Is Microthrombosis the Main Pathology in Coronavirus Disease 2019 Severity?-A Systematic Review of the Postmortem Pathologic Findings

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Repository Citation
Fahmy OH, Daas FM, Salunkhe V, Petrey JL, Cosar EF, Ramirez J, Akca O. (2021). Is Microthrombosis the Main Pathology in Coronavirus Disease 2019 Severity?-A Systematic Review of the Postmortem Pathologic Findings. COVID-19 Publications by UMMS Authors. https://doi.org/10.1097/CCE.0000000000000427. Retrieved from https://escholarship.umassmed.edu/covid19/249

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Critical Care Explorations

Is Microthrombosis the Main Pathology in Coronavirus Disease 2019 Severity?—A Systematic Review of the Postmortem Pathologic Findings

OBJECTIVES: This systematic review attempts to retrieve and report the findings of postmortem studies including the histopathologic data of deceased coronavirus disease 2019 patients and to review the manifestations of coronavirus disease 2019–associated thrombotic pathologies reported in the recent literature.

DATA SOURCES: PubMed, Excerpta Medica Database, and Cochrane library between December 1, 2019, and August 26, 2020.

STUDY SELECTION: Investigators screened 360 unique references, retrieved published autopsy series, and report on the postmortem histopathologic information on patients who had died of coronavirus disease 2019.

DATA EXTRACTION: Investigators independently abstracted all available data including study design, participant demographics, key histopathologic findings, disease severity markers, duration of hospital stay, and cause of death.

DATA SYNTHESIS: From the 65 eligible studies, 691 total completed autopsies were included in evidence synthesis. Histopathologic evaluation of the lungs revealed presence of diffuse alveolar damage in 323 of 443 patients and pulmonary microthrombi in 242 of 326 patients. Deep venous thrombosis and pulmonary embolism were found in 41% and ~15%, respectively, of the cadavers examined for thromboembolic events. D-dimer levels were generally higher in patients with severe clinical course of coronavirus disease 2019. Plasma levels of ferritin, lactate dehydrogenase, interleukin-6, and C-reactive protein were higher in non-survivors when compared with survivors. Overall, microthrombi and extensive angiogenesis of lung vasculature were the most common pathologic findings in the lungs and microthrombi in most of the assessed organ-tissue.

CONCLUSIONS: Diffuse alveolar damage was the most predominant feature in the lungs of coronavirus disease 2019 patients who underwent postmortem assessment. Widespread pulmonary microthrombosis and extensive pulmonary angiogenesis, in addition to frequent pulmonary and extrapulmonary microthrombotic and thromboembolic findings in patients with coronavirus disease 2019, appear to be consistent with the disease-specific hypercoagulability. Further discovery efforts in assessing the link between coronavirus disease 2019, hypercoagulable state, and immunothrombosis are warranted. In the interim, increased attention to anticoagulant treatment approaches in coronavirus disease 2019 patients is needed.

KEY WORDS: coronavirus disease 2019; D-dimer; diffuse alveolar damage; microvascular thrombosis; postmortem; severe acute respiratory syndrome coronavirus 2

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Coronavirus disease 2019 (COVID-19) has been diagnosed in more than 42 million people and has taken the lives of more than 1.1 million people globally (1). COVID-19 mainly presents as pneumonia. Within
the hospitalized patients, about 20% developed critical pneumonia similar to acute respiratory distress syndrome (ARDS) (2). Severe lung disease manifestation of COVID-19—whether true pneumonia, ARDS, or a distinct pneumonitis—has been serving as the main cause of the disease-related morbidity and mortality (3, 4). Although at the beginning of the pandemic, critically ill COVID-19 patients’ mortality was as high as 70%, as in our city’s example, it mostly averaged less than 40% (5).

To expand the medical knowledge about COVID-19 pneumonia, autopsy results of deceased COVID-19 patients were deemed to be crucial and of great interest in exploring the details of the disease pathogenesis. Knowing the pathology behind the severe illness and its postmortem findings will help to understand the disease process better and will likely lead to efforts of therapeutic discovery.

Diffuse alveolar damage (DAD) and thrombotic disease processes appear to contribute to the mortality of severe COVID-19. In this systematic review, we aimed to report the postmortem findings of deceased COVID-19 patients. Specific emphasis was given to pulmonary microthrombosis and widespread thrombotic manifestations in hospitalized COVID-19 patients.

Although similar systematic reviews have been published regarding postmortem pathologic manifestations of COVID-19 (6–8), in the present analysis, we aimed to include a larger number of studies with fewer restrictions by biopsy site or manifestation type for a more comprehensive and generalizable picture of the disease. Additionally, published postmortem reviews did not direct the focus to critical illness. Providing all available postmortem pathologic evidence in an abstracted form to the physicians managing these patients will likely have potential treatment implications.

**METHODS**

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Between December 1, 2019, and August 26, 2020, literature searches were conducted in PubMed, Cochrane, and Excerpta Medica Database. The following strategy was used in PubMed and adapted as appropriate for the other databases: (“COVID-19”[All Fields] OR “COVID-2019”[All Fields] OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept] OR “severe acute respiratory syndrome coronavirus 2”[All Fields] OR “2019-nCoV”[All Fields] OR “SARS-CoV-2”[All Fields] OR “2019mCoV”[All Fields] OR (“Wuhan”[All Fields] AND (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept] OR “coronavirus”[Supplementary Concept]) AND (2019/12[PDAT] OR 2020[PDAT]))) AND (“autopsy”[MeSH Terms] OR “autopsy”[All Fields] OR “autopsy”[All Fields] OR “autopsy”[All Fields] OR “postmortem”[All Fields] OR “postmortem”[All Fields] OR “post-mortem”[All Fields]). Results were filtered to English-language human studies published after December 2019. Content experts also screened reference lists of included trials and relevant narrative reviews. A total of 549 references were retrieved. After duplicates were extracted, 360 unique records remained for screening. To reduce the risk of bias, two researchers (O.H.F., F.M.D.) screened these remaining references according to the following inclusion criteria:

1. Studies presenting pathology, histology and/or laboratory findings.
2. Patients with positive reverse transcriptase-polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
3. Articles written in English or with an available translation.

Narrative reviews, editorials, and other publications without original data were excluded, although publications with incomplete data were included if additional data were provided by corresponding authors upon request. Studies were excluded from the data synthesis if SARS-CoV-2 was not confirmed in the deceased patients. Any screening conflicts were discussed with a third content expert reviewer available for resolution as needed. Of the 360 distinct references identified through database searching, 58 studies were eligible for inclusion. Seven additional studies were identified through hand search, for a total of 65 studies included in the evidence synthesis (Fig. 1). These studies were appraised for bias, methodological quality, and significance of results but were not excluded based on their individual limitations. Data were extracted and summarized in table form (Table 1). Methodological details of the reviewed articles are included in Supplemental Table 1 (http://links.lww.com/CCX/A616). The heterogeneous nature of published literature did not allow for a full meta-analysis.
RESULTS

The 65 included studies reported pathologic and histological findings of a combined total of 691 patients, of which 677 were deceased due to COVID-19. Three of these studies (Edler et al [37], Lindner et al [62], and Wichmann et al [19]) reported data from the same cohort of patients, although any duplicate data were counted only once in our analysis. Additionally, Varga et al [15], Magro et al [14], and Sharma et al [56] presented the histological findings of biopsies obtained from 14 alive COVID-19 patients during their hospital stay, and we included these data as they provided valuable information about the involvement of the endothelium, kidneys, and other organs in patients with COVID-19.

