Late Complications of COVID-19; a Systematic Review of Current Evidence

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Abstract: Introduction: COVID-19 is a new rapidly spreading epidemic. The symptoms of this disease could be diverse as the virus can affect any organ in the body of an infected person. This study aimed to investigate the available evidence for long-term complications of COVID-19. Methods: This study was a systematic review of current evidence conducted in November 2020 to investigate probable late and long-term complications of COVID-19. We performed a systematic search, using the keywords, in online databases including PubMed, Scopus, Science Direct, Up to Date, and Web of Science, to find papers published from December 2019 to October 2020. Peer-reviewed original papers published in English, which met the eligibility criteria were included in the final report. Addressing non-human studies, unavailability of the full-text document, and duplicated results in databases, were characteristics that led to exclusion of the papers from review. Results: The full-texts of 65 articles have been reviewed. We identified 10 potential late complications of COVID-19. A review of studies showed that lung injuries (n=31), venous/arterial thrombosis (n=28), heart injuries (n=26), cardiac/brain stroke (n=23), and neurological injuries (n=20) are the most frequent late complications of COVID-19. Conclusion: Since we are still at the early stages of the COVID-19 epidemic, it is too soon to predict what long-term complications are likely to appear in the survivors of the disease in years after recovery. Furthermore, the complexity of COVID-19 behaviors and targets in the human body creates uncertainty in anticipating long-term complications.

Keywords: Long Term Adverse Effects; Late Onset Disorders; COVID-19; SARS-CoV-2; post-acute COVID-19 syndrome

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1. Introduction

Coronavirus disease 2019 (COVID-19) is an extremely contagious infectious disease caused by SARS-CoV-2 (1). COVID-19 infection was first reported in Wuhan, China, and spread quickly and turned into an unprecedented global pandemic (2-5). The novel coronavirus affects not only the respiratory tract, but also other organs in the human body. COVID-19 could cause injuries in the lungs, liver, kidney, heart, vessels, and other organs (6). Respiratory failure and acute respiratory distress syndrome (ARDS) are the most common complications of severe COVID-19 infection; the majority of hospitalized COVID-19 patients suffer from severe lung injuries and fatal multi-organ failure as well as hemolytic anemia. However; super infection, acute liver, kidney, and cardiac injuries, shock, and hypoxic encephalopathy are less common symptoms (7-9). Some COVID-19 patients may also present signs of tissue damage including rhabdomyolysis or hemoptysis, which lead to cellular injury, release of heme proteins,
and collection of heme in body tissues (10). SARS-CoV-2 usually affects the respiratory system (11), nervous system involvement has also been reported in some recent studies among patients with COVID-19 (12). Coronaviruses can attack the neural tissue including microglia, astrocytes, and macrophages, and cause nerve injury through direct nerve infection (13). The nervous system injuries could manifest as headache, dizziness, seizure, impaired consciousness, acute cerebrovascular disease, and ataxia. The virus could also affect the peripheral nervous system (PNS) and cause olfactory dysfunction, dysgeusia, vision impairment, and neuropathic pain (12, 13). COVID-19 could also cause cardiac injuries such as cardiomyopathy and conduction system malfunction. Studies suggest the direct involvement of cardiac muscles in some patients (4, 14, 15). Generally, infectious myocarditis is the most common cardiac complication of COVID-19 infection. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptors to infect host cells, through which it can cause pneumonia and myocardial injuries. High expression of ACE2 receptors in the lungs and heart could increase the risk of myocardial injuries in COVID-19 patients (14). ACE2 is also expressed in the intravascular endothelium, intestinal epithelium, and the kidneys; therefore, these organs could be a target for SARS-CoV-2 infection. Tachyarrhythmia is also a common cardiovascular complication in COVID-19 patients. Electrocardiography and echocardiography could be used in diagnosing and predicting the prognosis in COVID-19 patients (16). Some COVID-19 patients could suffer from earache that may be a sign of sub-acute thyroiditis. Studies have shown that a few weeks after upper respiratory tract involvement, subacute thyroiditis may occur and it might be a late complication in patients with COVID-19 infection. Therefore, thyroid functions should be checked after discharge in patients with COVID-19 (17, 18). In addition, there is an abnormal rise in various biochemical parameters such as erythrocyte sedimentation rate (ESR), albumin levels, serum ferritin levels, lactate dehydrogenase (LDH) levels, and C-reactive protein (CRP) levels in the infected patients; on the other hand, the hemoglobin levels and lymphocyte count could reduce in these patients. These complications could lead to cytokine storm, causing multiple organ dysfunction (19, 20). The coronavirus pandemic showed that COVID-19 could affect many organs besides the lungs, like heart and brain, which increases the risk of long-term health problems. There are several ways that the infection can affect someone’s health. Much is still unknown about how COVID-19 will affect people over time. While most patients infected with COVID-19 recover quickly, the potential long-lasting problems caused by COVID-19 make it necessary to look for and study its late complications. This review aims to present a systematic review of late complications of COVID-19 and identify how prevalent these symptoms are and who is most likely to be affected by them.

