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Outcomes of COVID-19 Complications and their Possibilities as Potential Triggers of Stroke

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Introduction: There is limited literature on coronavirus disease 2019 (COVID -19) complications such as thromboembolism, cardiac complications etc. as possible trigger for stroke. Hence, we aim to evaluate the prevalence and outcomes of COVID-19 related cardiovascular complications and secondary infection and their possibility as potential triggers for the stroke. *Methods:* Data from observational studies describing the complications [acute cardiac injury (ACI), cardiac arrhythmias (CA), disseminated intravascular coagulation (DIC), septic shock, secondary infection] and outcomes of COVID−19 hospitalized patients from December 1, 2019 to June 30, 2020, were extracted following PRISMA guidelines. Adverse outcomes defined as intensive care units, oxygen saturation less than 90%, invasive mechanical ventilation, severe disease, and in−hospital mortality. The odds ratio and 95% confidence interval were obtained, and forest plots were created using random−effects models. A short review of these complications as triggers of stroke was conducted. *Results:* 16 studies with 3480 confirmed COVID-19 patients, prevalence of ACI [38%vs5.9%], CA [26%vs5.3%], DIC [4%vs0.74%], septic shock [18%vs0.36%], and infection [30%vs12.5%] was higher among patients with poor outcomes. In meta-analysis, ACI [aOR:9.93(95%CI:3.95−25.00], CA [7.52(3.29−17.18)], DIC [7.36

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(1.24−43.73)], septic shock [30.12(7.56−120.10)], and infection [10.41(4.47−24.27)] had higher odds of adverse outcomes. Patients hospitalized with acute ischemic stroke and intracerebral hemorrhage, had complications like pulmonary embolism, venous thromboembolism, DIC, etc. and had poor outcomes *Conclusion:* The complications like acute cardiac injury, cardiac arrhythmias, DIC, septic shock, and secondary infection had poor outcomes. Patients with stroke were having history of these complications. Long term monitoring is required in such patients to prevent stroke and mitigate adverse outcomes.

Key Words: COVID-19—Stroke—Septic shock—Coronary Artery Disease—Cardiac arrhythmia—Pulmonary embolism—Deep vein thrombosis—Disseminated intravascular coagulation

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Introduction

The coronavirus disease 2019 (COVID-19) has been a pandemic like no other seen in our times. It has impacted the entire globe affecting more than 180 countries with 81.9 million cases and 1.7 million deaths as of December 29, 2020.[1] Unlike other virus-related spread, COVID-19 since its early days is known to have a high infection rate as well as high mortality, which in turn has resulted in such a devastating impact across the world. The mortality rates among hospitalized patients with COVID-19 infection without stroke range from 22% to 45%[2,3], but the mortality was very high (38%) in stroke patients with COVID-19 infections.[4] It has inflicted significant personal, social as well as economic impact. SARS-CoV-2 is known to mainly affect the respiratory system. However, the emerging literature has reported its effect on multiple systems triggering cascades of conditions leading to hypercoagulable state, thromboembolism, septic shock, cardiac shock, multiorgan failure and even death.[5]

Cardiovascular disease (CVD) is the leading global cause of death, accounting for more than 17.3 million deaths in 2013, and the toll might reach 23.6 million by 2030.[6,7] Cerebrovascular disease (CeVD) remains one of the top causes of mortality and morbidity across the world.[6] Patients with CeVD and CVD usually have multiple deficits requiring prolonged hospitalizations and care. This in turn is likely to increase their exposure to COVID-19 in hospitals. COVID-19 patients are noted to have higher prevalence of comorbidities including CeVD and CVD, however pathophysiology contributing to such comorbidities and associated outcomes of such patients are unknown.[8−10]

Furthermore, the immune response, which is activated in response to viral infection, is believed to be causing widespread activation of coagulation cascades to variable extent, leading to disseminated intravascular coagulation (DIC). DIC is known to cause both thrombo-embolism as well as bleeding secondary to consumption of coagulation factors.[11] This can lead to CeVD (both ischemic as well as hemorrhagic) and CVD, along with affecting multiple organs. Such immunological and systemic cascades were noted in prior viral pandemics such as severe acute respiratory syndrome-coronavirus (SARS-CoV), Middle East respiratory syndrome-coronavirus (MERS-CoV) to various extent affecting different organ systems. Vigorous activation of coagulation cascades may explain COVID-19 related complications. Moreover, CVD on its own remains one of the major contributors to cascades leading to embolic CeVD. Multiple cardiovascular conditions such as cardiac shock, myocardial injury, cardiac arrhythmias; along with DIC lead to clot formation via various pathophysiology; and results in CeVD whenever that clot propagates to the brain.

