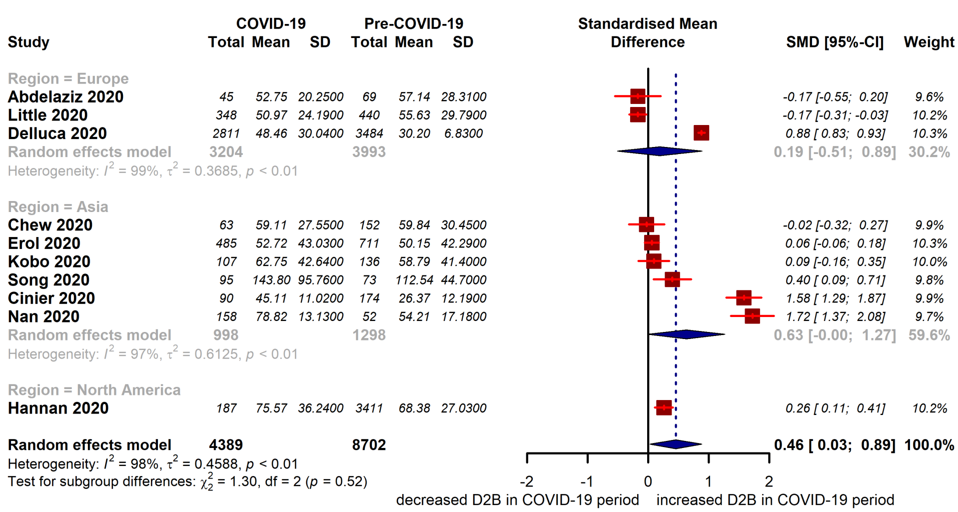

Fig. 4: Forest plot representing estimates of Standardized Mean Difference (SMD) of door-to-balloon time before versus during COVID-19 pandemic based on contents

Length of hospital stay

The length of hospital stay was reported by five studies (n=9448). Length of hospital stay (in days) was non-significantly longer during the pandemic than before it (SMD= 0.04; 95% CI: -0.19- 0.26; Fig. 5). Supplementary Fig. 4 represents publication bias via a funnel plot. Since the entire length of hospital stay time comparison had substantial variability, we employed a random-effect model (I^2 = 84%).

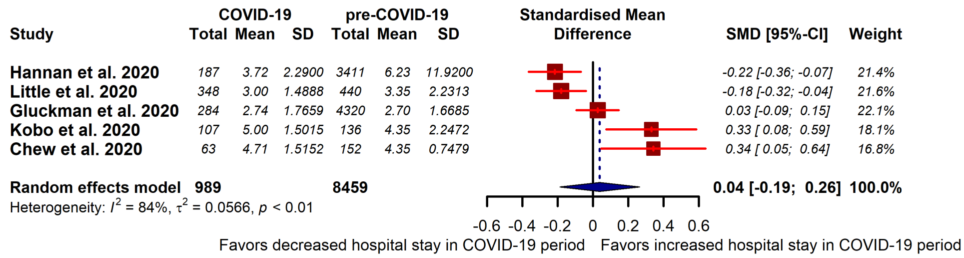

Fig. 5: Forest plot representing estimates of Standardized Mean Difference (SMD) hospital length of stay before versus during COVID-19 pandemic

Discussion

The present meta-analysis represented the worldwide outcomes, door-to-balloon time, and mortality rates based on the region of STEMI patients affected by delayed management caused by COVID-19 in the most recent pandemic era. Overall, the mortality rate and door-to-balloon time were significantly higher during the pandemic; however, the length of hospital stay was non-significantly longer in that period. Furthermore, in regional evaluation, mortality rate and door-to-balloon time remained significantly higher in European countries.

