Systematic Review of Microthrombi in COVID-19 Autopsies

Rafael Parra-Medina[a, b]   Sabrina Herrera[c]   Jaime Mejia[d]

[a]Research Institute, Pathology Department, Fundación Univeristaria de Ciencias de la Salud, Bogotá, Colombia; [b]Instituto Nacional de Cancerología, Pathology Department, Bogotá, Colombia; [c]Department of Pathology Las Américas, Medellin, Colombia; [d]Instituto de Patologia Mejia Jimenez, Department of Pathology, Cali, Colombia

Abstract

Background: Histopathological analysis can provide additional clues in COVID-19 understanding. During the last year, autopsy reports have revealed that diffuse alveolar damage (DAD) is the most significant observed finding. The aim of this study is to review cases in the literature about COVID-19 autopsies that reported microthrombi in different organs. ***Methods:*** We performed a systematic literature review in PubMed, Virtual Health Library (VHL), and Google Scholar. ***Results:*** In total, 151 autopsies were included, and 91 cases presented microthrombi in the lung (73%), heart (11.2%), kidney (24%), and liver (16.3%). The age range was between 27 and 96 years. Males were 64.8%. The patients with microthrombi had more comorbidities such as arterial hypertension (62%), obesity or overweight (64%), diabetes mellitus type 2 (51%), and heart disease (53%). The most common histopathological changes found in patients with lung microthrombosis were DAD in exudative phase (78%), pulmonary embolism (59%), and lung infarct (81%). Presence of microthrombi was associated with arterial hypertension ($p <$ 0.0001) and DAD in exudative and proliferative phases ($p =$ 0.02). ***Discussion:*** The analysis of these results shows that microthrombi in COVID-19 autopsies may be found in different organs and are more frequent in patients with comorbidities, pulmonary embolism, and lung infarct.

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Introduction

On January 30, 2020, the WHO declared COVID-19 a global pandemic. COVID-19 is caused by SARS-CoV-2, a type of coronavirus that can affect humans. SARS-CoV-2 shares 79.6% genome sequence with SARS-Cov and infects the same human lung alveolar epithelial cells through receptor-mediated endocytosis using the ACE2 receptor [1].

The symptoms of COVID-19 infection frequently appear after an incubation period of 1–14 days, commonly lasting 3–7 days but can extend up to 24 days. The most common symptoms that have been reported are fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.7%), shortness of breath (18.7%), sore throat (13.9%), and headache (13.6%). Some COVID-19 patients presented gastrointestinal symptoms such as diarrhea (3.8%) and vomiting (5.0%). In severe cases, patients
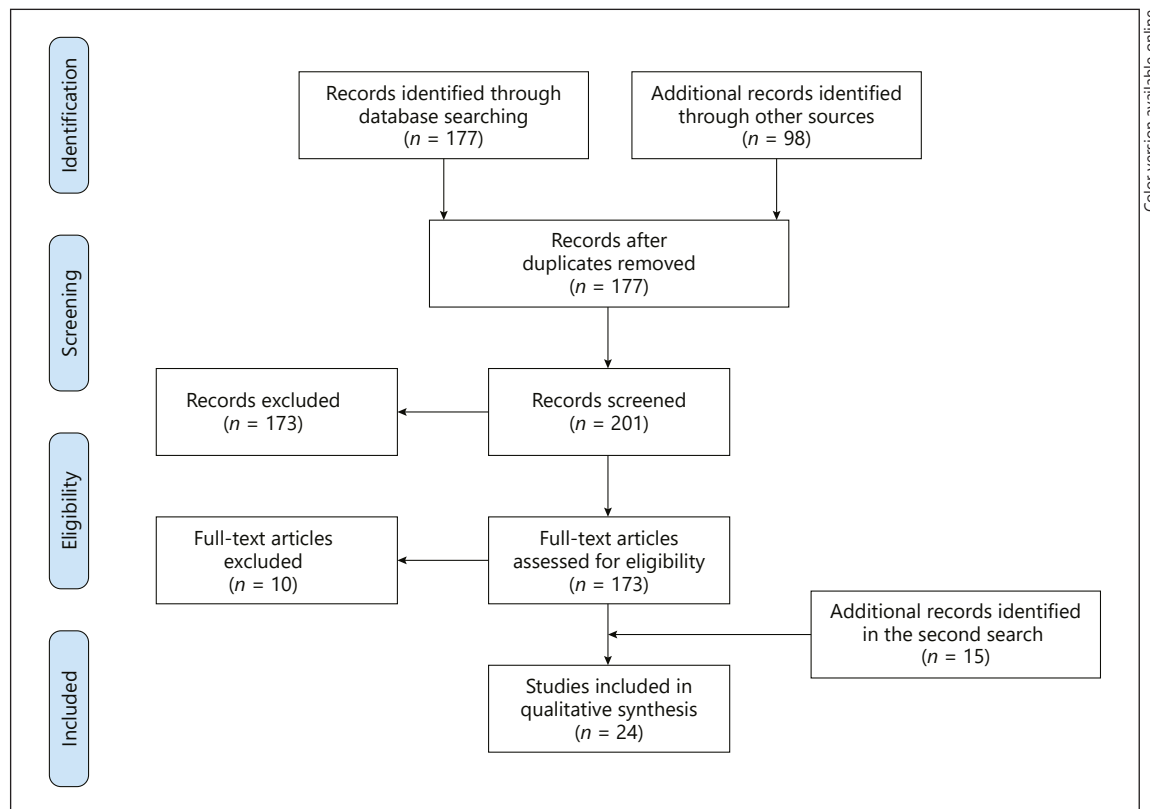
Fig. 1. Flowchart of the systemic literature review.