A recent study by Li et al., reported 4.6% of their COVID-19 patients had acute ischemic stroke, and 1 patient had intracerebral hemorrhage.[4] Additionally, small single center studies have reported the cardiovascular complications and secondary infection in COVID-19 patients. These results cannot be generalized due to sample size and geographic location. This greatly necessitates identification of patients who are at higher risk of developing COVID-19 related complications. Identification of such patients would be of great value to emphasize prevention of such complications as well as appropriate allocation of resources to mitigate such complications, and therefore de-impacting COVID-19 burden. In this meta-analysis, we aim to evaluate the prevalence and outcomes of COVID-19 related cardiovascular complications and secondary infection. We have also evaluated whether these complications could be potential triggers for strokes (AIS- acute ischemic stroke; ICH- intracerebral hemorrhage) and their associated outcomes in COVID-19 patients.

Methods

Endpoint

The aim of the study is to evaluate the role of cardiovascular complications and secondary infection in predicting outcomes in COVID-19 hospitalized patients. COVID-19 confirmation in individual studies was evaluated by reverse transcription PCR, antibody testing, and symptoms.

COVID-19 related complications are defined as acute cardiac injury (with evident rise in cardiac enzyme), cardiac arrhythmia, disseminated intravascular coagulation (DIC), secondary infection, and septic shock. Poor outcomes were defined by intensive care unit (ICU)

admission, oxygen saturation<90%, invasive mechanical ventilation (IMV) utilization, severe disease, and in-hospital mortality. Study-specific poor outcomes are mentioned in Table 1.[2,12–26]

Search strategy and selection criteria

A systematic search was conducted on published studies using MOOSE checklist and following PRISMA protocol from December 1, 2019 to June 30, 2020. We searched PubMed, Web of Science, Scopus, and medRxiv for observational studies that described laboratory findings of COVID-19 patients following keyword/MESH terms: ((COVID-19[Title/Abstract]) OR coronavirus [Title/Abstract]) OR SARS-CoV-2[Title/Abstract] OR 2019-nCoV [Title/Abstract]. Studies were included in this meta-analysis if they had details on COVID-19 complications and outcomes of hospitalized patients. Literature other than observational studies, non-English literature, non-full text, and animal studies were excluded. Flow diagram of the literature search and study selection process is described in Fig. 1.

Study selection

Abstracts were reviewed, and articles were retrieved and reviewed for availability of data on complications and outcomes of COVID-19 patients. Studies which gave details on outcomes were selected for quantitative analysis. Preeti Malik (PM) and Deep Mehta (DM) independently screened all identified studies and assessed full-texts to decide eligibility. Any disagreement was resolved through consensus with Urvish Patel (UP).

Data collection

From the included studies, we extracted the following variables: cardiac complications, acute cardiac injury, cardiac arrhythmias, DIC, septic shock, secondary infection and outcomes. Additionally, details on binary outcomes **(Defined in Table 1)** like ICU vs. non-ICU admission, severe vs non-severe disease, IMV vs no-IMV use oxygen saturation <90% vs >90%, in-hospital mortality vs discharged alive and survivors were collected using prespecified data collection forms by two authors (PM and DM) with a consensus with UP. We have presented the study characteristics like the first author's last name, publication month and year, country of origin, sample size, mean or median age, males, outcomes and definition of outcomes assessed in that individual study Table 1.

Statistical analysis

Data analysis was performed using Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). If the study has more than one outcome comparison, then we have used data from the most severe outcome in the analysis to minimize the overall selection bias of our study.

The Maentel–Haenszel formula was used to calculate dichotomous variables to obtain odds ratios (ORs) along with its 95% confidence intervals (95%CI) to describe the relationship of cardiac complications and outcomes of COVID-19 patients in each study. Random-effects models were used regardless of heterogeneity to estimate the combined effect and its precision, to give a more conservative estimate of the ORs and 95%CI. The I^2 statistic was used to assess statistical heterogeneity. The I^2 statistic of >50% was considered significant heterogeneity. $p<0.05$ was considered significant. Publication bias was assessed visually using funnel plots and the Newcastle-Ottawa Scale (NOS). Newcastle Ottawa Scale (NOS) was used to assess the quality and bias in the included studies, which rates selection, comparability, and outcome. All studies were assessed to be of moderate quality (**Supplemental file**).

The pooled OR and 95% CI are represented in the form of forest plots. Each square on the chart area represents individual study and the area of each square is equivalent to the weight of the study, which is the inverse of the study variance. The diamond represents the summary measures, and the width corresponds to the 95% CI.

