Background: The new coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused more than 210,000 deaths worldwide. However, little is known about the causes of death and the virus’s pathologic features.

Objective: To validate and compare clinical findings with data from medical autopsy, virtual autopsy, and virologic tests.

Design: Prospective cohort study.

Setting: Autopsies performed at a single academic medical center, as mandated by the German federal state of Hamburg for patients dying with a polymerase chain reaction–confirmed diagnosis of COVID-19.

Patients: The first 12 consecutive COVID-19–positive deaths.

Measurements: Complete autopsy, including postmortem computed tomography and histopathologic and virologic analysis, was performed. Clinical data and medical course were evaluated.

Results: Median patient age was 73 years (range, 52 to 87 years), 75% of patients were male, and death occurred in the hospital (n = 10) or outpatient sector (n = 2). Coronary heart disease and asthma or chronic obstructive pulmonary disease were the most common comorbid conditions (50% and 25%, respectively). Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients. Postmortem computed tomography revealed reticular infiltration of the lungs with severe bilateral, dense consolidation, whereas histomorphologically diffuse alveolar damage was seen in 8 patients. In all patients, SARS-CoV-2 RNA was detected in the lung at high concentrations; viremia in 6 of 10 and 5 of 12 patients demonstrated high viral RNA titers in the liver, kidney, or heart.

Limitation: Limited sample size.

Conclusion: The high incidence of thromboembolic events suggests an important role of COVID-19–induced coagulopathy. Further studies are needed to investigate the molecular mechanism and overall clinical incidence of COVID-19–related death, as well as possible therapeutic interventions to reduce it.

Primary Funding Source: University Medical Center Hamburg-Eppendorf.

Methods

Study Design

In response to the pandemic spread of SARS-CoV-2, the authorities of the German federal state of Hamburg ordered mandatory autopsies in all patients dying with a diagnosis of COVID-19 confirmed by polymerase chain reaction (PCR). The legal basis for this was section 25(4) of the German Infection Protection Act. Because of legal regulations, no COVID-19 death was exempted from this order, even if its clinical cause seemed obvious. The case series demonstrated herein consists of 12 consecutive autopsies, starting with the first known case.
### Table 1. Patient Characteristics and Autopsy Findings

| Case Number | Age, y | Sex | Preexisting Medical Conditions | Treatment | BMI, kg/m² | Clinical Cause of Death | PMI, d |
|-------------|--------|-----|---------------------------------|-----------|------------|------------------------|--------|
| 1           | 52     | Male | Obesity                         | CPR       | 38.8       | Sudden cardiac death    | 1      |
| 2           | 70     | Male | Parkinson disease, CHD, PAD, CKD| BSC       | 22.2       | Respiratory failure, pneumonia | 1      |
| 3           | 71     | Male | AH, nicotine abusus, granulomatous pneumopathy | CA, MV | 36.8 | Respiratory failure, pneumonia | 2      |
| 4           | 63     | Male | T2DM, obesity, bronchial asthma  | CA, MV, lysis of right ventricular thrombus, CPR | 37.3 | Cardiorespiratory failure, PE | 1      |
| 5           | 66     | Male | CHD                             | CPR       | 25.3       | Sudden cardiac death    | 2      |
| 6           | 54     | Female | Dementia, epilepsy, trisomy 21 | BSC       | 29.6       | Respiratory failure, aspiration pneumonia | 1      |
| 7           | 75     | Female | Atrial fibrillation, CHD, nicotine abusus | NIV | 26.3 | Respiratory failure, viral pneumonia | 4      |
| 8           | 82     | Male | Parkinson disease, T2DM, CHD    | BSC       | 27.8       | Respiratory failure, viral pneumonia | 1      |
| 9           | 87     | Female | Non-small cell lung cancer, COPD, CHD, CKD | BSC | 15.4 | Respiratory failure, viral pneumonia | 4      |
| 10          | 84     | Male | T2DM, AH, ulcerative colitis    | BSC       | 20.7       | Respiratory failure, viral pneumonia | 5      |
| 11          | 85     | Male | CHD, AH, bronchial asthma, atrial fibrillation | CA, MV, RRT | 30.0 | Cardiac arrest due to respiratory failure | 2      |
| 12          | 76     | Male | Obesity                         | CA, MV, CPR | 34.4 | PE | 3      |