As represented in the published clinical reports, the majority of pathologic findings were seen in the lungs ($n = 443$). However, many other histopathologic findings were reported from other organ systems, including heart ($n = 262$), brain ($n = 129$), liver ($n = 263$), kidneys ($n = 281$), prostate, testes, vascular system, and cutaneous tissue. Details related to the major organ systems were summarized below as well as in tables and figures (Tables 2–4) (Supplemental Table S2, http://links.lww.com/CCX/A617; Supplemental Table S3, http://links.lww.com/CCX/A618; Supplemental Table S4, http://links.lww.com/CCX/A619; Supplemental Table S5, http://links.lww.com/CCX/A620).

Respiratory System

Out of 443 patients with postmortem lung tissue samples evaluated histologically, 86% showed features of DAD in exudative and proliferative phases, characterized by alveolar edema, hyaline membrane (HM) formation, as well as some other changes such as intraalveolar fibrin deposition, and proliferation of pneumocytes and fibroblasts. DAD is a known hallmark feature of ARDS.

Another frequently observed key finding was the presence of vascular pathology including fibrin thrombi inside the pulmonary vasculature. Pulmonary thrombi were found in 242 of 326 autopsies examined (~74%). The thrombi were more often seen in the small and mid-sized vessels of the lung, in areas where DAD existed (40).
### TABLE 1.
Systematic Review of Postmortem Findings in Coronavirus Disease 2019

| References | Date of Publication | Study Design | No. of Participants | Males, % | Age, yr | In-Hospital Deaths, % | Country |
|------------|---------------------|--------------|---------------------|----------|---------|----------------------|---------|
| Xu et al (9) | February 17, 2020 | Autopsy report | 1 | 100 | 50 | 100 | China |
| Zhang et al (10) | March 12, 2020 | Case report | 1 | 100 | 72 | 100 | China |
| Su et al (11) | April 09, 2020 | Autopsy series | 26 | 73.1 | Median: 68 (range: 39–87) | NR | China |
| Tian et al (12) | April 14, 2020 | Autopsy series | 4 | 75 | Median: 76 (range: 59–81) | 100 | China |
| Dolhnikoff et al (13) | April 15, 2020 | Autopsy series | 10 | 50 | Mean: 67.8 (range: 33–83) | NR | Brazil |
| Magro et al (14) | April 15, 2020 | Case series | 5 | 60 | Median: 62 (range: 32–73) | 100 (n = 2) | United States |
| Varga et al (15) | April 20, 2020 | Case series | 3 | 66.7 | Median: 69 (range: 58–71) | 50 (n = 2) | Switzerland |
| Konopka et al (16) | April 28, 2020 | Autopsy report | 1 | 100 | 37 | 100 | United States |
| Menter et al (17) | May 04, 2020 | Autopsy series | 21 | 81 | Mean: 76 (range: 53–96) | 100 | Switzerland |
| Barton et al (18) | May 05, 2020 | Autopsy series | 2 | 100 | Range: 42–77 | 50 | United States |
| Wichmann et al (19) | May 06, 2020 | Prospective cohort study | 12 | 75 | Median: 73 (range: 52–87) | 83.3 | Germany |
| Buja et al (20) | May 07, 2020 | Autopsy series | 3 | 100 | Median: 48 (range: 34–62) | 33.3 | United States |
| Navarro Conde et al (21) | May 11, 2020 | Autopsy report | 1 | 100 | 69 | 100 | Spain |
| Grimes et al (22) | May 12, 2020 | Autopsy series | 2 | 100 | NR | 100 | United States |
| Craver et al (23) | May 03, 2020 | Autopsy report | 1 | 100 | 17 | 0 | United States |
| Lax et al (24) | May 14, 2020 | Prospective autopsy series | 11 | 72.7 | Mean: 80.55 (range: 66–91) | 100 | Austria |
| Adachi et al (25) | May 15, 2020 | Autopsy report | 1 | 0 | 84 | 100 | Japan |
| Yan et al (26) | May 18, 2020 | Autopsy report | 1 | 0 | 44 | 100 | United States |
| Ackermann et al (27) | May 21, 2020 | Comparative study | Coronavirus disease 2019 | 7 | 71.4 | Range: 66–96 | 100 | Germany |
| Schaller et al (28) | May 21, 2020 | Autopsy series | 10 | 70 | Median: 79 (range: 64–90) | 100 | Germany |
| Bryce et al (29) | May 22, 2020 | Autopsy series | 67 | 56.7 | Median: 69 (range: 34–94) | 100 | United States |
| Duarte-Neto et al (30) | May 22, 2020 | Autopsy series | 10 | 50 | Median: 69 (range: 33–83) | 100 | Brazil |

(Continued)
| References                          | Date of Publication | Study Design | **No. of Participants** | **Males, %** | **Age, yr** | **In-Hospital Deaths, %** | Country       |
|-------------------------------------|---------------------|--------------|-------------------------|--------------|-------------|----------------------------|---------------|
| The COVID-19 Autopsy Project (31)   | May 23, 2020        | Autopsy series | 1                       | 100          | 54          | 100                        | Spain         |
| Reichard et al (32)                 | May 24, 2020        | Autopsy report | 1                       | 100          | 71          | 100                        | United States |
| Aguiar et al (33)                   | May 26, 2020        | Autopsy report | 1                       | 0            | 31          | 0                          | Switzerland   |
| Sekulic et al (34)                  | May 26, 2020        | Autopsy series | 2                       | 100          | Range: 54–81 | 100                        | United States |
| Fox et al (35)                      | May 27, 2020        | Autopsy series | 10                      | NR           | Median: 64.5 | (range: 44–78)             | United States |
| Yang et al (36)                     | May 31, 2020        | Autopsy series | 12                      | 100          | Mean: 65 (range: 42–87) | NR           | China                     |
| Edler et al (37)                    | June 04, 2020       | Autopsy series | 80                      | 57.5         | Median: 82.4 | (range: 52–96)             | Germany       |
| von Weyhern et al (38)              | June 04, 2020       | Autopsy series | 6                       | 66.7         | Range: 58–82 | 100                        | Germany       |
| Suess et al (39)                    | 06/05, 2020         | Autopsy report | 1                       | 100          | 59          | 0                          | Switzerland   |
| Carsana et al (40)                  | June 08, 2020       | Autopsy series | 38                      | 86.8         | Mean: 69 (range: 32–86) | 100          | Italy                     |
| Solomon et al (41)                  | June 12, 2020       | Autopsy series | 18                      | 77.8         | Median: 62 (range: 53–75) | 100          | United States             |
| Konopka et al (42)                  | June 15, 2020       | Autopsy series | SARS-CoV-2 (positive)   | 8            | 62.5        | Range: 37–79               | United States |
|                                     |                     |              | SARS-CoV-2 (negative)   | 8            |             |                            |               |
| Beigmohammadi et al (43)            | June 19, 2020       | Autopsy series | 7                       | 71.4         | Mean: 67.85 (range: 46–84) | 100          | Iran                      |
| Schaefer et al (44)                 | June 19, 2020       | Autopsy series | 7                       | 71.4         | Median: 66 (range: 50–77) | 100          | United States             |
| Wang et al (45)                     | June 21, 2020       | Autopsy series | 2                       | 50           | Range: 53–62 | 100                        | China         |
| Rapkiewicz et al (46)               | June 25, 2020       | Autopsy series | 7                       | 42.9         | Range: 44–65 | 71.4                        | United States |
| Tombolini et al (47)                | June 29, 2020       | Autopsy series | 2                       | 0            | Range: 61–67 | 0                          | Italy         |
| Bosmuller et al (48)                | June 30, 2020       | Autopsy series | 4                       | 75           | Range: 59–79 | 75                         | Germany       |
| Youd et al (49)                     | June 30, 2020       | Autopsy series | 3b                      | 33.3         | Range: 73–88 | 0                          | United Kingdom |
| Prieto-Perez et al (50)             | July 3, 2020        | Autopsy series | 33                      | 63.6         | Median: 79 (range: 53–98) | 100          | Spain                     |
| Santana et al (51)                  | July 3, 2020        | Autopsy report | 1                       | 100          | 71          | 100                        | Brazil        |
| Dorward et al (52)                  | July 04, 2020       | Autopsy series | 11                      | 90.9         | Mean: 77 (range: 64–97)   | NR            | United Kingdom            |
| Flikweert et al (53)                | July 08, 2020       | Autopsy series | 7                       | 71.4         | Median: 74 (range: 58–83) | 100          | Netherlands               |