Results

Literature screening and characteristics of included studies

Review of the databases identified 45,377 articles, out of which 200 full text articles assessed for eligibility after removing duplicated articles, non-human studies, non-observational studies, and articles with non-English language. During the second round, 163 articles with insufficient clinical information on COVID-19 outcomes and complications were excluded and 37 articles on complications and outcomes were extracted for final evaluation. So, after detailed assessment and considering strict inclusion and exclusion criteria, as of June 30, 2020, we included 16 observational studies with 3480 confirmed cases of COVID-19 patients detailing cardiovascular complications/infections and outcomes. Meta-analysis random effects models quantified the study level impact of cardiovascular complications/infections on outcomes in COVID-19 hospitalized patients.

Acute cardiac injury: A total of 11 studies reported data on acute cardiac injury and outcomes giving a total sample size of 1361 COVID-19 patients for evaluation. The prevalence of acute cardiac injury was higher among patients with poor outcomes [38% (138/363) vs 5.9% (59/998); overall prevalence 14.47%]. Meta-analysis of all 11 studies showed that COVID-19 patient with acute cardiac injury had higher odds of poor outcomes with a pooled OR of 9.93 (95%CI:3.95–25.00; $p<0.00001$), with 75% heterogeneity between studies ($p<0.0001$) **(Fig. 2)**. To account for heterogeneity, we performed a sensitivity analysis by eliminating the 3 outlying studies on funnel

Table 1. *Study characteristics, design, outcomes and types of COVID-19 complications considered in this study.*

Study	Country	Sample size(N)	Mean/Median age(years)	Malesn (%)	Study design	Outcomes	Cardiovascular complications/ infections
Huang et al., Jan 2020[9]	China	41	49	30 (73.2)	Prospective single-center	ICU vs. Non-ICU	Acute cardiac injury Secondary infection Septic shock
Guan et al., Feb 2020[10]	China	1099	47	637 (58)	Retrospective multi-center	Severe vs Non-severe*	DIC Septic shock
Wang et al., Feb 2020[11]	China	138	56	75 (54.3)	Retrospective single-center	ICU vs. Non-ICU	Acute cardiac injury Cardiac arrhythmia Septic shock
Yang et al., Feb 2020[12]	China	52	59.7	35 (67.3)	Retrospective single-center	Survivor vs. Non-survivor	Secondary infection Acute cardiac injury
Chen et al., Mar 2020[13]	China	21	56	17 (81)	Retrospective single-center	Severe vs. Moderate**	Secondary infection Acute cardiac injury Septic shock
Ruan et al., Mar 2020[14]	China	150	67 (died) 50 (discharged)	102 (68)	Retrospective multi-center	Died vs. Discharged	Secondary infection
Wang et al., Mar 2020[15]	China	339	71	166 (49)	Retrospective single-center	Survivor vs. Non-survivor	Secondary infection Acute cardiac injury Cardiac arrhythmia Septic shock
Zhou et al., Mar 2020[16]	China	191	56	119 (62.3)	Retrospective multi-center cohort	Survivor vs. Non-survivor	Secondary infection Acute cardiac injury Septic shock
Goyal et al., Apr 2020[17]	USA	393	62.2	238 (60.6)	Retrospective multi-center	IMV vs. Non IMV	Secondary infection DIC Cardiac arrhythmia
Wan et al., Apr 2020[18]	China	135	47	72 (53.3)	Retrospective single-center	Severe vs. Mild**	Acute cardiac injury
Zhao et al, Apr 2020[19]	China	91	46	49 (53.8)	Retrospective single-center	Severe vs. Mild**	DIC Acute cardiac injury
Hong et al., May 2020[20]	South Korea	98	55.4	38 (38.8)	Retrospective single-center	ICU vs. Non-ICU	Acute cardiac injury Septic shock
Huang et. al., May 2020[21]	China	202	44	116 (57.4)	Retrospective multi-center	Severe vs Non-severe*	Septic shock
Zheng et al., May 2020[22]	China	34	66	23 (67.6)	Retrospective single-center	IMV vs. Non IMV	Acute cardiac injury

Table 1 (*Continued*)

Study	Country	Sample size(N)	Mean/Median age(years)	Malesn (%)	Study design	Outcomes	Cardiovascular complications/ infections
Wang et al., Jun 2020[23].	China	275	49	128 (46.5)	Retrospective single-center	Severe vs Non-severe**	DIC Septic shock
Zhang et al., Jun 2020[24]	China	221	55	108 (48.9)	Retrospective single-center	Severe vs Non-severe**	Acute cardiac injury Cardiac arrhythmia
Total		3480					