*AB = acute bronchitis; ACVB = aortocoronary venous bypass; AH = arterial hypertension; aPC = activated pneumocytes; BMI = body mass index; BSC = best supportive care; CA = catecholamine therapy; CB = chronic bronchitis; CHD = coronary heart disease; CKD = chronic kidney disease; Co = congestion of small vessels; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; DAD = diffuse alveolar damage; DVT = deep venous thrombosis; FB = fibroblasts; GC = giant cells; Gra = granulocytic infiltration; HI = hemorrhagic infarctions; HM = hyaline membranes; LAD = left anterior descending artery; LC = lymphocytes; MI = myocardial infarction; MV = mechanical ventilation; NET = neuroendocrine tumor; NIV = noninvasive ventilation; PAD = peripheral artery disease; PE = pulmonary embolism; PEG = percutaneous endoscopic gastrostomy; PIC = plasma cells; PMCT = postmortem computed tomography; PMI = postmortem interval; RCA = right coronary artery; RRT = renal replacement therapy; SM = squamous metaplasia; T2DM = type 2 diabetes mellitus; Thr = thrombi; VATS = video-assisted thoracoscopic surgery.*

SARS-CoV-2–positive death occurring in Hamburg (the second largest city in Germany, with 1.8 million inhabitants). All autopsies were performed at the Department of Legal Medicine of University Medical Center Hamburg-Eppendorf. The Ethics Committee of the Hamburg Chamber of Physicians was informed about the study (no. WF-051/20). The study was approved by the local clinical institutional review board and com-
Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

Table 1—Continued

| Cause of Death | Main Pathologic Findings | PMCT (Lungs) | Histology (Lungs) |
|----------------|--------------------------|--------------|------------------|
| PE, pneumonia  | PE, DVT, pneumonia, obesity, cardiomegaly (660 g), splenomegaly (500 g), hepatomegaly (3880 g), shock organs (liver, kidneys), atherosclerosis | Diffuse bilateral pulmonary consolidations in each lobe | DAD: aPC, FB, GC, sparse HM, slight fibrosis Additional findings: Co, Thr |
| Pneumonia      | Pneumonia, CHD (stents in LAD and RCA, status post MI, cardiac aneurysm), contractures (with Parkinson syndrome), purulent bronchitis, cardiomegaly (515 g), shock liver | No PMCT | DAD: aPC, HM, sparse LC Additional findings: focal Gra, CB, AB |
| PE, pneumonia  | PE, DVT, pneumonia, status post VATS (due to unspecified granuloma), CHD, anasarca, atherosclerosis | Emphysema; fine reticular pattern in each lobe; consolidations in the right lower and left lower lobes | DAD: SM, FB, aPC, HM Additional findings: focal Gra, CB, AB |
| PE, pneumonia  | PE, DVT, pneumonia, obesity, cardiomegaly (605 g), ischemic colitis, shock liver | No PMCT | DAD: FB, aPC, HM, SM Additional findings: HI, Thr |
| Pneumonia      | Pneumonia, DVT, CHD, status post MI | Consolidations in each lobe; reticular pattern in the right upper and lower lobes in each left lobe | DAD: aPC, FB, HM, necrosis, LC Additional findings: surrounding small vessels, Thr |
| Pneumonia      | Pneumonia, kidney infarctions, PEG tube | Consolidations in the right upper and middle lobes and in parts of the left upper and lower lobes; ground glass opacities in the right upper and lower lobes and in the left upper lobe; reticular pattern in the right middle and lower lobes and in each left lobe | Gra, AB, Co (no DAD) |
| Pneumonia      | Pneumonia, lung emphysema, CHD, left cardiac dilatation, calcification of the mitral ring, cardiac pacemaker, atherosclerosis | Reticular pattern in each lobe; small areas of consolidation in the right lower, left upper, and lower lobes | DAD: HM, aPC, SM Additional findings: emphysema, Co |
| Bronchopneumonia| Pneumonia, emphysema, DVT, CHD, status post ACVB, status post MI with left cardiac aneurysm, atherosclerosis | Emphysema; diffuse consolidations in each lobe; reticular pattern in the right upper and lower lobes and in the left lower lobe; bilateral pleural effusion | Gra, emphysema (no DAD) |
| Purulent bronchitis | Pneumonia, purulent bronchitis, CHD, status post MI, cachexia, bullous emphysema, NET in the lung, atherosclerosis | Emphysema; round tumor in the right lower lobe; small areas of consolidation in the right upper and lower lobes and in the left upper lobe; reticular pattern in the right upper and lower lobes in each left lobe | Gra, AB, emphysema (no DAD) Additional findings: NET composed of small cells |
| Pneumonia, septic encephalopathy | Pneumonia, emphysema, septicemia, status post MI, atrophic kidneys | Reticular pattern in the right upper and lower lobes and in each left lobe; consolidations in the right middle and lower lobes and in each left lobe; ground glass opacities in the right upper and middle lobes and in parts of the left upper lobe; bilateral pleural effusion | Emphysema, Co, Gra, CB, fibrosis (no DAD) |
| Pneumonia      | Pneumonia, DVT, minor PE, emphysema, CHD, cardiomegaly (650 g), atherosclerosis | Diffuse consolidations in each lobe; reticular pattern in the right middle and lower lobes and in each left lobe; ground glass opacities in the right upper and middle lobes and in the left upper lobe; bilateral pleural effusion | DAD: HM (sparse), GC, aPC Additional findings: emphysema, Co, Gra |
| PE             | PE with lung infarctions, DVT, pneumonia, purulent tracheobronchitis, pneumonia, cardiomegaly (745 g), emphysema, obesity | No residual ventilation in either lung except for small areas in the right upper middle lobes and in the left upper lower lobes; bilateral pleural effusion | DAD: HM, aPC, fibrosis Additional findings: LC, PIC, HI, Thr, Co |