(Continued)
Intravascular and intramural fibrin thrombi as well as areas of infarcts were observed in a few patients (24, 29, 30, 46, 65, 73). In a study by Lindner et al. (62), a high viral load of SARS-CoV-2 RNA was identified in the myocardial tissue of 16 patients of the 24 evaluated. Myocarditis and myocardial infarction were reported only in 4.2% and 3.8% of the examined patients. 

**TABLE 1. (Continued). Systematic Review of Postmortem Findings in Coronavirus Disease 2019**

| References       | Date of Publication | Study Design       | No. of Participants | Males, % | Age, yr | In-Hospital Deaths, % | Country |
|------------------|---------------------|-------------------|---------------------|----------|---------|------------------------|---------|
| Stone et al (54) | July 08, 2020       | Autopsy report    | 1                   | 0        | 76      | 100                    | United States |
| Sonzogni et al (55) | July 12, 2020       | Autopsy series    | 48                  | NR       | Mean: 71 (range: 32–86) | NR       | Italy |
| Sharma et al (56) | July 13, 2020       | Case series       | 10                  | 50       | Mean: 65 (range: 45–77) | 50c      | United States |
| Bradley et al (57) | July 16, 2020       | Autopsy series    | 14                  | 42.9     | Median: 73.5 (range: 42–84) | 100      | United States |
| Grosse et al (58) | July 16, 2020       | Autopsy series    | 14                  | 64.3     | Median: 81 (range: 55–94) | 100      | Austria |
| Prilutski et al (59) | July 18, 2020       | Autopsy series    | 4                   | 75       | Range: 64–91      | 100      | United States |
| Golmai et al (60) | August 31, 2020     | Autopsy series    | 12                  | 83.3     | Range: 49–92      | 100      | United States |
| Conklin et al (61) | July 24, 2020       | Retrospective cohort study | 16 | NR       | NR       | 100                    | United States |
| Lindner et al (62) | July 27, 2020       | Autopsy series    | 39                  | 41       | Median: 83 (inter-quartile range: 78–89) | NR       | Germany |
| Schwensen et al (63) | July 28, 2020       | Autopsy report    | 1                   | 0        | In her 80s       | 100      | Denmark |
| Santoriello et al (64) | July 29, 2020       | Autopsy series    | 42                  | 69       | Median: 71.5 (range: 38–97) | 85.7     | United States |
| Cirstea et al (65) | August 05, 2020     | Autopsy report    | 1                   | 0        | 30        | 0                     | Romania |
| Ducloyer et al (66) | August 06, 2020     | Autopsy report    | 1                   | 100      | 75        | 0                     | France |
| Kantonen et al (67) | August 06, 2020     | Autopsy series    | 4                   | 75       | Range: 38–90     | 100 (n = 2) | Finland |
| Cipolloni et al (68) | August 09, 2020     | Autopsy series    | 2d                  | 100      | Range: 42–70     | 50       | Italy |
| Remmelink et al (69) | August 12, 2020     | Autopsy series    | 17                  | 70.6     | Median: 72 (range: 49–91) | 100      | Belgium |
| Okudela et al (70) | August 13, 2020     | Autopsy report    | 1                   | 0        | 93        | 100                   | Japan |
| Skok et al (71) | August 20, 2020     | Autopsy series    | 19e                  | 60.7     | Median: 82.5 (range: 66–96) | 100      | Austria |
| Roden et al (72) | August 21, 2020     | Autopsy series    | 8                   | 87.5     | Median: 79 (range: 69–96) | 100      | United States |
| Nadkarni et al (73) | August 26, 2020     | Autopsy series    | 26                  | 61.5     | NR        | 100                   | United States |

NR = not reported, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

*Alive subjects were included in the study.

*The study included nine participants; however, only three tested positive for SARS-CoV-2 and included in the review.

*Biopsies were taken from alive patients; however, on follow-up, five patients died, and five patients survived.

*The study included two SARS-CoV-2 positive patients in addition to one control.

*The study included 28 participants; however, only 19 were autopsied and included in the review.

**Heart**

Intravascular and intramural fibrin thrombi as well as areas of infarcts were observed in a few patients (24, 29, 30, 46, 65, 73). In a study by Lindner et al. (62), a high viral load of SARS-CoV-2 RNA was identified in the myocardial tissue of 16 patients of the 24 evaluated. Myocarditis and myocardial infarction were reported only in 4.2% and 3.8% of the examined patients.
patients, respectively. Microthrombi were found in 7.3% of the patients (Table 3). Although these numbers are prevalent enough to be reported in here, they are less prevalent than expected when compared with the clinical reports from patients recovering from COVID-19 (74).

Brain

Microthrombi were seen in postmortem brain tissue samples of 4.7% of the patients. Encephalitis was reported only in one study (38). Encephalitis and/or meningitis were reported in 5.4% of evaluated patients. Hemorrhagic lesions were seen in six of 129 examined brains. Ischemic lesions and infarcts were reported in 9.3% of patients.

Kidneys

Microthrombi were reported in the kidney tissue samples of 12.1% of the patients.

Liver

Postmortem examination of the liver revealed thrombosis and microthrombosis in 27.4% of evaluated cases.

Vascular System

Intravascular thrombi were reported in various organ systems. We presented these findings for each organ system under the respective section in Tables 2–4 and reported endothelial and thrombotic changes under the vascular system section separately in Supplemental Table S5 (http://links.lww.com/CCX/A620).

In addition to the microthrombi, 41% of 110 postmortem assessments reported deep vein thrombosis (DVT). Wichmann et al (19) reported bilateral leg involvement in all patients who developed DVT. In total, pulmonary embolism (PE) was reported in 39 of 257 deceased COVID-19 patients. Interestingly, prostatic vein plexus thrombosis was observed in 15 male patients (37). Three patients demonstrated cutaneous coagulopathy (14).