*Using the American Thoracic Society guidelines for community-acquired pneumonia;
**World Health Organization and the National Health Commission of China interim guidelines defined disease severity and improvement as follows: Mild cases: The mild clinical symptoms and no pneumonia in imaging. Moderate cases: symptoms like fever and respiratory tract symptoms, etc., and pneumonia can be seen in imaging. Severe cases: Meeting any of the following — respiratory distress, respiratory rate $\geq$ 30 breaths/min; $SpO_2 \leq 93\%$ at rest; and $PaO_2/FIO_2 \leq 300$. Patients with >50% lesion progression within 24 to 48 hours. Critical/extremely severe cases: if they have one of the following: respiratory failure requiring mechanical ventilation, shock, and other organ failure requiring ICU treatment.IMV- Invasive Mechanical VentilationDIC-Disseminated Intravascular Coagulation

plot (Zhou et al., Wan et al., and Hong et al.) (**Supplemental file**). Results after sensitivity analysis also showed significant pooled OR of 7.95 (95%CI:3.86-16.37; p<0.00001) with 47% heterogeneity in the data (p=0.07).

Cardiac arrhythmia: The prevalence of cardiac arrhythmia was higher among patients with poor outcomes [26% (75/286) vs 5.3% (36/679); overall prevalence 10.50%]. Meta-analysis of 4 studies including 965 confirmed COVID-19 patients showed that COVID-19 patient with cardiac arrhythmia had 7.52 times higher odds of poor outcomes compared to better outcomes (95%CI:3.29−17.18; p<0.00001) with 62% heterogeneity (p=0.05) **(Fig. 3)**. Sensitivity analysis performed by removing one outlying study of Wang et al. on funnel plot (**Supplemental file**) also showed significant association between cardiac arrhythmia and poor outcomes with pooled OR of 11.51 (95%CI:6.06-21.85; p<0.00001) with no heterogeneity in the data (p=0.99).

Disseminated intravascular coagulation (DIC): A total of 4 studies reported data on DIC and outcomes, including 1858 COVID-19 patients. The prevalence of DIC was higher among patients with poor outcomes in comparison to non-poor outcomes [4% (15/378) vs 0.74% (11/1480); overall prevalence 1.4%]. Meta-analysis of all 4 studies showed that DIC in COVID-19 patients had higher odds of poor outcomes compared to better outcomes with a pooled OR of 7.36 (95%CI:1.24−43.73; p=0.03), with 54% heterogeneity between studies (p=0.09). **(Fig. 4)**. We performed a sensitivity analysis by eliminating study by Zhou et al. in order to account for heterogeneity between the studies (**Supplemental file**). Results after sensitivity analysis also showed significant pooled OR of 20.81 (95%CI:3.56-121.59; p=0.0007) with 0% heterogeneity in the data (p=0.75).

Septic shock: A total of 9 studies reported data on septic shock and outcomes giving a total sample size of 2404 COVID-19 patients for evaluation. The prevalence of septic shock was higher among patients with poor outcomes in comparison to non-poor outcomes. [18% (78/433) vs 0.36% (7/1971); overall prevalence 3.54%]. Meta-analysis of all 9 studies showed that COVID-19 patient with septic shock had 30.12 times higher odds of poor outcomes compared to better outcomes (95%CI:7.56−120.10; p<0.00001), with significant heterogeneity between studies (p=0.006; I^2=62%) **(Fig. 5)**. Sensitivity analysis performed by removing two outlying studies (Wang et al. and Zhou et al.) on funnel plot (**Supplemental file**) also showed significant association between Septic shock and poor outcomes with pooled OR of 36.8 (95%CI:13.31-101.66; p<0.00001) with 0% heterogeneity in the data (p=0.51).

Secondary infection: We analyzed 7 studies with 1187 confirmed COVID-19 patients to evaluate association between secondary infection and outcomes. The prevalence of secondary infection was higher among patients with poor outcomes in comparison to non-poor outcomes. [30% (112/373) vs 12.5% (102/814); overall prevalence 18.03%]. In meta-analysis, patients with secondary