2. Methods

2.1. Study design and setting

This study was a systematic review of current evidence conducted in October 2020 and subsequently updated on November 4, 2020. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was employed.

2.2. Data sources

We performed a systematic search using the keywords in the online databases including PubMed, Scopus, Science Direct, Up to Date, and Web of Science. All the related papers and reports published in English from December 2019 through October 2020 were retrieved and then updated in November 2020. Our search strategy in each of the above-mentioned databases included several combinations of keywords in the following orders: A. “Coronavirus” OR “COVID-19” OR “SARS-CoV-2” OR “Novel Coronavirus” OR “2019-nCoV” [Title/Abstract] B. “Clinical characteristics” OR “clinical feature” OR “clinical manifestation” [Title/Abstract] C. “Consequences” OR “Chronic complications” OR “Late complications” OR “Long-term effects” [Title/Abstract]. D. [A] AND [B] AND [C]

2.3. Study selection

The most relevant studies based on titles and abstracts were retrieved by three independent investigators. The full contents of the retrieved papers were reviewed, and the most relevant papers were selected based on the eligibility criteria. The relevant data were extracted and organized in tables. The peer-reviewed original papers published in English that met the eligibility criteria were included in the final report. The exclusion criteria were as follows: – Papers addressing non-human studies including in vitro investigations or publications concentrating on animal experiments, or discussing COVID-19 in general, without reference to the keywords of this study. – Unavailability of the full-text document. – Duplicated results in databases.

2.4. Data extraction

We used the data extraction sheet (Table 2) to summarize the information of the authors, type of article (e.g., case series), country of origin, study population, and clinical symptoms (late complications in this study). Two independent investigators gathered this information and further organized them in the Tables. All the selected articles were cross-checked by other authors to ensure no duplications or overlap exists in the content.
2.5. Quality assessment

For bias risk assessment, two independent reviewers rated the quality of included studies by applying the National Institute of Health (NIH) Quality Assessment Tools for Case Series Studies. For this purpose, we have designed a table and evaluated the studies according to NIH questionnaire (Table 1). A third independent investigator was consulted to resolve probable difference of opinions in any case. The full text of select articles was fully read and the key findings were extracted. The final report including the key findings is summarized in Table 2.

3. Results

We retrieved 1325 documents using a systematic search strategy. After an initial review of retrieved articles, 542 duplicates were removed, and the titles and abstracts of the remaining 783 articles were reviewed. Applying the selection criteria, 718 articles were excluded, and only 65 articles met the inclusion criteria and were included in the final review (Figure 1). We identified 10 potential late complications of COVID-19 including neurological injuries, lung, liver, kidney, and heart injuries, thromboembolism, cardiac/brain stroke, encephalopathy, and psychological distress. Furthermore, some studies have pointed out other complications such as hypoproteinemia, septic shock, and multiple organ dysfunction syndromes (Table 1). Review of studies showed that lung injuries (n=31), venous/arterial thrombosis (n=28), heart injuries (n=26), cardiac/brain stroke (n=23), and neurological injuries (n=20) were the most frequent late complications of COVID-19. Frequencies of identified late complications of COVID-19 are demonstrated in Figure 2.