DISCUSSION

Similarly with SARS-CoV and other viruses from the same family, major pathologic respiratory system finding of this COVID-19 cohort of autopsies was epithelial changes. Mainly, DAD and HM formation, which generally corresponds to the clinical course of ARDS. PEs were reported in 15% of the patients, but a coexisting DVT was not necessarily found in patients who had documented PE (24, 75). Another peculiar finding was the type or observed shape of pulmonary emboli, which conformed to the walls of pulmonary arteries. This finding led many to hypothesize that these pulmonary emboli are in fact pulmonary thrombi, which were formed in the lung vasculature (24, 46, 75).

Possibly, the most interesting finding of this report is the abundance of microvascular damage, which was reported as microvascular thrombi. Interestingly, microthrombi was not only reported in the lungs, but it was also shown in the other organ systems including brain, kidneys, spleen, heart, and liver at significant prevalence. In addition to interesting predominance of microthrombi, multiple reports presented various levels of endothelial injury. Endothelial injury may suggest a triggering mechanism, which may possibly being initiated by hypercoagulable and hyperinflammatory pathways. Patterns of endothelial injury and microthrombi formation may happen simultaneously, or one may follow the other (8). Immunothrombotic dysregulation appears to strongly contribute to the disease severity in COVID-19 (76).

Intravascular microthrombosis is not specific to COVID-19; it is seen in ARDS due to various other causes, such as sepsis and trauma. However, the prevalence and extensiveness of microthrombi in patients with COVID-19-associated DAD is more prominent compared with other severe disease states (27). Microthrombi in the lungs were observed in up to 42% of evaluated patients with nontraumatic ARDS of other causes, whereas our review detected pulmonary (micro) thrombosis in 74% of patients with COVID-19 (77). To shed more light on the difference of SARS-CoV-2 from other respiratory viruses, Ackermann et al (27) examined the lungs of deceased patients with COVID-19 and compared them with the lungs of patients who died of H1N1-associated ARDS as well as to the uninfected lungs that were donated but not transplanted. First, the mean lung weight was found to be much higher in patients who died of influenza compared with those who died of SARS-CoV-2 infection, and this was explained by the extensive interstitial edema and severe
### TABLE 2. Summary of Postmortem Findings in the Lung Tissue

| References                | No. of Evaluated Deceased Patients With Laboratory Confirmed Coronavirus Disease 2019 | Diffuse Alveolar Damage/Hyaline Membrane, n | Vascular (micro)Thrombi, n | PE/Infarct, n |
|---------------------------|-----------------------------------------------------------------------------------|---------------------------------------------|-----------------------------|---------------|
| Xu et al (9)              | 1                                                                                 | 1                                           | NR                          | NR            |
| Zhang et al (10)          | 1                                                                                 | 1                                           | NR                          | NR            |
| Tian et al (12)           | 4                                                                                 | 4                                           | 2                           | NR            |
| Dolhnikoff et al (13)     | 10                                                                                | 10                                          | 8                           | NR            |
| Magro et al (14)          | 2                                                                                 | 1                                           | NR                          | NR            |
| Varga et al (15)          | 2                                                                                 | 1                                           | NR                          | NR            |
| Konopka et al (16)        | 1                                                                                 | 1                                           | NR                          | NR            |
| Menter et al (17)         | 21                                                                                | 16                                          | 5/11                        | PE (4)        |
| Barton et al (18)         | 2                                                                                 | 1                                           | 1                           | PE (0)        |
| Wichmann et al (19)       | 12                                                                                | 8                                           | 5                           | PE (5)        |
| Buja et al (20)           | 3                                                                                 | 2                                           | 1                           | PE (1)        |
| Navarro Conde et al (21)  | 1                                                                                 | 1                                           | Mid-sized PAT (1)           | NR            |
| Grimes et al (22)         | 2                                                                                 | 0                                           | 2                           | PE (2)        |
| Craver et al (23)         | 1                                                                                 | 0                                           | 0                           | PE (0)        |
| Lax et al (24)            | 11                                                                                | 10                                          | PAT (11)                    | Infarcts (9)  |
|                           |                                                                                   |                                             |                             | PE (0)        |
| Adachi et al (25)         | 1                                                                                 | 1                                           | NR                          | NR            |
| Yan et al (26)            | 1                                                                                 | 1                                           | NR                          | NR            |
| Ackermann et al (27)      | 7                                                                                 | 7                                           | 7                           | PE (0)        |
| Schaller et al (28)       | 10                                                                                | 10                                          | NR                          | NR            |
| Bryce et al (29)          | 25a                                                                               | 22                                          | 21/23                       | PE (4)        |
| Duarte-Neto et al (30)    | 10                                                                                | 10                                          | 8                           | NR            |
| The COVID-19 Autopsy Project (31) | 1                          | 1                                           | 1                           | NR            |
| Aguiar et al (33)         | 1                                                                                 | 1                                           | NR                          | NR            |
| Sekulic et al (34)        | 2                                                                                 | 2                                           | 0                           | NR            |
| Fox et al (35)            | 10                                                                                | 10                                          | 10                          | NR            |
| Edler et al (37)          | 80                                                                                | 8/12b                                       | NR                          | PE (17)       |
| von Weyhern et al (38)    | 6                                                                                 | 5                                           | NR                          | Infarct (1)   |

Note: NR denotes not reported.
| C-Reactive Protein, mg/L | Interleukin-6, pg/mL | D-dimer, ng/mL |
|--------------------------|----------------------|---------------|
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | NR                   | NR            |
| NR                       | Range: 103–278 (n = 5) | Range: 400–10,400 (n = 5) |
| Median: 189 (range: 18–348) (n = 10) | NR | Median: 23,100 (range: 5,700 to > 200,000) (n = 5) |
| Range: 43–272 | NR | NR |
| Range: 238–3,467 | NR | Range: 439–15,532 (n = 7) |
| Range: 1.32–3.4 | NR | NR |
| 114 | At T0: undetectable | At death: 397 |
| NR | NR | NR |
| NR | NR | NR |
| Mean at T0: 139 (range: 15–529) (n = 28) | Mean at T0: 379 (range: 45–1,406) (n = 14) | Mean at T0: 4,400 (range: 600–17,200) (n = 22) |
| Mean at death: 235 (range: 26–476) (n = 35) | Mean at death: 451 (range: 10–3,181) (n = 26) | Mean at death: 7,400 (range: 700–19,200) (n = 32) |
| Median: 81 (range: 23–110.5) | NR | Range: 28–89 (n = 2) |
| NR | NR | NR |
| Postmortem: 48 | NR | NR |
| NR | NR | NR |
| NR | NR | Range: 249–47,559 (n = 6) |
| NR | NR | NR |
| Range: 67.5–304.4 | 180.4–1,226 | NR |