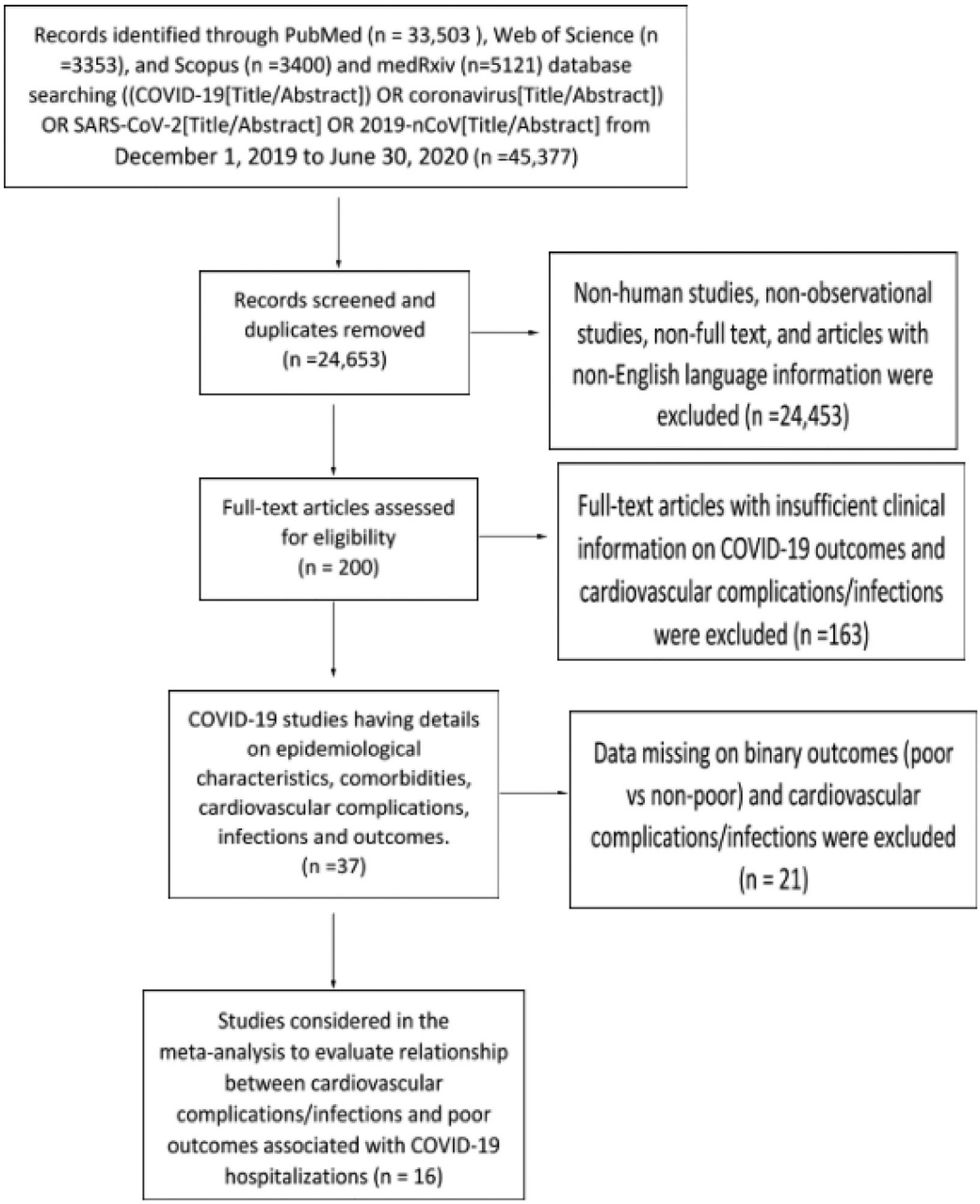

Fig. 1. *Flow diagram of literature search and study selection process of COVID-19 outcomes and cardiovascular complications/infections.*

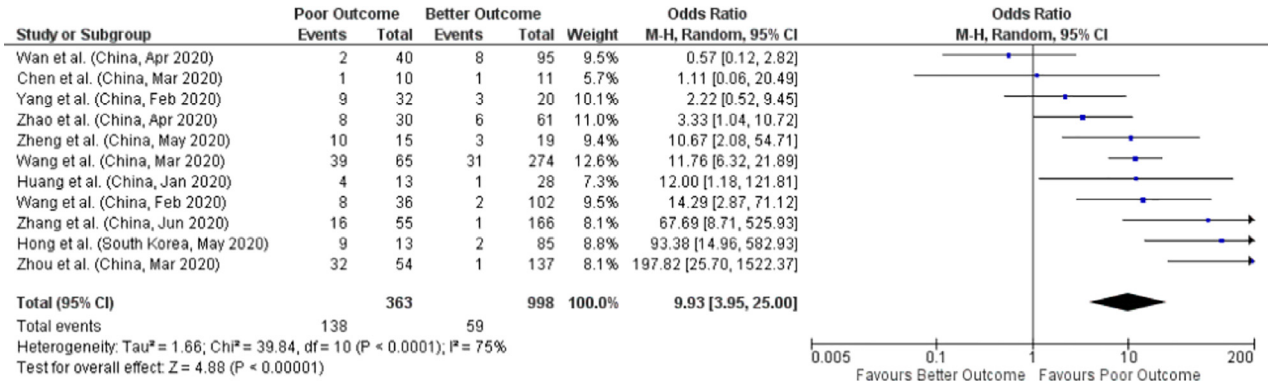

Fig. 2. *Forest plot of acute cardiac injury and outcome in COVID-19 hospitalized patients.*