Applied with the Declaration of Helsinki. In all deceased patients, postmortem computed tomography (PMCT) and a complete autopsy, including histopathologic and virologic evaluation, were performed. Clinical records were checked for preexisting medical conditions and medications, current medical course, and antemortem diagnostic findings.

PMCT, Autopsy, and Histologic Examination

Computed tomographic examination was done at the Department of Legal Medicine with a Philips Bril-
(using personal protection equipment with proper donning and doffing), following guidelines from the German Association of Pathologists, which are closely aligned with relevant international guidelines. The recently published recommendations for the performance of autopsies in cases of suspected COVID-19 were taken into account (10). The interval from death to postmortem imaging and autopsy (postmortem interval) ranged from 1 to 5 days. During autopsy, tissue samples for histology were taken from the following organs: heart, lungs, liver, kidneys, spleen, pancreas, brain, prostate and testes (in males), ovaries (in females), small bowel, saphenous vein, common carotid artery, pharynx, and muscle.

For virologic testing, we took small samples of heart, lungs, liver, kidney, saphenous vein, and pharynx and sampled the venous blood.

Tissue samples for histopathologic examination were fixed in buffered 4% formaldehyde and processed via standard procedure to slides stained with hematoxylin-eosin. For the lung samples, we also used the keratin marker AE1/AE3 (Dako) for immunohistochemistry.

Quantitative SARS–CoV-2 RNA Reverse Transcription PCR From Tissue

Tissue samples were ground by using ceramic beads (Precellys lysing kit) and extracted by using automated nucleic acid extraction (MagNA Pure 96 [Roche]) according to manufacturer recommendations. For virus quantification in tissues, a previously published assay was adopted with modifications (11). One-step real-time PCR was run on the LightCycler 480 system (Roche) by using a 1-step RNA control kit (Roche) as master mix. The Ct (cycle threshold) value for the target SARS-CoV-2 RNA (fluorescein) and whole-process RNA control (Cy5) was determined by using the second derivative maximum method. For quantification, standard in vitro-transcribed RNA of the E gene of SARS-CoV-2 was used (12). These samples were also analyzed in a study focusing on renal tropism of SARS-CoV-2 (Puelles V, et al. Multi-organ and renal tropism of SARS-CoV-2. In preparation).

Table 2. Overview of Laboratory Results Taken at the Time of Hospitalization*

| Case Number | Hemoglobin, g/dL | MCV, fL | Platelets, × 10⁹/L | Leukocytes, × 10⁹/L | INR | aPTT, s | D-dimer, μkat/L | LDH, μkat/L | Creatinine, μmol/L |
|-------------|------------------|--------|-------------------|-------------------|-----|--------|---------------|-------------|-----------------|
| Normal range | 14.0–17.5 | 80.0–94.0 | 150–400 | 3.8–11.0 | NA | – | 23–30 | <500 | 2.00–4.10 | 53.4–99.1 |
| 1 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 2 | 12.1 | 92 | 144 | 7.4 | 1.3 | NA | NA | NA | 5.92 | 228.8 |
| 3 | 14.9 | 100 | 190 | 9.2 | 2.1 | 42 | NA | 6.32 | 102.9 |
| 4 | 13.3 | 88 | 478 | 7.1 | 1.1 | 21 | 23,100 | 11.07 | 65.6 |
| 5 | 14.4 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 6 | 14.0 | 95 | 135 | 3.4 | 1.0 | 30 | 28,800 | 7.97 | 76.3 |
| 7 | 12.1 | 98 | 125 | 6.9 | 1.5 | 57 | 2100 | 9.84 | 99.1 |
| 8 | 14.8 | 79 | 186 | 7.1 | 1.2 | 29 | >200,000 | 10.50 | 129.6 |
| 9 | 10.7 | 98 | 210 | 5.3 | 1.0 | 23 | NA | 2.70 | 99.1 |
| 10 | 16.5 | 88 | 219 | 15.5 | 1.1 | 29 | 5700 | 11.40 | 83.9 |
| 11 | 9.9 | 78 | 304 | 11.6 | 1.1 | 45 | 28,800 | 7.97 | 67.1 |
| 12 | 16.8 | 90 | 141 | 3.8 | 0.95 | 32 | NA | 6.32 | 102.9 |

aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CRP = C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; NA = not available; PCT = procalcitonin.

* Patients in cases 1 and 5 died out of the hospital after a sudden cardiac arrest. Values are either nonexisting (case 1) or taken from a blood gas analysis (case 5).

RESULTS

Clinical Data

The median age of the 12 patients included in this study was 73 years (interquartile range, 18.5); 25% were women. For all patients, preexisting chronic medical conditions, such as obesity, coronary heart disease, asthma or chronic obstructive pulmonary disease, peripheral artery disease, diabetes mellitus type 2, and neurodegenerative diseases, could be identified (Table 1). Two patients died out of the hospital after unsuccessful cardiopulmonary resuscitation, 5 died after treatment in the intensive care unit, and the remaining 5 had an advanced directive for best supportive care and died in the non-intensive care ward. Laboratory results for clinical chemistry, hematology, and coagulation were not available for the patients who died out of the hospital. In the remaining patients, the most striking features of the initial laboratory test were elevated levels of lactate dehydrogenase (median, 7.83 μkat/L [range, 2.71 to 11.42 μkat/L]), D-dimer (available for 5 patients; median, 495.24 nmol/L [range, 20.38 to >1904.76 nmol/L]), and C-reactive protein (median, 189 mg/L [range, 18 to 348 mg/L]), as well as mild
thrombocytopenia in 4 of 10 patients. A procalcitonin test had been performed in 6 patients, and the results were negative in all but 1 patient with pneumonia (case 10). Table 2 provides an overview of the initial laboratory results.

**PMCT**

In 2 cases (2 and 4), PMCT was not possible for logistic reasons. In the remaining cases, PMCT demonstrated mixed patterns of reticular infiltrations and severe, dense, consolidating infiltrates in both lungs in the absence of known preexisting pathology (such as emphysema or tumor). A juxtaposition of antemortem and postmortem findings is demonstrated in Figure 1. A complete summary of PMCT findings is presented in Table 1.

**Autopsy**

In 4 cases (1, 3, 4, and 12), massive pulmonary embolism was the cause of death, with the thrombi deriving from the deep veins of the lower extremities. In another 3 cases (5, 8, and 11), fresh deep venous thrombosis was present in the absence of pulmonary embolism. In all cases with deep venous thrombosis, both legs were involved (Figure 2). In 6 of the 9 men (two thirds) included in the study, fresh thrombosis was also present in the prostatic venous plexus (Appendix Figure 1, available at Annals.org).

In all 12 cases, the cause of death was found within the lungs or the pulmonary vascular system. However, macroscopically differentiating viral pneumonia with subsequent diffuse alveolar damage (a histologic diagnosis) from bacterial pneumonia was not always possible. Typically, the lungs were congested and heavy, with a maximum combined lung weight of 3420 g in case 11. The mean combined lung weight was 1988 g (median, 2088 g). Standard lung weights for men and women are 840 g and 639 g, respectively (13, 14). Only cases 6 and 9 presented with a relatively low lung weight: 550 g and 890 g, respectively (Appendix Table 1, available at Annals.org). The lung surface often displayed mild pleurisy and a distinct patchy pattern, with pale areas alternating with slightly protruding and firm, deep reddish blue hypercapillarized areas. On the cutting surfaces, this pattern was also visible (Figure 2). The consistency of the lung tissue was firm yet friable. In 8 cases, all parts of the lungs were affected by these changes. Cases 6, 7, and 9—occurring in the 3 women of the case series—presented with changes compatible with focal purulent bronchopneumonia. Macroscopically, no changes were observed outside the lungs and respiratory tract, except for splenomegaly in 3 cases, which suggested a viral infection.

