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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 triggers 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% vs 5.9%], CA [26% vs 5.3%], DIC [4% vs 0.74%], septic shock [18% vs 0.36%], and infection [30% vs 12.5%] 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 (2.61–20.67)]...
mortality and morbidity across the world. Patients with cerebrovascular disease (CeVD) remains one of the top causes of mortality was very high (38%) in stroke patients with contributing to such comorbidities and associated outcomes including CeVD and cardiovascular disease (CVD), however pathophysiology of such patients are unknown.8

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) 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 1.12–38

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 Mantel–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 I² statistic was used to assess statistical heterogeneity. The I² 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
| Study                  | Country          | Sample size(N) | Mean/Median age(years) | Malesn (%) | Study design            | Outcomes                                                                 | Cardiovascular complications/ infections                  |
|-----------------------|------------------|----------------|------------------------|------------|-------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------|
| Huang et al., Jan 2020 | 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  | China            | 1099           | 47                     | 637 (58)   | Retrospective multi-center | Severe vs Non-severe* | DIC | Septic shock | Acute cardiac injury | Septic shock |
| Wang et al., Feb 2020  | China            | 138            | 56                     | 75 (54.3)  | Retrospective single-center | ICU vs. Non-ICU | Acute cardiac injury | Septic shock | Septic shock |
| Yang et al., Feb 2020  | China            | 52             | 59.7                   | 35 (67.3)  | Retrospective single-center | Survivor vs. Non-survivor | Secondary infection | Acute cardiac injury |
| Chen et al., Mar 2020  | China            | 21             | 56                     | 17 (81)    | Retrospective single-center | Severe vs. Moderate** | Secondary infection | Acute cardiac injury | Septic shock |
| Ruan et al., Mar 2020  | China            | 150            | 67 (died) 50 (discharged) | 102 (68)   | Retrospective multi-center | Died vs. Discharged | Secondary infection | Acute cardiac injury |
| Wang et al., Mar 2020  | China            | 339            | 71                     | 166 (49)   | Retrospective single-center | Survivor vs. Non-survivor | Secondary infection | Acute cardiac injury | Septic shock |
| Zhou et al., Mar 2020  | 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 | USA              | 393            | 62.2                   | 238 (60.6) | Retrospective multi-center | IMV vs. Non IMV | Secondary infection | Cardiac arrhythmia | Acute cardiac injury |
| Wan et al., Apr 2020   | China            | 135            | 47                     | 72 (53.3)  | Retrospective single-center | Severe vs. Mild** | DIC | Acute cardiac injury | Septic shock |
| Zhao et al, Apr 2020   | China            | 91             | 46                     | 49 (53.8)  | Retrospective single-center | Severe vs. Mild** | DIC | Acute cardiac injury | Septic shock |
| Hong et al., May 2020  | South Korea      | 98             | 55.4                   | 38 (38.8)  | Retrospective single-center | ICU vs. Non-ICU | Septic shock | Septic shock | Septic shock |
| Huang et al., May 2020 | China            | 202            | 44                     | 116 (57.4) | Retrospective single-center | Severe vs Non-severe* | IMV vs. Non IMV | Acute cardiac injury |
| Zheng et al., May 2020 | China            | 34             | 66                     | 23 (67.6)  | Retrospective single-center | IMV vs. Non IMV | Acute cardiac injury | Septic shock | Septic shock |
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; I²=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 infection.
Fig. 1. Flow diagram of literature search and study selection process of COVID-19 outcomes and cardiovascular complications/infections.

| Study or Subgroup       | Poor Outcome Events | Better Outcome Events | Odds Ratio M-H, Random, 95% CI |
|-------------------------|---------------------|-----------------------|--------------------------------|
| Event Total             | Weight             |                       |                                |
| Wan et al. (China, Apr 2020) | 2                  | 8                     | 5.37 (1.2, 2.32)               |
| Chen et al. (China, Mar 2020) | 1                  | 11                    | 5.7 (3.08, 23.49)              |
| Yang et al. (China, Feb 2020) | 9                  | 20                    | 2.22 (1.52, 3.44)              |
| Zhao et al. (China, Apr 2020) | 8                  | 61                    | 3.12 (1.04, 10.72)             |
| Zheng et al. (China, May 2020) | 10                 | 19                    | 4.67 (2.08, 54.71)             |
| Wang et al. (China, Mar 2020) | 39                 | 31                    | 12.19 (5.32, 21.99)            |
| Huang et al. (China, Jan 2020) | 4                  | 1                     | 12.00 (1.18, 12.91)            |
| Wang et al. (China, Feb 2020) | 8                  | 102                   | 14.34 (7.87, 21.17)            |
| Zhang et al. (China, Jun 2020) | 16                 | 166                   | 6.76 (3.71, 5.25)              |
| Hong et al. (South Korea, May 2020) | 9                  | 85                    | 8.93 (4.69, 92.93)             |
| Zhou et al. (China, Mar 2020) | 32                 | 54                    | 197.82 (25.70, 1522.37)        |
| Total (95% CI)          | 363                | 998                   | 9.93 (3.95, 25.00)             |

Total events: 138, 59
Heterogeneity: Tau^2 = 1.68, Chi^2 = 39.84, df = 10 (P < 0.0001), I^2 = 75%
Test for overall effect: Z = 4.86 (P < 0.00001)

Fig. 2. Forest plot of acute cardiac injury 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.

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**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.