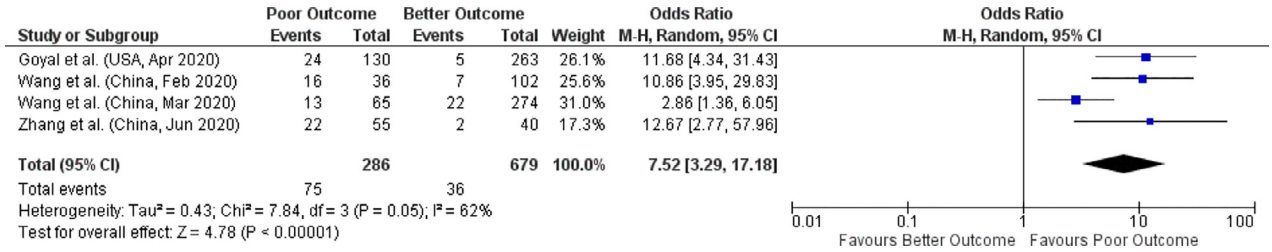

Fig. 3. *Forest plot of cardiac arrhythmia and outcome in COVID-19 hospitalized patients.*

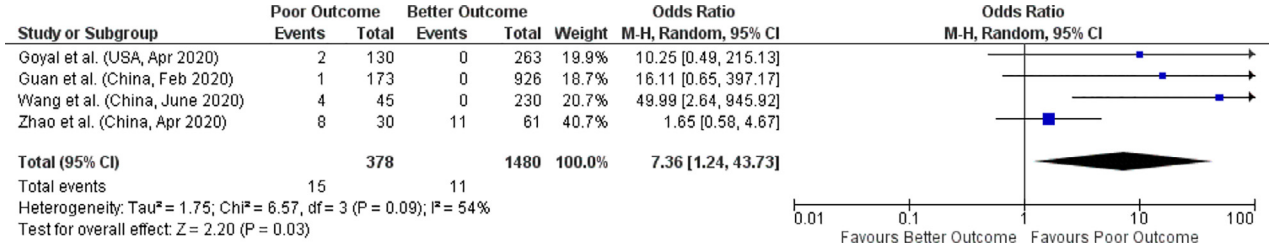

Fig. 4. *Forest plot of disseminated intravascular coagulation (DIC) and outcome in COVID-19 hospitalized patients.*

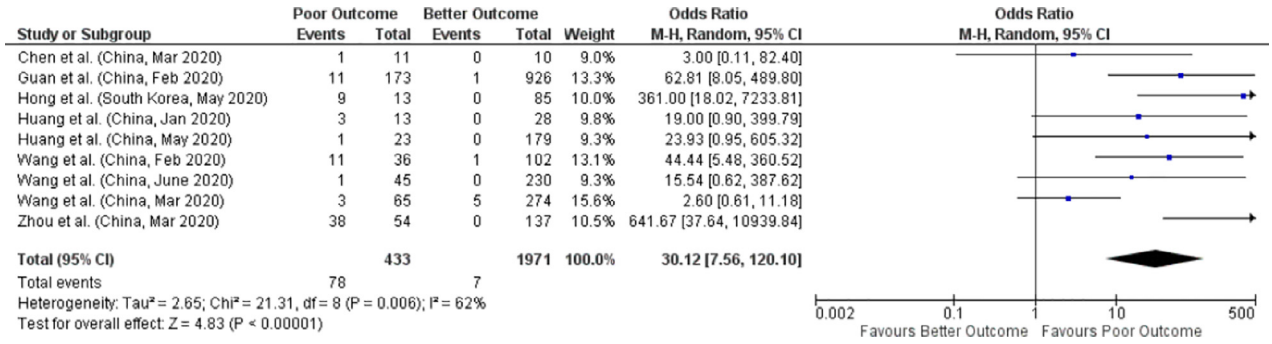

Fig. 5. *Forest plot of Septic Shock and outcome in COVID-19 hospitalized patients.*

infection had higher odds of poor outcomes compared to better outcomes with pooled OR of 10.41 (95%CI:4.47−24.27; p<0.00001) with 45% heterogeneity (p=0.09) **(**Fig. 6).