may develop pneumonia, acute respiratory distress syndrome, acute cardiac problems, and multiorgan failure [2].

Many scientific studies have focused in understanding the viral infection mechanism; however, a histopathological analysis could uncover additional clues about COVID-19 [3]. Throughout history, autopsies have played a very important role in identifying emerging and re-emerging infectious diseases [4]. In the last months, several changes associated with the virus infection or as a secondary effect of the treatment have been reported in the respiratory, cardiovascular, urinary, gastrointestinal, reproductive, and immune systems, among others [5, 6]. Polak et al. [3] published a systematic review about the observed changes in COVID-19 autopsies. Their recount was mainly focused on pulmonary pathological findings, proposing to categorize changes as epithelial, vascular, or fibrotic. They also found that an epithelial pattern of lung injury occurs early in the course of the disease, even before the onset of symptoms in some cases, and persisting throughout the clinical course, but gradually declining by 28 days after the onset of symptoms.

During the COVID-19 pandemic, autopsy findings have contributed to a better comprehension of the disease and to develop therapeutic options considering the presence of thrombotic events that might be an indication of a serious derangement of the clotting balance. We have performed a systematic review to discuss the location and findings associated with evidence of microthrombi in COVID-19 autopsies.

Materials and Methods

Search Strategy
A systematic review of PubMed and Virtual Health Library (VHL), from inception through March 30, 2020, was performed to find articles providing information about autopsy findings in patients infected with SARS-CoV-2. The following strings were used to do the search: (SARS-CoV-2 or COVID-19) and autopsy. Manual search was performed in Google (Google LLC, Mountain View, CA, USA). Included studies were available in English and Spanish. Preprint manuscripts in databases such as bioRxiv and medRxiv were also considered. Articles published until September 30, 2020, were manually added to acquire more data.

Study Selection and Data Extraction

Case reports or series cases with histopathological findings in autopsies of patients infected with COVID-19 and presence of microthrombi were included. Three authors (R.P.M., S.H., and J.M.) independently screened the articles and extracted relevant information. Disagreements about source relevance were resolved by consensus. The following data were extracted from the autopsies that presented microthrombi: author, number of cases, total number of cases, comorbidities, and histopathological findings. Articles without this information on each case were removed.