4. Discussion

One of the most important unknown features of COVID-19 is the duration of symptoms. In the early stages of the disease, the experts believed that the recovery time for mild cases of COVID-19 is 1-2 weeks (21). However, later in many patients, the symptoms lasted for 8 to 10 weeks or even longer, and in some cases, the initial symptoms were replaced by long-term complications such as lung or cardiac injuries (22). Since COVID-19 is a novel virus, there are limited studies about its late complications; it is just a few months since the recovery of the first patients in China. However, the available evidence suggests that the coronavirus can cause long-term complications in an infected person as it may cause major injuries to the heart, kidneys, brain, and even blood vessels (6, 10, 23, 24). The available evidence indicates the recurrence of symptoms in some patients who presented with severe initial symptoms (2, 25, 26). The key question is "what causes the recurrence of symptoms?". It may be caused by the recurrence or persistence of the primary COVID-19 infection or super infection with another virus or even bacteria due to the compromised immune system (27). In addition, the systemic and multorgan involvement in advanced phases of COVID-19 pneumonia can cause renal failure, liver dysfunction, thrombocytopenia, and coagulation disorders (28). Therefore, the survivors may present a variety of long-term complications in different organs, including a post-recovery syndrome that doctors call "post-COVID lung disease" (29). By looking at the organs affected during an infection, one can imagine what organs are likely to be affected by long-term complications of COVID-19 infection (30). The most common long-term complication of COVID-19 is lung disease (8, 29, 31). Most of the COVID-19 patients could be recovered completely except for some minor complications such as cough and shortness of breath. However, a certain proportion of patients have excessive lung damage, and some of them develop pulmonary fibrosis (32). Autopsy studies demonstrated the predominance of microvascular thrombosis in the lungs, coincident with markers of inflammation, which is a hallmark of prolonged infection and sepsis (33). Severe lung involvement in COVID-19 patients could increase the likelihood of progression to chronic lung disease and lead to long-term complications (8, 33). COVID-19 patients may experience both venous and arterial thrombosis due to severe inflammation and hypoxia, long immobilization, and diffuse intravascular coagulation (27, 28). Klok et al. reported the incidence rate of thrombotic complications to be 31% among ICU patients with severe COVID-19 infection (27). The results of another study reported the high number of arterial and, in particular, venous thrombo-embolic late complications (34). Poggiali et al. described two patients with COVID-19 pneumonia who developed venous thromboembolism and reported hypoxia and sepsis as the potential risk factors for vein thromboembolism (VTE)(35). Recent studies reported an increased risk of heart failure in COVID-19 patients (26, 28, 30). Moreover, episodes of clinical myocarditis have been observed (15). Heart injuries related to COVID-19 may occur over the course of the disease (36). Late involvement of cardiac muscle has been documented in a study by Puntmann et al. In this study, the researchers investigated the cardiac complications in 100 recovered patients; 78% of patients had cardiac involvement in cardiac magnetic resonance imaging (MRI), 76% had detectable high-sensitivity troponin, and 60% had abnormal native T1 and T2, which indicates the presence of active myocardial (37). Compared to the control group with similar preexisting conditions, left ventricle ejection fraction was lower and the ventricular size was higher in COVID-19 patients. In addition, 32% of patients had late gadolinium enhancement and 22% of them had pericardial involvement (36, 37). COVID-19 can cause damage to the central nervous system, with po-
tentially long-term consequences (38-41). Late neurological complications of COVID-19, whether caused by the virus or by the triggered inflammation, include decreased awareness and absorption, disturbed memory, and dysfunction of the peripheral nervous system (42). In one study from China, more than a third of hospitalized patients with confirmed COVID-19 had neurological symptoms, including dizziness, headaches, impaired consciousness, vision, taste/smell impairment, and nerve pain. These symptoms were more common in patients with severe disease, where the incidence increased to almost 47 percent (43). Another study in France found neurologic features in 58 of 64 critically ill COVID-19 patients (25).