Discussion

In our meta- analysis of 16 studies with 3480 confirmed COVID-19 patients, we found that complications such as DIC, acute cardiac injury, cardiac arrhythmias, septic shock and secondary infection were significantly associated with poor outcomes in COVID-19 patients. The variable course of illness ranging from asymptomatic to severely ill with complications affecting different systems makes it crucial to collect strong evidence to determine the patient's condition in a timely manner and predict complications. The complications considered in our study reflect catastrophic developments in the course of the disease and thus help clinicians in recognizing the severity of the disease.

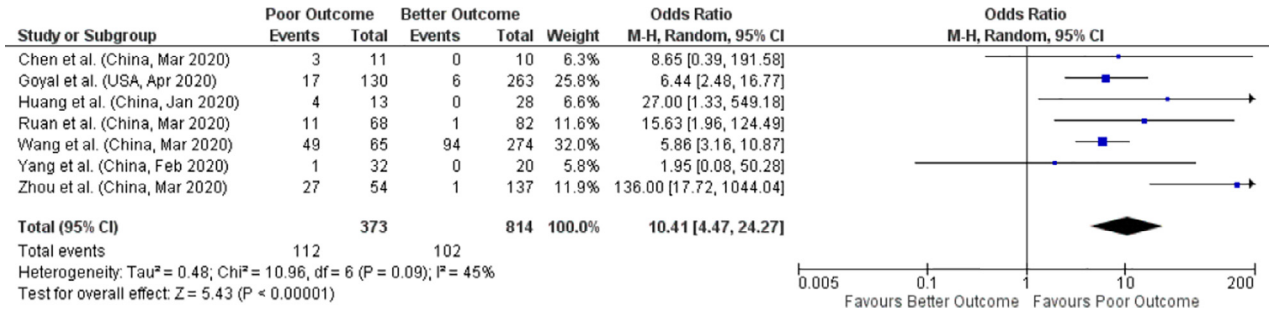

Fig. 6. *Forest plot of Secondary Infection and outcome in COVID-19 hospitalized patients.*

Table 2. *Studies showing the concurrent presence of COVID-19 related complications and stroke*

Study	Country	Sample size(n)	Study design	Post-COVID-19 Complications as possible trigger of stroke	Patients with type of detected strokes	Outcomes of Stroke
Li et al. Jul 2020[8]	China	219	Retrospective single-center study	Increased inflammatory response and hypercoagulable state	AIS (10) and ICH (1)	AIS: 5 died ICH: 1 died
Helms et al., Jun 2020[33]	France	58	Observational series	Encephalopathy, prominent agitation and confusion, and corticospinal tract signs.	AIS (3)	N/A
Klok et al., Jul 2020[34]	Netherlands	184	Observational multi-center	Pulmonary embolism, venous thrombo-embolism, Arterial thromboembolism	AIS (3)	N/A
Varatharaj et al., Jun 2020[35]	United Kingdom	125	Cross-specialty surveillance study	Cerebral vasculitis, unspecified encephalopa-thy and encephalitis	AIS (57) and ICH (9)	N/A
Yaghi et al., May 2020[36]	USA	3,556	Retrospective, cohort study	Higher D-dimer levels at the time of stroke	AIS (32)	14 died, 10 criti-cally ill
Lodigiani et al., Jul 2020[37]	Italy	388	Retrospective, single center	Venous thromboembolism, pulmonary embolism, deep vein thrombosis, Acute coronary syndrome/ myocar-dial infarction, disseminated intravas-cular coagulation	AIS (9)	3 required ICU, 2 died
Avula et al., Jul 2020[38]	USA	4	Case series	Pneumonia	AIS (4)	3 required mechan-ical ventilation followed by death
Beyrouti et al., Apr 2020[39]	United Kingdom	6	Case series	Deep venous thrombosis	AIS (6)	1 died
Morassi et al., May 2020[40]	Italy	6	Case series	Encephalopathy, abnormal coagulation studies	AIS (4) and ICH (2)	AIS: 3 died ICH: 2 died

AIS- Acute ischemic stroke; ICH- Intracerebral hemorrhage.
N/A- not applicable.