Due to heterogeneity of terms used in the studies, we grouped those terms into two diffuse alveolar damage (DAD) phases. Terms such as hyaline membranes, interstitial and intra-alveolar edema, collapsed alveoli, and necrosis of endothelial cells were grouped as the exudative phase. Terms such as organizing or remnants of the hyaline membrane, interstitial and intra-alveolar proliferation of fibroblasts or myofibroblasts, and proliferation of type II pneumocyte were grouped as the proliferative phase.

Data Synthesis and Analysis

Univariate analysis was applied to determine distribution of clinical and pathological findings. Based on the presence or absence of microthrombi, the data were divided into groups, and the χ^2 test was used to determine statistically significant differences between microthrombi and clinical and pathological findings. Statistical significance was established at $p < 0.05$.

Results

Systematic Review

A total of 275 articles within the reviewed databases were retrieved, and 74 of those articles were recognized as duplicates. A total of 201 full-text articles were assessed for eligibility (COVID-19 autopsies). Twenty-eight full-text articles with COVID-19 autopsies were reviewed [7]. Fifteen articles were added in the second search. Finally, 24 articles that contained interpretable data and fulfilled the eligibility criteria were included (microthrombi observed in the histopathology with established characteristics in each patient were included) [8–29]. From the included articles, 18 were case reports and 6 had >10 cases. The flowchart for the systematic literature reviewed and articles included in the analysis is shown in Figure 1.

Characteristics of Patients with Microthrombi

In total, 151 autopsies were included. Ninety-one autopsies detected microthrombi. Eighty-five autopsies had cases with microthrombi in the lung, 9 in the heart, 13 in the kidneys, 7 in the liver, and 2 in the trachea. The age range was between 27 and 96 years. 64.8% of the patients were male (*n* = 59). The following comorbidities were reported: 61.5% cases with arterial hypertension, 63.6% cases with obesity or overweight, 52.3% cases with diabetes mellitus, and 52.9% cases with heart disease. Other conditions also reported are listed in Table 1 and online suppl. Table 1 (see www.karger.com/doi/10.1159/000515104 for all online suppl. material). The statistical analysis showed association between arterial hypertension (*p* < 0.0001) and the presence of microthrombi.

Lung

All autopsies evaluated lung tissue [8–29] and showed DAD in different stages. DAD in the exudative phase was reported in 32 patients and DAD in the proliferative phase in 8 patients. Fifty-one cases showed changes in both exudative and proliferative phases. In 20 cases, the DAD could not be further classified. Damiani et al. [16] classified 4 patients with features of a more advanced proliferative phase of DAD (late fibrotic disease). Bronchopneumonia was observed in 32 cases. Cases with coinfections such as *Candida glabrata, Pseudomonas aeruginosa,* and *Staphylococcus epidermidis,* among others, were reported [16].

Microthrombosis was reported in 73% (85/116 cases), and 78% had DAD in the exudative phase and 63% had DAD in the exudative and proliferative phase (*p* = 0.02). Fifty-nine percent had pulmonary embolism and 81% had lung infarct, and in 100% of the cases, vasculitis was reported.

Heart

Heart tissue was evaluated in 10 articles (59 patients) [10–13, 21, 23, 25, 27, 28, 30]. Fifty-one cases showed changes associated with pre-existing pathologies such as myocardial hypertrophy and myocardial interstitial fibrosis. In 9 patients (11.2%), microthrombi in the heart were reported [14, 25, 30]. The range of the age in these patients was between 27 and 64 years. Five were male, and 6 had arterial hypertension and 4 obesity. They presented nonspecific symptoms like fever, chills, dyspnea, cough, and depression.

Kidney

Kidney tissue was evaluated in 7 articles (*n* = 62 patients) [9, 11, 12, 23, 27, 30, 31]. Acute tubular damage was the most common finding. Arteriosclerosis was observed in 49 cases, and microthrombi were detected in the glomeruli of 13 cases (24%). In several cases, viral particles in some glomerular endothelial cells were identified.