5. Conclusion

Since we are still at the early stages of the COVID-19 epidemic, it is too soon to predict what long-term complications are likely to appear in the survivors of the disease in years after recovery. Furthermore, the complexity of COVID-19 behaviors and variety of its targets in the human body create uncertainty in anticipating long-term complications. However, several ongoing studies are set up to examine the physical, psychological, and socio-economic consequences of the COVID-19.

6. Declarations

6.1. Acknowledgment
The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, and Department of Global Health and Socioepidemiology, Kyoto University.

6.2. Author contributions
(1) The conception and design of the study: Esmaeil Mehraeen, SeyedAhmad SeyedAlinaghi
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(4) Drafting the article: Pegah Mirzapour, Esmaeil Mehraeen
(5) Revising it critically for important intellectual content: SeyedAhmad SeyedAlinaghi, Omid Dadras
(6) Final approval of the version to be submitted: Esmaeil Mehraeen, Omid Dadras

6.3. Ethics approval and consent to participate
The present study was extracted from the research project with code IR.KHALUMS.REC.1399.001 entitled “Investigation of effective drugs for people affected by Coronavirus disease 2019 (COVID-19) in selected hospitals in Ardabil” conducted at Khalkhal University of Medical Sciences in 2020.

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This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.5. Consent to publication
Not applicable

6.6. Availability of data and material
The authors stated that all information provided in this article are available.

6.7. Competing interests
The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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Table 1: Quality ratings of included studies based on NIH quality assessment (QA) tool for case series studies

| First Author               | Question | Rating |
|----------------------------|----------|--------|
|                            | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | #1 | #2 |
| Ali Sepehrinezhad (21)     | Yes | Yes | CD | CD | NA | Yes | CD | NA | Yes | Fair | Fair |
| Filatov A (22)             | Yes | Yes | CD | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Helms J (25)               | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Heneka MT (2)              | Yes | Yes | CD | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Kochi AN (26)              | Yes | Yes | CD | NA | NA | Yes | CD | NA | Yes | Fair | Fair |
| Klok FA (27)               | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Klok FA (30)               | Yes | Yes | NR | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Kunutsor SK(44)            | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Landi A (28)               | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Lazar HL (45)              | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Lee M (46)                 | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Liabeuf S(47)              | Yes | Yes | CD | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Liu B (48)                 | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Lorenzo-Villalba N(49)     | Yes | Yes | NR | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Loungani RS(50)            | Yes | Yes | NR | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Lodigiani C(34)            | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Long B (51)                | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Lopez M (52)               | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Ma J (53)                  | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Ma L (54)                  | Yes | Yes | NA | CD | NA | Yes | CD | NA | Yes | Fair | Fair |
| Mao L(43)                  | Yes | Yes | CD | NA | NA | Yes | CD | NA | Yes | Fair | Fair |
| Mauro V(55)                | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Mendoza-Pinto C(56)        | Yes | Yes | NR | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Nobile B (57)              | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Nogueira MS (29)           | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Orsi FA(33)                | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Oudkerk M(58)              | Yes | Yes | NA | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Palmer K (59)              | Yes | Yes | NA | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Poggioli E (35)            | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Parry AH (60)              | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Patel VG (61)              | Yes | Yes | NA | NA | NA | Yes | CD | NA | Yes | Fair | Fair |
| Paul P (62)                | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Paybast S (42)             | Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Pryce-Roberts A(38)        | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Puntmann VO(37)            | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Rey JR (63)                | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Roche J(A64)               | Yes | Yes | NA | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Rosen RJ(65)               | Yes | Yes | NA | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Saban-Ruiz J (66)          | Yes | Yes | NR | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Sheraton M (39)            | Yes | Yes | CD | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Siguret V (67)             | Yes | Yes | CD | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Silingardi R (68)          | Yes | Yes | CD | CD | NA | Yes | CD | Yes | Yes | Fair | Fair |
| Silverman – Chen Lin DA (69)| Yes | Yes | CD | NA | NA | Yes | CD | Yes | Yes | Fair | Fair |

NA: not applicable; NIH: National Institutes of Health; NR: not reported; CD: cannot determine