The pathophysiology of cardiac injury in COVID-19 is not completely understood. There are a few studies supporting direct injury whereas others in support of indirect injury due to systemic release of pro-inflammatory cytokines like interleukin-1 (IL-1), beta interferon-gamma (IFN-γ), macrophage inflammatory protein (MIP)-1A, tumor necrosis factor (TNF)-α and IL-6.[27–29] Cardiac involvement was found in 58% of patients who have recovered from COVID-19 in a study.[30] Isolated studies have reported that myocardial injury has been associated with poor outcomes in hospitalized patients as well as other complications like acute kidney injury and coagulation disorders.[31,32] Cardiac biomarkers like CK-MB and TnI were found to be higher in those who were critically ill/ admitted to the ICU in some studies.[13,14] A study by Goyal et al. showed that 18.5% (24/130) patients who were on invasive mechanical ventilation developed some form of arrhythmia vs. only 1.9% (5/263) in patients who did not require invasive mechanical ventilation.[19] In another study by Wang et. al, 20% (13/65) patients who died developed some form of arrhythmia vs. 8% (22/274) in patients who survived.[17] This arrhythmogenic effect could be a direct effect of the virus, hypoxia, inflammatory stress or medications like hydroxychloroquine. Excessive inflammation, disseminated intravascular coagulation (DIC), immobilization or a combination of these could lead to venous thromboembolism.[33] Many studies have shown abnormalities in the coagulation pathway and elevated d-dimer levels.[19,34]

Table 2[4,35–42] described the studies showing characteristics of patient admitted with stroke following post-COVID-19 complications, types of stroke and outcomes of strokes. In most of studies post COVID-19 complications was thromboembolism due to either hypercoagulable state or increased inflammatory response, eventually leading to ischemic stroke with poor outcome which either required invasive mechanical ventilation, ICU admission or died during hospitalization. Hence, we can assume that these COVID-19 complications can be possible trigger for stroke.

Merkler et al. found that the risk of acute ischemic stroke was 1.6% in COVID-19 patients coming to the emergency department or admitted in the hospital. The likelihood of ischemic stroke remained high (odds ratio 7.6; 95% CI 2.3-25.2) in the cohort of COVID-19 patients compared to influenza cohort after age, sex and race adjusted analysis with influenza cohort.[43] Larson et al summarized all prior studies to explore and understand pathophysiology behind cardiovascular and cerebrovascular complications related to COVID-19. The article suggested three potentially interconnected mechanisms: virus induced activation of coagulation cascades leading to hypercoagulable state and stroke; viral induced systemic inflammation and immunological disturbances leading to cardiac injury/ arrhythmias and thromboembolism to brain; virus induced endothelial dysfunction which is a known risk factor ischemic stroke.[44] Thakkar et al., performed a literature review and discussed different cardiovascular and cerebrovascular complications. This review article finds different forms of cardiac complications such as myocarditis, acute coronary syndrome, arrhythmias, cardiac arrest, cardiac tamponade via different suggested mechanism, mainly direct organ damage via direct viral entry from angiotensin converting enzyme 2 receptors and systemic release of proinflammatory cytokines. Above mentioned cardiac complications, suggests direct binding of virus on ACE2 receptors of endothelial cells and a procoagulant state both of which are triggers for acute ischemic stroke. Additionally, coagulation abnormalities secondary to coronavirus and blood pressure control derangements are triggers for hemorrhagic stroke in COVID-19 patients.[45] Qureshi et al. suggested avoiding antiplatelet medication in suspected or confirmed COVID-19 infection if possible, for the first 24 h after receiving intravenous rt-PA (IV tPA) and endovascular mechanical thrombectomy (EVT) in AIS patients. Patients with suspected or confirmed COVID-19 infection, single or dual antiplatelet medication may be considered in who do not receive IV tPA and/or EVT. There is no evidence of superiority of one antiplatelet agent over another in secondary prevention of AIS.[46]

Limitations: Our study has a few limitations. Patient population across different studies has a wide range heterogeneity. This metanalysis is subject to bias due to selected studies' designated outcomes and choice of comparators in the respective studies. Additionally, most of our studies included in analysis are from China, and may not be representative of the general population in other countries. Secondary infection definitions were not mentioned in individual studies. The type of stroke mentioned in Table 2 are 'detected' strokes (as opposed to those that remain undiagnosed) and the location, size etc. is not reported. Despite these limitations, meta- analysis of 16 studies with 3480 confirmed COVID-19 patients, we found that complications such as DIC, acute cardiac injury, cardiac arrhythmias, septic shock and secondary infection were significantly associated with poor outcomes in COVID-19 patients.

Conclusion

The complications like acute cardiac injury, cardiac arrhythmias, DIC, septic shock, and secondary infection not only had higher prevalence but also had higher odds of poor outcomes in COVID-19 hospitalization. In review, COVID-19 patients hospitalized with AIS and ICH, had history of systemic inflammation, coagulation abnormalities or complications like cardiac arrhythmias, systemic thrombosis, DIC, etc. which may have caused stroke. Long term monitoring is suggested in these patients as they are at risk of developing or worsen arrythmias and may lead to complications triggered stroke.

Author contributions

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Declaration of Competing Interest

The authors report no disclosures relevant to the manuscript. The authors declare that there is no conflict of interest.

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Supplementary materials

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