(Continued)
### TABLE 2. (Continued).
Summary of Postmortem Findings in the Lung Tissue

| References                  | No. of Evaluated Deceased Patients With Laboratory Confirmed Coronavirus Disease 2019 | Diffuse Alveolar Damage/Hyaline Membrane, n | Vascular (micro)Thrombi, n | PE/Infarct, n |
|-----------------------------|----------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------|---------------|
| Suess et al (39)            | 1                                                                                     | 1                                         | 1                           | NR            |
| Carsana et al (40)          | 38                                                                                    | 38                                        | 33                          | NR            |
| Konopka et al (42)          | 8                                                                                     | 7                                         | 7                           | NR            |
| Beigmohammadi et al (43)    | 7                                                                                     | 5                                         | NR                          | NR            |
| Schaefer et al (44)         | 7                                                                                     | 7                                         | 5                           | NR            |
| Wang et al (45)             | 2                                                                                     | 2                                         | 2                           | NR            |
| Rapkiewicz et al (46)       | 7                                                                                     | 7                                         | 4                           | PE (0)        |
| Tombolini et al (47)        | 2                                                                                     | 2                                         | 2                           | NR            |
| Bosmuller et al (48)        | 4                                                                                     | 2                                         | 3                           | NR            |
| Youd et al (49)             | 3                                                                                     | 3                                         | 0                           | NR            |
| Prieto-Perez et al (50)     | 20                                                                                    | 20                                        | 12                          | NR            |
| Santana et al (51)          | 1                                                                                     | 0                                         | 1                           | NR            |
| Dorward et al (52)          | 11                                                                                    | 8                                         | 8                           | NR            |
| Flikweert et al (53)        | 7                                                                                     | 1                                         | 6                           | NR            |
| Stone et al (54)            | 1                                                                                     | 1                                         | 1                           | NR            |
| Bradley et al (57)          | 14                                                                                    | 12                                        | 5                           | PE (2)        |
| Grosse et al (58)           | 14                                                                                    | 14                                        | Microthrombi (11)           | Infarcts (2)  |
|                             |                                                                                        |                                            | Mid-sized PAT (5)           | PE (1)        |
| Prilutskiy et al (59)       | 4                                                                                     | 4                                         | NR                          | NR            |
| Schwensen et al (63)        | 1                                                                                     | 1                                         | 0                           | PE (1)        |
| Cirstea et al (65)          | 1                                                                                     | 1                                         | 1                           | NR            |
| Ducloyer et al (66)         | 1                                                                                     | 1                                         | NR                          | NR            |
| Cipolloni et al (68)        | 2                                                                                     | 2                                         | 2                           | NR            |
| Remmelink et al (69)        | 17                                                                                    | 15                                        | 11                          | Infarcts (4)  |
|                             |                                                                                        |                                            |                             | PE (3)        |
| Okudela et al (70)          | 1                                                                                     | 1                                         | 1                           | PE (0)        |
| Skok et al (71)             | 19                                                                                    | 19                                        | PAT (19)                    | Infarcts (16) |
|                             |                                                                                        |                                            |                             | PE (0)        |
| Roden et al (72)            | 8                                                                                     | 6                                         | Microthrombi (5)            | NR            |
|                             |                                                                                        |                                            | PAT (2)                     |               |
| Nadkarni et al (73)         | 26                                                                                    | 15                                        | 15                          | PE (4)        |
| **Summary**                 | **443**                                                                                | **323/375** (86.1%)                        | **242/326** (74.2%)         | **PE: 39/257** (15.2%) |

NR = not reported, PAT = pulmonary arterial thrombi, PE = pulmonary embolism, T0 = at admission.

*Of a total pool of 67 patients.

Histological examination of lungs was performed in only 12 of the 80 study participants.
| C-Reactive Protein, mg/L | Interleukin-6, pg/mL | d-dimer, ng/mL |
|--------------------------|----------------------|----------------|
| NR                       | NR                   | NR             |
| NR                       | NR                   | >10× the upper limit of normal range (n = 26) |
| NR                       | NR                   | NR             |
| NR                       | NR                   | NR             |
| Range at peak: 125.8–148.3 | Range at peak: 20.28–27.9 | NR |
| Range at peak: 169–379 (n = 5) | Range at peak: < 5 to 834 (n = 5) | Range at peak: 320 to > 52,926 (n = 4) |
| NR                       | NR                   | NR             |
| NR                       | NR                   | NR             |
| NR                       | NR                   | NR             |
| Median: 10.9 (range: 0.5–40.1) | Median: 40.6 (range: 6.7–241.4) | Median: 3,114 (522–64,533) |
| 12                       | NR                   | NR             |
| NR                       | NR                   | NR             |
| NR                       | NR                   | At T0: 3,592    |
| Range at T0: 0.3–39 (n = 14) | Range at T0: 34.1–1,133 (n = 9) | Range at T0: 1,240–13,100 (n = 14) |
| Range at death: 2–40.3 (n = 14) | Range at death: 34.4–13,000 (n = 9) | Range at death: 950 to > 35,200 (n = 14) |
| Range: 77.7–365.1        | NR                   | NR             |
| NR                       | NR                   | NR             |
| NR                       | NR                   | NR             |
| 163                      | NR                   | NR             |
| NR                       | NR                   | NR             |
| Range: 27–270 (n = 17)   | NR                   | 899–8,531 (n = 8) |

NR = not reported, PAT = pulmonary arterial thrombi, PE = pulmonary embolism, T0 = at admission.

Of a total pool of 67 patients.

Histological examination of lungs was performed in only 12 of the 80 study participants.
### Table 3. Summary of Postmortem Findings in the Heart and Brain Tissues

| References            | No. of Patients Evaluated | Main Pathologic Findings                                      | Potential Mechanistic Biomarkers |
|-----------------------|---------------------------|---------------------------------------------------------------|----------------------------------|
|                       |                           | Cardiac System—Heart                                           | CRP, mg/L | IL-6, pg/mL | d-dimer, ng/mL |
| Menter et al (17)     | 21                        | Acute MI (1)                                                   | NR        | Range: 103–278 (n = 5) | Range: 400–10,400 (n = 5) |
| Barton et al (18)     | 2                         | Acute ischemic injury (1)                                     | NR        | NR          | NR             |
|                       |                           | Lymphocytic myocarditis (1)                                   | NR        | NR          | NR             |
|                       |                           | Lymphocytic pericarditis (3)                                  | NR        | NR          | NR             |
| Craver et al (23)     | 1                         | Eosinophilic myocarditis (1)                                  | NR        | NR          | NR             |
| Lax et al (24)        | 11                        | Endocardial mural thrombi in left ventricle (1)               | Range: 238.1–3,466.7 (n = 11)    | NR          | Range: 439–15,532 (n = 7) |
|                       |                           | Thrombosis of a myocardial vein (1)                          | NR        | NR          | NR             |
|                       |                           | Focal lymphocytic infiltrate (1)                              | NR        | NR          | NR             |
| Schaller et al (28)   | 10                        | Mild lymphocytic myocarditis (4)                              | NR        | NR          | NR             |
|                       |                           | Epicarditis (2)                                               | NR        | NR          | NR             |
| Bryce et al (29)      | 25a                       | Small vessel thrombi in areas of epicardial inflammatory infiltrates (3) | Mean at T0: 139.1 (range: 15.1–528.9) (n = 28) | Mean at T0: 375.8 (range: 45.5–1,406) (n = 14) | Mean at T0: 4,400 (range: 600–17,200) (n = 22) |
|                       |                           | Patchy epicardial mononuclear infiltrate (15)                 | Mean at death: 235 (range: 26.2–475.8) (n = 35) | Mean at death: 450.7 (range: 10.4–3,181) (n = 26) | Mean at death: 7,400 (range: 700–19,200) (n = 32) |
| Duarte-Neto et al (30) | 10                       | Mild lymphomononuclear myocarditis (2)                       | Median: 8.12 (range: 23–110.5)    | NR          | Range: 28.435–89.513 (n = 2) |
|                       |                           | Fibrin microthrombi (2)                                       | NR        | NR          | NR             |
| Edler et al (37)      | 12                        | Lymphocytic myocarditis (1)                                   | NR        | NR          | NR             |
| Beigmohammadi et al (43)| 7              | Interstitial inflammation (4)                                 | NR        | NR          | NR             |
| Rапкевич и al (46)    | 7                         | Platelet-rich fibrin microthrombi (7)                        | Range at peak: 169–379 (n = 5)    | Range at peak: < 5 to 834 (n = 5)    | Range at peak: 320 to > 52,926 (n = 4) |
|                       |                           | Cardiac venous thrombosis (2)                                 | NR        | NR          | NR             |
|                       |                           | Early ischemic injury (3)                                     | NR        | NR          | NR             |
|                       |                           | Mural fibrin thrombi (2)                                      | NR        | NR          | NR             |
| Bradley et al (57)    | 14                        | Focal lymphocytic myocarditis (1)                             | NR        | NR          | NR             |