**Fig. 6.** Forest plot of Secondary Infection and outcome in COVID-19 hospitalized patients.
| 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     | 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 | France           | 58              | Observational series                | Encephalopathy, prominent agitation and confusion, and corticospinal tract signs. | AIS (3)                                | N/A                |
| Klok et al., Jul 2020  | Netherlands      | 184             | Observational multi-center          | Pulmonary embolism, venous thromboembolism, Arterial thromboembolism | AIS (3)                                | N/A                |
| Varatharaj et al., Jun 2020 | United Kingdom | 125             | Cross-specialty surveillance study  | Cerebral vasculitis, unspecified encephalopathy and encephalitis | AIS (57) and ICH (9)                   | N/A                |
| Yaghi et al., May 2020 | USA              | 3,556           | Retrospective, cohort study         | Higher D-dimer levels at the time of stroke                | AIS (32)                               | 14 died, 10 critically ill |
| Lodigiani et al., Jul 2020 | Italy     | 388             | Retrospective, single center        | Venous thromboembolism, pulmonary embolism, deep vein thrombosis, Acute coronary syndrome/myocardial infarction, disseminated intravascular coagulation | AIS (9)                                | 3 required ICU, 2 died |
| Avula et al., Jul 2020 | USA              | 4               | Case series                        | Pneumonia                                                 | AIS (4)                                | 3 required mechanical ventilation followed by death |
| Beyrouti et al., Apr 2020 | United Kingdom | 6               | Case series                        | Deep venous thrombosis                                   | AIS (6)                                | 1 died              |
| Morassi et al., May 2020 | 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.
COVID-19 COMPLICATIONS AS STROKE TRIGGERS

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.15,34

Table 2 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.34 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.35 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 arrhythmias 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

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.105805.

References

1. Worldometer COVID-19 CORONAVIRUS PANDEMIC (2020) Available from: https://www.worldometers.info/coronavirus/#countries [cited 20.08.20].
2. 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 Medicine 2020.
3. Outcomes M. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934-943. https://doi.org/10.1001/jamainternmed.2020.0994.
4. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020;5(3):279-284.
5. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. Current Problems in Cardiology. 2020.
6. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation 2020.
7. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med 2015.
8. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med 2020.
9. Richardson S, Hirsch JS, Narasimhan M, Crawford F, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA - J Am Med Assoc 2020.
10. Kaur N, Gupta I, Singh H, Karia R, Ashraf A, Habib A, et al. Epidemiological and clinical characteristics of 6635 COVID-19 patients: a pooled analysis. SN Compr Clin Med [Internet] 2020;2(8):1048-1052. https://doi.org/10.1007/s42399-020-00393-y. Available from:
11. McGonagle D, O’Donnell JS, Sharif K, Emery P, Bridge-wood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol [Internet] 2020;2(7):e437-e445. https://doi.org/10.1016/S2665-9913(20)30121-1.
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020.
13. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020.
14. 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 - J Am Med Assoc 2020.
15. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020.
16. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020.
17. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect 2020.
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.
19. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of covid-19 in New York City. N Engl J Med 2020.
20. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020.
21. Zhao XY, Xu XX, Yin H Sen, Hu QM, Xiong T, Tang YY, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. BMC Infect Dis 2020.
22. Hong KS, Lee KH, Chung JH, Shin KC, Choi EY, Jin HJ, et al. Clinical features and outcomes of 98 patients hospitalized with sars-cov-2 infection in daegu, south korea: a brief descriptive study. Yonsei Med J 2020.
23. Huang R, Zhuid L, Xue L, Liu L, Yan X, Wang J, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu Province, China: a retrospective, multicenter study. PLoS Negl Trop Dis 2020.
24. Zheng Y, Sun Ljun, Xu M, Pan J, Zhang Y tao, Fang X ling, et al. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. J Zhejiang Univ Sci B. 2020.

25. Wang Y, Liao B, Guo Y, Li F, Lei C, Zhang F, et al. Clinical characteristics of patients infected with the novel 2019 coronavirus (SARS-CoV-2) in Guangzhou, China. Open Forum Infect Dis; 2020.

26. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol. 2020.

27. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz 2020.

28. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020.

29. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol 2020.

30. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, et al. Cardiac involvement in patients recovered from COVID-19 identified using magnetic resonance imaging. JACC Cardiovasc Imaging 2020.

31. He XW, Lai JS, Cheng J, Wang MW, Liu YJ, Xiao ZC, et al. Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients. Zhonghua Xin Xue Guan Bing Za Zhi 2020.

32. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol; 2020.

33. Roy S, Mazumder T, Banik S. The association of cardiovascular diseases and diabetes mellitus with COVID-19 (SARS-CoV-2) and their possible mechanisms. SN Compr Clin Med 2020.

34. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emergency Med 2020.

35. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020.

36. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020.

37. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry; 2020.

38. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. Stroke; 2020.

39. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020.

40. Avula A, Nalleballe K, Narula N, Sapoiznikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun 2020.

41. 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.

42. Morassi M, Bagatto D, Cobelli M, D’Agostini S, Gigli GL, Bna C, et al. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol 2020.

43. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. JAMA Neurol 2020.

44. Larson AS, Savastano L, Kadirvel R, Kallmes DF, Hassan AE, Brinjikji W. Coronavirus disease 2019 and the cerebrovascular-cardiovascular systems: what do we know so far? J Am Heart Ass 2020.

45. Thakkar S, Arora S, Kumar A, Jaswaney R, Faisaluddin M, Ammad Ud Din M, et al. A systematic review of the cardiovascular manifestations and outcomes in the setting of coronavirus-19 disease. medRxiv; Jan2020.08.09.20171330.

46. Qureshi AI, Abd-allaah F, Al-senani F, Ay tac E, Borhani-haghigi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: Report Internat Panel. 2020;15(5):540–54.