Liver

Liver tissue was evaluated in 7 articles (*n* = 66) [11, 12, 23, 25, 27, 30, 32]. Steatosis was reported in 45 cases, cen-

Table 1. Characteristics of patients included in the review

	Micro-thrombi (n = 91)	%	Non-micro-thrombi (n = 60)	%	Total (n =151)	p value
Age, range, years	27–96		39–94		34–96	
Gender*						
Male	59	57.8	43	42.2	102	0.66
Female	28	62.2	17	37.8	45	
Comorbidities						
Asthma	5	83.3	1	16.7	6	0.07
Cancer	6	33.3	12	66.7	18	0.24
Heart disease	18	52.9	16	47.1	34	0.13
Respiratory disease	10	52.6	9	47.4	19	0.66
Diabetes mellitus type 2	20	51.3	19	48.7	39	0.94
Dementia	5	62.5	3	37.5	8	0.24
Arterial hypertension	59	61.5	37	38.5	96	**<0.0001**
Obesity or overweight	42	63.6	24	36.4	66	0.39
Smoking	8	38.1	13	61.9	21	**0.02**
Histopathological findings						
Lung						
DAD, exudative	25	78.2	7	21.8	32	0.46
DAD, proliferative	8	100	0	0	8	0.10
DAD, exudative and proliferative	32	62.8	19	37.2	51	**0.02**
DAD, nonclassified	11	55	9	45	20	**0.04**
DAD, with fibrotic changes	4	100	0	0	4	0.28
Pulmonary embolism	16	59.3	11	40.7	27	0.06
Lung infarct	13	81.2	3	18.8	16	0.6
Emphysema	2	16.7	10	83.3	12	**<0.0001**
Cytopathic viral effect	8	80	2	20.0	10	0.46
Bronchopneumonia (focal or diffuse)	23	45.1	28	54.9	51	**<0.0001**
Vasculitis	9	100	0	0	9	0.05
Heart						
Myocardial hypertrophy	25	49	26	51	51	**0.04**
Interstitial fibrosis	11	40.7	16	59.3	27	**0.03**
Myocarditis	2	100	0	0	2	0.32
Pericarditis	1	50	1	50	2	0.67
Kidney						
Acute tubular damage	19	38	31	62	50	0.17
Diabetic nephropathy	1	25	3	75	4	0.18
Arteriosclerosis	19	36.5	33	63.5	52	0.06
Liver						
Steatosis	31	68.9	14	31.1	45	0.25
Shock necrosis	4	80	1	20	5	0.51
Lymphocytic inflammatory infiltrate	5	71.4	2	28.6	7	0.59
Centrilobular congestion	6	37.5	10	62.5	16	**0.004**
Spleen						
Reduce white pulp	2	40	3	60	5	0.32
Red pulp hemorrhages	3	100	0	0.00	3	0.20

DAD, diffuse alveolar damage. Values in bold indicate statistical significance. * Data not available for Fox et al. [18].

trilobular congestion in 16 cases, and necrosis in 5 cases. Rapkiewicz et al. [26] found 7 cases with microthrombi (16.3%), one with cirrhosis and the other case with zone 3 necrosis with a hepatic vein thrombus.

Spleen

Three articles reported spleen findings (n = 23) [11, 12, 25]. Five cases showed reduced white pulp, and 3 cases had red pulp hemorrhages.

Discussion

Autopsy is a valuable medical tool in understanding the progression of disease which can eventually lead to the investigation of new therapeutic options. In the present review, we found the presence of microthrombi in 60% of autopsies. Microthrombi were detected in the lung, trachea, heart, kidneys, and liver along with other variable findings that may be related with the virus infection or secondary to treatment. We found that the patients with microthrombi had more comorbidities, namely, arterial hypertension (62%), obesity or overweight (64%), diabetes mellitus type 2 (51%), and heart disease (53%). In the statistical analysis, the presence of microthrombi was significantly associated with a clinical history of arterial hypertension ($p < 0.0001$) (Table 1).