(Continued)
# TABLE 3. (Continued).
Summary of Postmortem Findings in the Heart and Brain Tissues

## Cardiac System—Heart

| References            | No. of Patients Evaluated | Main Pathologic Findings | Potential Mechanistic Biomarkers |
|-----------------------|---------------------------|--------------------------|---------------------------------|
| Grosse et al (58)     | 14                        | Acute MI (3)             | Range at T0: 0.3–39 (n = 14)    |
|                       |                           |                          | Range at T0: 34.1–1,133 (n = 9)  |
|                       |                           |                          | Range at death: 2–40.3 (n = 14)  |
|                       |                           |                          | Range at death: 34.4–1,133 (n = 9) |
|                       |                           |                          | Range at death: 950 to > 35,200 (n = 14) |
| Lindner et al (62)    | 39                        | SARS-CoV-2 RNA in myocardial tissue (24) with viral load more than 1,000 copies per µg RNA in (16) | NR | NR | NR |
| Cirstea et al (65)    | 1                         | Intracardiac thrombus (1) | NR | NR | NR |
| Remmelink et al (69)  | 17                        | Acute MI (2)             | Range: 27–270 (n = 17) | NR | 899–8,531 (n = 8) |
| Nadkarni et al (73)   | 26                        | Microthrombi (4)         | NR | NR | NR |
| Summary               | 26b                       | Myocarditis (4.2%), MI (3.8%), microvascular/mural thrombi (7.3%) | |

## Neurologic System—Brain

| References            | No. of Patients Evaluated | Main Pathologic Findings | Potential Mechanistic Biomarkers |
|-----------------------|---------------------------|--------------------------|---------------------------------|
| Bryce et al (29)      | 20a                       | Widespread microthrombi, often associated with acute, small, and patchy infarction (6) | Mean at T0: 139.1 (range: 15.1–528.9) (n = 28) |
|                       |                           |                          | Mean at T0: 375.8 (range: 45.5–1,406) (n = 14) |
|                       |                           |                          | Mean at death: 235 (range: 26.2–475.8) (n = 35) |
|                       |                           |                          | Mean at death: 450.7 (range: 10.4–3,181) (n = 26) |
|                       |                           |                          | Mean at death: 7,400 (range: 700–19,200) (n = 32) |
| Reichard et al (32)   | 1                         | Acute disseminated encephalomyelitis-like picture (1) | NR | NR | NR |
|                       |                           | Cerebral white matter hemorrhagic lesions (1) |
|                       |                           | Cortical microscopic infarcts (1) |
| von Weyhern et al (38) | 6                         | Encephalitis (5)         | Range: 67.5–304.4 |
|                       |                           | Lymphocytic meningitis (6) | Range: 180.4–1,226 |
| Solomon et al (41)    | 18                        | Nonspecific acute ischemic hypoxic injury (18) | NR | NR | NR |

(Continued)
### TABLE 3. (Continued).
Summary of Postmortem Findings in the Heart and Brain Tissues

| References                  | No. of Patients Evaluated | Main Pathologic Findings                                                                 | Potential Mechanistic Biomarkers |
|-----------------------------|---------------------------|-----------------------------------------------------------------------------------------|----------------------------------|
|                             |                           |                                                                                         | CRP, mg/L | IL-6, pg/mL | D-dimer, ng/mL |
| **Cardiac System—Heart**    |                           |                                                                                         |         |             |               |
| Bradley et al (57)          | 5c                        | Punctate subarachnoid hemorrhages and punctate brainstem hemorrhages (1)                  | NR       | NR          | NR            |
|                             |                           | Range at T0: 0.3–39 (n = 14)                                                             | Range at death: 2–40.3 (n = 14)  | Range at death: 34.4–13,000 (n = 9) | Range at death: 950 to > 35,200 (n = 14) |
| Grosse et al (58)           | 7                         | Acute cerebral infarction (1)                                                            | Range at T0: 34.1–1,133 (n = 9) | Range at T0: 1,240–13,100 (n = 14) |
|                             |                           | Range at death: 1,240–13,100 (n = 9)                                                    | Range at death: 1,240–13,100 (n = 9) | Range at death: 1,240–13,100 (n = 9) | Range at death: 1,240–13,100 (n = 9) |
|                             |                           | Range at death: 34.1–1,133 (n = 9)                                                     | Range at death: 34.1–1,133 (n = 9) | Range at death: 34.1–1,133 (n = 9) | Range at death: 34.1–1,133 (n = 9) |
| Conklin et al (61)          | 1                         | Widespread microvascular injury (petechial hemorrhages and microscopic ischemic lesions) (1) | NR       | NR          | NR            |
| Kantonen et al (67)         | 4                         | Ischemic injuries, widespread microhemorrhages in white and deep gray matter (1)         | NR       | NR          | NR            |
|                             |                           | Mild to moderate hypoxic injuries (3)                                                    | NR       | NR          | NR            |
| Remmelink et al (69)        | 11d                       | Cerebral focal necrosis (3) SARS-CoV-2 in the brain by reverse transcriptase-polymerase chain reaction (9) | Range: 27–270 (n = 17) | NR          | Range: 899–8,531 (n = 8) |
| Nadkarni et al (73)         | 26                        | Cerebral infarction (2)                                                                 | NR       | NR          | NR            |
| **Summary**                 | 129b                      | Encephalitis/meningitis (5.4%) Hemorrhage (4.7%) Ischemia/infarct/stroke (9.3%) Thrombosis/microvascular thrombi (4.7%) |         |             |               |

CRP = C-reactive protein, IL-6 = interleukin-6, MI = myocardial infarction, NR = not reported, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, T0 = at admission.

1Of a total pool of 67 patients.

2This number includes organs that were examined and did not show significant histopathologic findings; however, those were counted toward the total number of organs examined.

1Of a total pool of 14 patients.

2Of a total pool of 17 patients with significant histopathologic findings.