*The NIH Quality Assessment Tool for Case Series Studies contains nine questions: 1 = Was the study question or objective clearly stated?, 2 = Was the study population clearly and fully described, including a case definition?, 3 = Were the cases consecutive?, 4 = Were the subjects comparable?, 5 = Was the intervention clearly described?, 6 = Were the outcome measures clearly defined, 7 = Was the length of follow-up adequate?, 8 = Were the statistical methods well-described?, 9 = Were the results well-described?
Table 1 Quality ratings of included studies based on NIH quality assessment (QA) tool for case series studies

| First Author | *Question | Rating |
|--------------|-----------|--------|
| Singh Y (23) | Yes       | Fair   |
| Stevens DV (70) | Yes     | Fair   |
| Strafella C (40) | Yes   | Fair   |
| Tian D (71) | Yes       | Fair   |
| Thomas W (72) | Yes      | Fair   |
| Terpos E (73) | Yes     | Fair   |
| Varatharaj A (41) | Yes | Fair   |
| Varatharajah N (24) | Yes | Fair   |
| Wagener F (10) | Yes     | Fair   |
| Wang X (6) | Yes       | Fair   |
| Zhu H (74) | Yes       | Fair   |
| Abboud H (75) | Yes    | Fair   |
| Khan S (76) | Yes       | Fair   |
| Khandait H (77) | Yes  | Fair   |
| Msigwa S (78) | Yes    | Fair   |
| Sheikh A B (79) | Yes  | Fair   |
| Siripanthong B (80) | Yes | Fair   |
| Vonck K (81) | Yes      | Fair   |
| Wijeratne T (82) | Yes  | Fair   |
| Yachou Y (83) | Yes     | Fair   |
| Zaim S (84) | Yes      | Fair   |

NA: not applicable; NIH: National Institutes of Health; NR: not reported; CD: cannot determine

*The NIH Quality Assessment Tool for Case Series Studies contains nine questions: 1 = Was the study question or objective clearly stated?, 2 = Was the study population clearly and fully described, including a case definition?, 3 = Were the cases consecutive?, 4 = Were the subjects comparable?, 5 = Was the intervention clearly described?, 6 = Were the outcome measures clearly defined, 7 = Was the length of follow-up adequate?, 8 = Were the statistical methods well-described?, 9 = Were the results well-described?
Figure 1: Flow diagram of the selection process of articles identified.
Figure 2: Frequency of identified late complications of COVID-19.
| ID | First author | Study type | Country | Study Population | Late complications | Neurologic | Long disease | Liver disease | Heart damage | Thrombosis | Kidney disease | Stroke |
|----|--------------|------------|---------|------------------|-------------------|------------|-------------|--------------|--------------|------------|--------------|--------|
| 1  | Sepehrinezhad (21) | Perspective Review | Iran | Patients with neurological complications | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Encephalopathy |
| 2  | Helmers J (28) | Case Report | USA | 44-year-old male | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 3  | Filatov A (22) | Editorial | France | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 4  | Hienroo MT (24) | Review | Germany | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 5  | Klok FA (27) | Review | Italy | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 6  | Klok FA (30) | Case-control | Netherlands | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 7  | Klok FA (30) | Case-control | Netherlands | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 8  | Lodigiani C (20) | Letter to Editor | UK | COVID 19 patients admitted to the ICU | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 9  | Liabeuf S (47) | Cohort France | COVID 19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 10 | Landi A (28) | Letter to Editor | Italy | COVID19 patients admitted to ICU | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 11 | Augen H (45) | Commentary USA | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 12 | Lee M (46) | Letter to Editor | China | COVID 19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 13 | Loungani SK (50) | Cohort France | COVID 19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 14 | Loungani SK (50) | Cohort USA | COVID 19 Patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 15 | Lorenzo-Villalba N (49) | Case Report | France | a patient hospitalized for COVID-19 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 16 | Long B (51) | Cohort USA | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 17 | Lopez S (52) | Letter to Editor | China | COVID19 patients admitted to hospital | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 18 | Ma J (53) | Review USA | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 19 | Ma L (54) | Research article China | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 20 | Mao L (43) | Research article China | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |
| 21 | Mauro V (55) | Point of view Italy | COVID19 patients | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | – |

DVT: Deep vein thrombosis; GI: gastrointestinal; PTE: pulmonary thromboembolism; DIC: disseminated intravascular coagulation.
| ID | First author | Study type | Country | Study Population | Late complications | Stroke |
|----|--------------|------------|---------|------------------|-------------------|--------|
| 24 | Mendizábal-Pinto C (56) | Letter to Editor | Mexico | COVID-19 patients | x | x | x | √ | √ | √ | x | Elevated D-dimer, and coagulation abnormalities, catastrophic antiphospholipid syndrome (CAPS), multiple small vessel occlusions, multiorgan system failure |
| 25 | Nobile B (57) | Letter to Editor | France | COVID-19 patients using Chloroquine | √ | √ | x | x | x | x | Psychological distress, ischemic attacks, leading to brain inflammation and lesions |
| 26 | Nogueira MS (29) | Review | Brazil | COVID-19 patients | x | √ | x | x | x | x | Pneumonia, acute respiratory distress syndrome (ARDS), and lymphadenopathy |
| 27 | Orsi FA (33) | Review | Brazil | Hospitalized COVID-19 patients | x | √ | x | x | √ | x | Septic shock or multiple organ dysfunction, ARDS, Hypercoagulability |
| 28 | Oudkerk M (58) | Special Report | Netherlands | COVID-19 patients | x | √ | x | x | √ | x | G1 damage, vascular endothelial damage |
| 29 | Palmer K (59) | Review | Italy | COVID-19 patients with non-communicable disease (NCD) | x | √ | x | √ | √ | x | Psychological distress, exacerbated chronic NCD conditions (e.g., asthma, chronic obstructive, congestive cardiac failure) |
| 30 | Peggiali E (35) | Case Report | Italy | An 82-year-old woman, A 64-year-old man | x | √ | x | x | √ | x | Venous thromboembolism, Deep Pulmonary Embolism |
| 31 | Parry AH (66) | Letter to Editor | India | COVID-19 patients with pneumonia | x | √ | x | x | √ | x | Diffuse alveolar damage, acute respiratory distress syndrome, pulmonary vascular damage, PTE |
| 32 | Patel VG (61) | Letter to Editor | Netherlands | COVID-19 patients with prostate cancer | x | √ | x | x | x | x | – |
| 33 | Paul P (62) | Letter to Editor | USA | COVID-19 patients | x | √ | x | x | x | x | ARDS, pneumonia, multiple organ failure, infective myocarditis |
| 34 | Payhaas S (62) | Letter to Editor | USA | COVID-19 patients | √ | √ | x | x | x | x | x | GI disease, infracranial hemorrhage, hypoxia and hypogoeusia, disorientation, third nerve palsy |
| 35 | Pryce-Roberts AC (68) | Review | UK | COVID-19 patients | √ | x | x | x | x | x | Venous thromboembolism, disorientation, encephalitis, meningocencephalitis, and encephalopathy |
| 36 | Puntschnigg VG (62) | Clinical trial | Germany | Patients recently recovered From COVID-19 | x | x | x | √ | x | x | – |
| 37 | Ray JR (63) | Letter to editor | Spain | Patients attended due to COVID-19 | x | √ | x | √ | √ | x | Acute coronary syndrome |
| 38 | Roche JA (64) | Hypothesis | USA | COVID-19 patients with deregulated BK signaling | x | √ | x | x | x | x | – |
| 39 | Rosen BJ (65) | Letter to editor | USA | COVID-19 patients | x | x | x | √ | x | – | – |
| 40 | Salama-Fraz J (66) | Review | Spain | Cardiometabolic health/medicine | x | x | x | √ | x | – | – |
| 41 | Sharan M (39) | Review | USA | Patients with neurological complications | √ | x | x | x | x | x | Guillain-Barré syndrome |
| 42 | Siqueira V (67) | Letter to the editor | France | Thrombotic complications in critically ill COVID-19 | x | x | x | √ | x | – | Acute limb ischemia-Pulmonary Embolism-Aortic floating thrombus |
| 43 | Stingard R (68) | Letter to the editor | Italy | Acute limb ischemia in COVID-19 patients | x | x | x | √ | x | x | – |
| 44 | Streetman-Chen Lin DA (69) | Review | USA | COVID-19 patients | x | √ | x | x | x | x | – |