DAD in different stages was a major finding. Of the patients with microthrombosis, 87% had DAD in the exudative phase and 67% had DAD in the exudative and proliferative phase. The lung injury may explain the ventilation-perfusion alteration that these patients have. The SARS-CoV-2 virus may induce more severe alveolar epithelial changes compared with the other respiratory viruses [33]. DAD associated with the SARS-CoV-2 virus has shown similarities with other coronaviruses (SARS-CoV-1 and Middle East respiratory syndrome) at the histopathological level [33]. In contrast to the SARS-CoV-2 virus, in H1N1 virus autopsies, more extensive necrosis and hemorrhage in the lungs were observed. Also, there were more CD8+ T cells, CD57 NK cells, and granzyme B+ cells [34] compared to the SARS-CoV-2 virus that usually shows paucity of CD8+ T cells and CD57+ NK cells [33]. We observed microthrombi in 73% of COVID-19 patients, while in the literature, it has been observed in 58% of SARS-CoV-1 and 24% of H1N1 influenza patients [35, 36].

Thrombi formation in severe COVID-19 may be due several factors such as upregulation of procoagulant mechanisms, downregulation of natural anticoagulants, resistance to fibrinolysis, and endothelial damage [37]. D-dimer is a product of the coagulation with clinical utility; this is a fibrin degradation product that is present in the blood following degradation of blood clots by fibrinolysis. D-dimer is a sensitive test to diagnose thrombotic states, including pulmonary embolism and disseminated intravascular coagulation [38, 39]. A systematic review and meta-analysis showed that serum D-dimer concentrations in patients with severe COVID-19 are significantly higher than the patients with less severe forms [38].

The endothelial damage in severe COVID-19 can be assimilated to a vasculopathy syndrome characterized by microvasculitis, endothelial degeneration, and resultant basement membrane zone disruption and reduplication [40]. Magro et al. [40, 41] found microthrombi formation in the lung, kidneys, brain, heart, skin, and liver associated with thrombotic vasculopathy and with complement system activation (C4d deposits, terminal complement components C5b-9 [membrane attack complex], and mannose-binding lectin-associated serine protease 2). The complement system can be directly activated by the virus or by the proinflammatory-associated response [42]; the endothelial injury and proinflammatory cytokines can influence the development of vasculitis [43]. Besides, the complement system is an associated factor to the hypercoagulable status in SARS-CoV-2 infection [42].

Leukocytoclastic vasculitis has been reported in COVID-19 patients; in our data, all patients with reported vasculitis had microthrombosis. The inflammatory cells may be cuffed around (periarteritis) and/or inside (panarteritis) the affected vascular wall [44]. Endothelial damage may be directly caused by virus infection [45] or by the systematic secondary inflammatory response that ensues [43]. These features along with the pre-existing endothelial dysfunction associated with chronic diseases (hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease, among others) [46] could explain the severity seen in certain COVID-19 patients [47]. However, some cases had thrombi formation without atherosclerosis [26]. Ackermann et al. [45] found SARS-CoV-2 virus particles within the endothelial cells and significant changes in the morphology of ACE-positive endothelial cells. The changes found were disruption of intercellular junctions, cell swelling, and loss of contact with the basal membrane. They also found distorted vascularity with structurally deformed capillaries, the presence of sprouting, and intussusceptive angiogenesis. The finding of intussusceptive angiogenesis was significantly correlated with increasing duration of hospitalization ($p < 0.001$) [45].

Megakaryocytes and platelets are also involved in thrombi formation. Rapkiewicz et al. [26] found 7 cases with high number of megakaryocytes in the cardiac microvasculature, glomeruli, and lungs associated with microthrombi in the lung, trachea, heart, kidneys, and liver. Four of these 7 patients were treated with anticoagulation (enoxaparin [$n = 3$] or unfractionated heparin [$n = 3$]) and/or antiplatelet treatment (aspirin [$n = 1$]). Megakaryocytes count increased in COVID-19 hearts compared to other

acute respiratory distress syndromes ($p = 0.02$). In the bone marrow, megakaryocytes were mildly increased with morphologic features indicating active platelet production and contained virions as identified by electron microscopy.