Fibrin deposition in the influenza lungs. Intravascular thrombi were found in pulmonary arteries and alveolar capillaries in all of the patients in both the COVID-19 and H1N1 groups. However, the thrombi were nine times more widespread in the COVID-19 cohort, and the extent of angiogenesis was nearly three times higher in the COVID-19 lungs. Possibly, the profound immunothrombosis in the lungs of COVID-19 patients is the cause of ischemia and subsequent angiogenesis (78). Newly formed blood vessels will further increase inflammation. Pulmonary microthrombosis can justify the near-normal compliance, high-elasticity phenotype of COVID-19, but with ventilation perfusion mismatch, and severe hypoxemia (79).
### TABLE 4.
Summary of Postmortem Findings in the Kidneys and Liver Tissues

| References                | No. of Patients Evaluated | Main Pathologic Findings                                                                 | Potential Mechanistic Biomarkers | CRP, mg/L            | IL-6, pg/mL | θ-dimer, ng/mL |
|---------------------------|---------------------------|-----------------------------------------------------------------------------------------|----------------------------------|----------------------|-------------|----------------|
| Su et al (11)             | 26                        | Glomerular segmental fibrin thrombi and endothelial injury (3) ATI (26)                   | NR                               | NR                   | Median: 2,860 (range: 900 to > 8,000) (n = 20) |
| Menter et al (17)         | 17                        | DIC with small fibrin thrombi in glomerular capillaries (3)                              | NR                               | Range: 103–278 (n = 5) | Range: 400–10,400 (n = 5) |
| Wichmann et al (19)       | 12                        | Kidney infarctions (1) Shock kidneys (1)                                                | Median: 189 (range: 18–348) (n = 10) | NR                   | Median: 23,100 (range: 5,700 to > 200,000) (n = 5) |
| Bryce et al (29)          | 25a                       | Thromboemboli (1)                                                                       | Mean at T0: 139.1 (range: 15.1–528.9) (n = 28) | Mean at T0: 375.8 (range: 45.5–1,406) (n = 14) | Mean at T0: 4,400 (range: 600–17,200) (n = 22) |
|                           |                           |                                                                                         | Mean at death: 235 (range: 26.2–475.8) (n = 35) | Mean at death: 450.7 (range: 10.4–3,181) (n = 26) | Mean at death: 7,400 (range: 700–19,200) (n = 32) |
| Buja et al (20)           | 3                         | Fibrin-platelet thrombus in kidney (1)                                                  | NR                               | NR                   | NR          | NR             |
| Adachi et al (25)         | 1                         | Glomerular microthrombi (suggestive of early DIC) (1)                                    | Range during admission: 1.32–3.4 | NR                   | NR          | NR             |
| Duarte-Neto et al (30)    | 8b                        | Fibrin microthrombi in glomeruli (6)                                                    | Median: 8.12 (range: 23–110.5) | NR                   | Range: 28.435–89.513 (n = 2) |
| Rapkiewicz et al (46)     | 7                         | Platelet-rich fibrin microthrombi in scattered peritubular capillaries and venules (7)  | Range at peak: 169–379 (n = 5) | Range at peak: < 5 to 834 (n = 5) | Range at peak: 320 to > 52,926 (n = 4) |
|                           |                           | Thrombotic microangiopathy in glomeruli (1)                                             | Thrombotic microangiopathy (1)    |                      |             |                |
| Sharma et al (56)         | 10                        | Acute tubular necrosis (10) Thrombotic microangiopathy (2) Endothelial injury (4)       | NR                               | NR                   | NR          | NR             |
| Bradley et al (57)        | 14                        | Organizing thrombus in a small renal vein (1)                                           | NR                               | NR                   | NR          | NR             |
| Golmai et al (60)         | 12                        | Acute tubular necrosis (12)                                                             | NR                               | NR                   | NR          | NR             |
| Santoriello et al (64)    | 42                        | Fibrin thrombi (6) ATI (19)                                                             | Median: 245.7 (range: 82.07 to > 300) (n = 30) | Median: > 315 pg/mL (range: 36 to > 315 pg/mL) (n = 26) | Median: 10,200 ng/mL (range: 580 to > 20,000 ng/mL) (n = 28) |

(Continued)
TABLE 4. (Continued).
Summary of Postmortem Findings in the Kidneys and Liver Tissues

| References                  | No. of Patients Evaluated | Main Pathologic Findings | Potential Mechanistic Biomarkers |
|-----------------------------|---------------------------|--------------------------|---------------------------------|
|                            |                           |                          | CRP, mg/L | IL-6, pg/mL | D-dimer, ng/mL |
|                             |                           |                          |           |             |                |
| Cirstea et al (65)          | 1                         | Widespread focal microthrombi (1) | NR        | NR          | NR              |
| Nadkarni et al (73)         | 26                        | Microthrombi (2)         | NR        | NR          | NR              |
| Summary                     | 281c                      | Microthrombi (12.1%)     |           |             |                 |
| Hepatobiliary System–Liver  |                           |                          |           |             |                 |
| Study No of Patients Evaluated | Main Pathologic Findings |                          | Potential Mechanistic Biomarkers |
| Menter et al (17)           | 17                        | Liver shock necrosis (5) | NR        | Range: 103–278 (n = 5) | Range: 400–10,400 (n = 5) |
| Wichmann et al (19)         | 12                        | Shock liver (3)          | Median: 189 (range: 18–348) (n = 10) | NR | Median: 23,100 (range: 5,700 to > 200,000) (n = 5) |
| Lax et al (24)              | 11                        | Central vein thrombosis (1) | Range: 238.1–3,466.7 | NR | Range: 439–15,532 (n = 7) |
| Bryce et al (29)            | 22a                       | Early organizing thrombi in portal venules (15) | Mean at T0: 139.1 (range: 15.1–528.9) (n = 28) | Mean at T0: 375.8 (range: 45.5–1,406) (n = 14) | Mean at T0: 4,400 (range: 600–17,200) (n = 22) |
|                             |                           | Acute venous outflow obstruction (5) | Mean at death: 235 (range: 26.2–475.8) (n = 35) | Mean at death: 450.7 (range: 10.4–3,181) (n = 26) | Mean at death: 7,400 (range: 700–19,200) (n = 32) |
| Duarte-Neto et al (30)      | 10                        | Fibrin microthrombi in hepatic sinusoids (1) | Median: 8.12 (range: 23–110.5) | NR | Range: 28.435–89.513 (n = 2) |
| Rapkiewicz et al (46)       | 7                         | Platelet-fibrin microthrombi in hepatic sinusoids (6), Ischemic hepatic necrosis (2) | Range at peak: 169–379 (n = 5) | Range at peak: < 5 to 834 (n = 5) | Range at peak: 320 to > 52,926 (n = 4) |
| Sonzogni et al (55)         | 48                        | Complete portal thrombosis (11), partial portal thrombosis (24), complete sinusoidal thrombosis (6), partial sinusoidal thrombosis (7) | NR | NR | NR |
| Nadkarni et al (73)         | 26                        | Microthrombi (1)         | NR        | NR          | NR              |
| Summary                     | 263c                      | Thrombosis/microvascular thrombi (27.4%) |           |             |                 |

ATI = acute tubular injury, CRP = C-reactive protein, DIC = disseminated intravascular coagulation, IL-6 = interleukin-6, NR = not reported, T0 = at admission.

*Of a total pool of 67 patients.

*Of a total pool of 10 patients.

*This number includes organs that were examined and did not show significant histopathologic findings; however; those were counted toward the total number of organs examined.
Critically ill patients with COVID-19 were found to have elevated circulating markers of endothelial dysfunction (80). Furthermore, higher levels of endothelial biomarkers, including interleukin (IL)–6, tumor necrosis factor-alpha, inter-cellular adhesion molecule 1, and caspase-1, were present in the lungs of deceased patients with COVID-19 compared with H1N1 lungs (81). There is a number of possible explanations for the causes of observed endothelial dysfunction in the patients with severe COVID-19. First, SARS-CoV-2 was found in endothelial cells in several autopsies, where it caused diffuse endothelial inflammation and endotheliitis (15, 48). This endothelial disruption activates the proinflammatory and procoagulant pathways (82). COVID-19–related endotheliitis may serve as a trigger for generalized microcirculatory dysfunction and related microthrombi. Predisposing factors to endothelial dysfunction such as male sex, smoking, hypertension, diabetes, obesity, and cardiovascular disease are also associated with severe COVID-19, and these factors may contribute to profound endotheliitis (15).