**Legend:** DVT: Deep vein thrombosis; GI: gastrointestinal; PTE: pulmonary thromboembolism; DIC: disseminated intravascular coagulation.
Table 2: Identified late complications of COVID-19

| ID  | First author       | Study type     | Country | Study Population | Late complications                  | Neurologic | Lung disease | Liver disease | Heart damage | Thrombosis | Kidney disease | Stroke |
|-----|--------------------|----------------|---------|-----------------|--------------------------------------|------------|--------------|---------------|--------------|------------|----------------|--------|
| 45  | Singh Y (23)       | Letter to the editor | India   | Cellular metabolism mediated complications in COVID-19 infection | x          | √            | x             | x             | ×          | √            | ×                  | Cell death triggered by ferroptotic stress |
| 46  | Stevens D (76)     | Case-Study     | USA     | Complications of Orbital Emphysema in a COVID-19 Patient | x          | x            | x             | x             | x          | x             | x                  | –                  |
| 47  | Stradella C (60)   | Analytic       | Italy   | Analysis of ACE2 Genetic Variability Among Populations | √          | √            | x             | x             | x          | ×            | x                  | Sepsis               |
| 48  | Tian H (71)        | Review         | China   | COVID-19 patients | x          | x            | x             | x             | x          | x            | x                  | –                  |
| 49  | Thomas W (72)      | Letter to the editor | United Kingdom | Thrombotic complication of a patient with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | –                  |
| 50  | Terpos E (73)      | Review         | Greece  | Hematologic complications in COVID-19 patients | x          | x            | x             | √             | x          | x            | –                  | –                  |
| 51  | Varatharaj A (41)  | Case-control   | UK      | COVID-19 patients | √          | x            | x             | x             | x          | x            | √                  | Thrombotic complication of a patient with COVID-19 |
| 52  | Varatharajah N (24) | Letter to the editor | USA     | Microthrombotic complications of patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | Hematologic complications in COVID-19 patients |
| 53  | Wagemer F (10)     | Viewpoint      | Netherlands | COVID-19 patients | x          | x            | x             | x             | x          | x            | x                  | Coagulation abnormality |
| 54  | Wang X (6)         | Research article | China   | Chronic diseases among patients with COVID-19 | x          | x            | x             | x             | √          | x            | x                  | –                  |
| 55  | Zhe H (74)         | Review         | USA     | patients with COVID-19 | x          | √            | √             | x             | x          | x            | x                  | Coagulopathy-DIC |
| 56  | Abhous H (75)      | Review         | Morocco  | patients with COVID-19 | x          | √            | x             | x             | x          | x            | x                  | –                  |
| 57  | Khan S (76)        | Review         | Malaysia | patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | –                  |
| 58  | Khandait H (77)    | Research article | India   | patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | Coagulopathy-DIC-Pulmonary Embolism-Deep vein thrombosis |
| 59  | Magewa S S(78)     | Review         | China   | patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | –                  |
| 60  | Sheikh A B (79)    | Case-report     | USA     | 56-year-old man with COVID-19 | x          | x            | x             | √             | x          | x            | x                  | –                  |
| 61  | Arjapandian E (80) | Review         | UK      | patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | Myocarditis           |
| 62  | Vonck K (81)       | Review         | Belgium | patients with COVID-19 | √          | x            | x             | x             | x          | x            | x                  | –                  |
| 63  | Wijeratne T (82)   | Research article | India   | patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | –                  |
| 64  | Yachou Y (83)      | Review         | Russia  | patients with COVID-19 | x          | x            | x             | x             | x          | x            | x                  | –                  |
| 65  | Zaim S (84)        | Review         | UK      | patients with COVID-19 | √          | x            | √             | x             | x          | x            | x                  | –                  |

DVT: Deep vein thrombosis; GI: gastrointestinal; PTE: pulmonary thromboembolism; DIC: disseminated intravascular coagulation.