Mortality

In the present study, the pooled odds ratio of STEMI patients' mortality during the pandemic versus before, increased significantly. In line with our study, the mortality rate related to STEMI has increased significantly in different parts of the globe (12, 41, 42). Several factors were found to be responsible for the more severe outcome among this group of patients during the most recent pandemic. Firstly, more severe cases with higher markers for myocardial necrosis (serum troponin high-sensitivity and creatinine kinase levels) (12, 41, 43), a worsened intracoronary thrombotic burden (9), and a lower left ventricular ejection fraction (44) presented to emergency departments (ED). Furthermore, ACS cases surge by the infection was previously confirmed during the seasonal flu outbreaks in the last decades (45, 46). Secondly, one main reason for worse outcomes could be the significant delay in seeking medical contact (11), with at least a 7-fold increase in symptoms onset to hospital admission and a 50% rate of late presentation in STEMI during the COVID-19 pandemic (11, 12, 41-46). Hospital admissions of STEMI patients showed a marked decrease compared with the previous year (11, 12, 43-47); notably, a decrease by half was reported in the very first 2 months after the outbreak (41). This reduction was also irrespective of patient characteristics and the regional prevalence of COVID-19 (48).

An almost 4-fold (82.5 to 318 min) increase in median time from symptoms' initiation to ambulance arrival was also reported (42). In addition to the fact that patients put off seeking medical care, on the other hand, in the pandemic era, ambulance service was severely lacking due to the unexpected surge in demand (49). In-hospital mortality was found to climb in the Iranian registry from 2.8% to 9.7% compared with before the pandemic (12). The regional investigation of STEMI mortality was not different in North America (50) and Asia according to results from different countries (51), including Singapore

Western (52), Turkey (33), and China (40). However, European countries regarded this significantly differently (29, 32, 37).

Door to Balloon time

The other crucial factor in the outcome is the door-to-balloon length of time, and time management is strongly associated with morbidity and mortality in these patients (53). Our pooled analysis of mean door-to-balloon time during pandemics compared to before the COVID-19 period showed a significant increase. This could be caused by the time consumed for adaption of precaution measurements and wearing personal protective equipment (PPE) by the medical staff, especially in case of unknown status of COVID-19 in an urgent case (48, 54). This elevation in the door-to-balloon period was reported in many countries with various income and geographical locations .

Interestingly, a study from southern China compared STEMI patients in 2019 and 2020. Despite the significant increase in door-to-balloon time from 57.5 to 79 min in 2020, the mortality rate and length of hospitalization remained the same (55). In a study of 1785 patients in Saudi Arabia, the overall STEMI cases and those managed by reperfusion therapy were reduced. The goal of door-to-balloon time of fewer than 90 min was achieved in 73.1% during the pandemic in 2020; however, the period over 12 h between the onset of symptoms to the balloon was significantly higher in 2020 (17.2%) compared to pre-pandemic time (<3%) (56).

Length of hospital stay

In a meta-analysis, the overall length of hospital stay was the same as in the pre-pandemic era . It is in accordance with our results, rendering that length of hospital stay was not significantly longer during the pandemic than before the outbreak. However, an observational study indicated an extension in the duration of in-hospital stay, which was particularly impacted by cardiology care unit stay with extremely severe clinical conditions and reduced ventricular function, which required more intensive and targeted treatments (57). In a study of 1785 STEMI patients, the median length of in-hospital stay was not significantly different in the pre-pandemic era in 2018 and 2019 (both 4 d) and during the pandemic in 2020 (3 d) (56).

Strengths and limitations

Most studies included in our meta-analysis were prospective cohorts which was the strength of this study. One of the limitations of our study was the evaluation of mortality during hospitalization of STEMI patients. Studies with longer follow-up time in terms of mortality might provide the complementary effects of the pandemic on the prognosis of these patients. In addition, our findings might be subjected to publication bias due to including only English publications.

Conclusion

The present study summarizes all available data on impact of the COVID-19 on the care and management of STEMI patients. During the COVID-19 pandemic the odds of mortalities and mean door-to-balloon time irrespective of geographic location significantly increased than prior to it. The length of hospital stays increased non-significantly compared to before COVID-19 pandemic. Studies with a longer follow-up time are needed to investigate the outcomes of STEMI patients.

The COVID-19 pandemic is associated with increased mortality and door-to-balloon delay that might be attributable to the strict infection control measures in outbreak. Studies with a longer follow-up time are needed to investigate the outcomes of STEMI patients.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgment

No financial support was received.

Conflict of interest

The authors declare that there is no conflict of interests.

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