Significant proinflammatory state exhibited in patients with severe COVID-19, and the considerable cytokine production are evidenced by elevated IL-6, C-reactive protein (CRP), and ferritin as demonstrated by multiple retrospective cohort studies (Supplemental Table S6, http://links.lww.com/CCX/A621). Five studies categorized patients with COVID-19 as survivors and nonsurvivors and reported their laboratory values and anticoagulant administration during the hospitalization (83–87). A summary of these data is available in Supplemental Table S6 (http://links.lww.com/CCX/A621). The significant inflammatory state and cytokine production activate the endothelium. This activation turns on the coagulation cascade and results in hypercoagulable state. IL-6, CRP, and D-dimer levels were significantly higher in nonsurvivors compared with survivors. IL-6 was reported in two studies (83, 85), and the range of median IL-6 was 11–152.4 pg/mL in nonsurvivors compared with 6.3–45.8 in survivors. CRP, which was reported in two studies (84, 85), ranged from 130 to 174.4 in nonsurvivors, compared with a range of 40.9–93.9 mg/L in survivors. D-dimer levels were significantly higher in the nonsurvivor group of COVID-19 patients; ranging from 1.74 to 5.2 µg/mL compared with the survivors where laboratory values were ranging from 0.6 to 1.47 µg/mL (83–87).

Another factor that causes endothelial disruption is hyperviscosity (88). Fibrinogen, a glycoprotein complex and clotting factor (Factor I), is a major contributor of plasma viscosity (89). An elevation in plasma fibrinogen levels leads to higher blood viscosity and subsequent increase in thrombotic risk. Elevated fibrinogen levels in patients with COVID-19 cause hyperviscosity, which plays a significant factor in the pathophysiology of COVID-19–induced coagulopathy. Bowles et al (90) reported positive lupus anticoagulant test in 31 of 34 patients with COVID-19 who had prolonged activated partial thromboplastin time (with a mean of 35.5 s). Lupus anticoagulant is known to be associated with high risk of thrombosis. That is one more element that might be contributing to the profound hypercoagulability associated with COVID-19 (90).

These elements can also explain the growing recognition of the extrapulmonary microthrombi and thromboemboli. Microthrombi were observed occasionally in the vasculature of the kidneys and the liver. The exclusion of these organs from many autopsy reports, as well as minimally invasive (biopsy-like) autopsies of these organs, renders the histological evidence insufficient. More extensive open autopsies will likely lead to a better understanding behind the reported elevated liver biomarkers (55, 91), as well as acute kidney injury, hematuria, and proteinuria in COVID-19 patients (56). Although possible credible explanations are available such as direct viral injury and the considerable elevated cytokine production, determining the exact pathway is critical.

Despite one study reporting five patients under the age of 50 presenting with strokes and later found to be SARS-CoV-2 positive (92), our review of brain autopsies revealed infrequent thrombotic complications in brain. However, when compared with influenza, stroke risk was 7.6 times higher (0.2% vs 1.6%) in COVID-19 (93). COVID-19 was recently reported as an independent risk factor for stroke and increased mortality in hospitalized patients (94). Interestingly, nonspecific neurologic symptoms such as dizziness, headache, and impaired consciousness are common (~36%) in COVID-19, and even more common (~46%) in severe cases (95). Overall, the incidence of meningoencephalopathy was reportedly very low.

Cardiac dysfunction and arrhythmias have been reported in patients with unfavorable COVID-19 course (96–98). SARS-CoV-2 was reported to be present in myocardial cells, with a significant viral load of more than 1,000 copies per microgram RNA in 41% of the evaluated
patients (62). None of these heart tissue samples revealed the expected inflammatory response to the viral presence in the myocardial tissue nor were the clinical signs and symptoms of myocarditis observed. There is a paucity of histological evidence of myocarditis in the autopsies that we compiled in our review in spite of the fact that myocardial cells highly express angiotensin-converting enzyme 2 receptors (99). Very few recent work reported lymphocytic infiltrate in the heart (20, 35, 37, 46, 57, 100). However, a cardiovascular magnetic resonance assessment of 100 patients who recovered from COVID-19–related ARDS showed that 78% of patients had ongoing cardiac involvement, and 60% of the patients had ongoing myocardial inflammation (74). These findings may suggest that some of the postmortem cardiac assessments possibly missed discovering an existing focal myocarditis site. Of note, troponin was found to be elevated in many patients with COVID-19, and it was associated with a poorer prognosis (96–98). In light of the insufficient histological findings to support myocarditis, the elevated troponin can also be explained by mechanisms other than inflammation and myocarditis. For example, right ventricular strain due to PM and/or thrombosis or cardiac vein thrombosis (20, 101).

Limitations of this report need to be addressed. First, although this systematic review includes data from previously published postmortem reports of COVID-19 deaths, the systematic review protocols may have been insufficient to capture autopsy data published in other study types. More importantly, knowing that globally COVID-19–related deaths passed the one million mark, our total number of 691 postmortem reports may not necessarily accurately represent the complete pathology of severe disease. Second, a postmortem examination may bias results toward an exaggerated pathology, which may not be seen in an average patient experiencing a less severe course of the same disease process. Third, autopsy reports may not always be specifically focused on the clinical cause of death or the presumed clinical mechanisms behind it. Histopathologic examination of alive patients with a less severe course of COVID-19, albeit challenging, might reveal more in depth data that can provide comprehensive and plausible pathophysiologic explanation of the course of COVID-19.

In this systematic review, we aimed to abstract all available postmortem data from 65 studies representing a total of 691 patients. Postmortem findings of COVID-19 patients summarize the final stages of disease in critically ill. Understanding the pathology behind these cases is crucial for critical care professionals. Multiple studies demonstrated evidence supporting the importance of anticoagulation and antiplatelet therapy (86, 102–104). In a large trial, Paranjpe et al (103) studied mechanically ventilated COVID-19 and reported nearly double number of deaths in patients who did not receive therapeutic-dose of anticoagulation. In an observational study by Chow et al (102), aspirin use—defined as receiving aspirin within the 7 days prior to hospitalization and/or the 24 hours following admission—was associated with a significant reduction in ICU admission and invasive mechanical ventilation needs. It is possible that antiplatelet agents may have beneficial effect, but this is neither tested under prospective controlled studies at this point nor any significant effect of such therapy was assessed in the setting where anticoagulation therapy was applied.

Therefore, highlighting the impact of thrombotic pathology is paramount in extrapolating the mechanism of disease and will likely lead to potential therapeutic approaches. We believe that reporting widespread occurrence of thrombotic complications will draw attention to the urgent need of performing randomized controlled trials addressing the benefits of administering various doses of anticoagulant and—possibly—antiplatelet therapies in critically ill COVID-19 patients.

CONCLUSIONS

In this systematic review of postmortem data, we are reporting an association between widespread thrombotic process and mortality. Although microvascular thrombi were abundant in the lung tissue, they were observed at significant percentages in most tissue and organs including liver, kidneys, brain, and heart.

ACKNOWLEDGMENTS

We very much appreciate the extreme hard work of all members of the Center of Excellence for Research in Infectious Diseases.

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