Neutrophil extracellular traps (NETs) are another factor that interact with the coagulation activation due to the infection [48]. The presence of NETs has been observed in different diseases [49, 50] like in acute respiratory distress syndrome [50]. In COVID-19 patients, high levels of NETs in the blood have been observed [51]. Other factors contributing to coagulation have been found in different studies. Zuo et al. [52] found elevated levels of cell-free DNA, myeloperoxidase-DNA, and citrullinated histone H3. Buja et al. [12] found, in electron microscopy, precipitated fibrin and entrapped neutrophils within alveolar capillaries as well as larger deposits of fibrin in alveolar spaces.

Pulmonary embolism was present in 59% of patients with microthrombi in the lungs. Pulmonary embolism occurred in hospitalized patients and in patients who died in an outpatient or domestic setting [53]. In the cohort of Edler et al. [53], there were 76 cases classified as COVID-19 deaths. On those cases, the most frequent cause of death was pneumonia followed by pulmonary artery embolism combined with pneumonia. Pulmonary embolism has been found with absence of coexisting deep venous thrombosis [28, 53]. The presence of deep venous thrombosis has been associated with a higher rate of admissions to the intensive care unit ($p = 0005$) and more deaths ($p = 0.001$) [54]. In the meta-analysis conducted by Henrina et al. [55], which included 1,237 subjects, they found that venous thromboembolism in patients hospitalized was associated with higher mortality (RR 2.48 [1.35, 4.55], $p = 0.003$), intensive care unit admission (RR 2.32 [1.35, 4.55], $p < 0.0001$), and mechanical ventilation (RR 2.73 [1.56, 4.78], $p = 0.001$). The presence of macrothrombi has also been reported in the cerebral venous sinus [56], prostatic venous plexus [28, 53], esophageal veins [53], liver central vein [57], arterial thrombosis in the spleen [33], abdominal aorta [58], aortoiliac, low inguinal, upper limb vessels [59], and testis [12, 33].

We realize that there are limitations in the present study. First, the clinical characteristics of the included cases could not be thoroughly retrieved. Second, almost every case report and serial cases were limited to the changes observed in the heart, liver, or kidneys. Few studies had complete autopsies; in consequence, information from other organs is rather fragmented. Third, a comprehensive statistical analysis is hampered due to the dispersed and fragmented information in the articles reviewed. Fourth, the clinical information and the histopathological characteristics of the case reports or the series of cases were limited. Consequently, the quality of each article was not assessed as it was undesirable [60]. However, valuable information has been collected which we deem useful to advance in the understanding of the disease.

In conclusion, our systematic review provides a summary of cases with fibrin microthrombi in COVID-19 autopsies. We found microthrombi in the lung, trachea, heart, kidneys, and liver. Patients with microthrombi had more comorbidities (hypertension, obesity or overweight, diabetes mellitus type 2, and heart disease) and pulmonary embolism, lung infarct, and vasculitis. The development of thrombi formation is due to the activation of megakaryocytes, platelets, complement system, endothelial injury, and changes induced by severe inflammation, which constitute a complex vasculopathy syndrome. The multiorgan thrombosis in COVID-19 patients despite the anticoagulation therapy may explain the symptoms, signs, and laboratory tests present in different stages of the disease. Therefore, it is crucial to consider adequate therapeutic strategies to prevent thrombosis formation and avoid certain side effects of the infection.

Statement of Ethics

Ethical approval was not required because this study is a systematic review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Rafael Parra-Medina: acquisition, analysis, and interpretation of data/references and drafting and approving the manuscript. Sabrina Herrera: acquisition, analysis, and interpretation of data/references and approving the manuscript. Jaime Mejia: analysis, interpretation of data, and approving the manuscript.

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