During autopsy, all cases except for case 6 presented with preexisting heart disease, including high-grade coronary artery sclerosis (7 of 12); myocardial scarring, indicating ischemic heart disease (6 of 12); and congestive cardiomyopathy. Mean heart weight was 503 g (median, 513 g). In addition to this finding, the most common accompanying diseases were pulmonary emphysema (6 of 12) and ischemic enteritis (3 of 12). Often these conditions were known to the treating physician before death (compare columns 4 and 10 of Table 1). The macroscopic autopsy findings are presented organ by organ in Appendix Table 2 (available at Annals.org) and the lung findings in Table 1.

A clear trend toward obesity was observed among the cases (mean body mass index, 28.7 kg/m²; median, 28.7 kg/m²). However case 9, involving a patient with known neuroendocrine tumor of the lung, presented with severe cachexia (body mass index, 15.4 kg/m²). The comorbid conditions found are summarized in Table 1.

**Histology**

Histopathology of the lungs showed diffuse alveolar damage, consistent with early acute respiratory distress syndrome in 8 cases. Predominant findings were hyaline membranes (Figure 3, A and B), activated pneumocytes, microvascular thromboemboli, capillary congestion, and protein-enriched interstitial edema. As described by Wang and colleagues (15), a moderate degree of inflammatory infiltrates concurred with clinically described leukopenia in patients with COVID-19 and predominant infiltration of lymphocytes fit the pic-
In later stages, squamous metaplasia was present (Figure 3, C). Long-term changes, such as destruction of alveolar septae and lymphocytic infiltration of the bronchi, were often visible as preexisting conditions. Four cases (6, 8, 9, and 10) showed no diffuse alveolar damage but extensive granulocytic infiltration of the alveoli and bronchi, resembling bacterial focal bronchopneumonia. Histologically, thromboemboli were detectable in cases 1, 3, 4, and 5 (Figure 3, D). Microthrombi were regularly found within small lung arteries, occasionally within the prostate, but not in other organs.

In addition to the lung changes described in Table 1, there were isolated histologic findings that might indicate a viral infection. The pharyngeal mucosa was examined in 7 cases. In 6 of them, hyperemia and alternating dense, predominantly lymphocytic infiltrates were found as signs of chronic pharyngitis. In 1 case (case 3), lymphocytic myocarditis was seen in the right ventricle (Appendix Figure 2, available at Annals.org). The remaining histologic changes were compatible with shock changes in part of the deceased patient (liver, kidneys, intestine) or corresponded to the macroscopically determined virus-independent preexisting pathology (such as ischemic cardiomyopathy).

Apart from findings related to SARS-CoV-2 infection, patients showed other histopathologic findings related to their chronic preexisting conditions, including hypertrophy of myocardial fibers or scarring of the myocardium. The peripheral veins, including those occluded by thrombi, showed no abnormalities on hematoxylin-eosin staining.

**PCR Results**

Quantitative reverse transcription PCR detected SARS-CoV-2 RNA in the lungs of all 12 patients (range, $1.2 \times 10^4$ to $9 \times 10^9$ copies/mL) and in the pharynx of 9 patients. Six patients showed moderate viremia ($<4 \times 10^4$ copies/mL). In 5 of these patients, viral RNA was also detected in other tissues (heart, liver, or kidney) in concentrations exceeding viremia. Patients without viremia showed no or a low virus load in the other tissues. Only 4 patients had detectable viral RNA in the brain and saphenous vein.

**DISCUSSION**

In this autopsy study of 12 consecutive patients who died of COVID-19, we found a high incidence of deep venous thrombosis (58%). One third of the patients had a pulmonary embolism as the direct cause of death. Furthermore, diffuse alveolar damage was demonstrated by histology in 8 patients (67%).

To our knowledge, this is the first case series summarizing and comparing clinical data of consecutive COVID-19 cases with findings obtained by a full autopsy, supplemented by PMCT, histology, and virology. The high rate of death-causing pulmonary embolism at autopsy correlates well with the unsuccessful resuscitation of 3 of 4 patients, 2 of whom died out of the hospital. Apart from that, no preclinical evidence had been reported of pulmonary embolism or deep venous thrombosis.

In studies that examined deceased patients with COVID-19 without relying on autopsy, no increased rates of pulmonary embolism were observed clinically. However, it is known that many cases of pulmonary embolism remain clinically overlooked and are often associated with sudden, unexpected death. This may have been aggravated by the method for diagnosing COVID-19 in Germany, which is based on PCR tests rather than computed tomographic imaging because of concerns about infection of medical staff and other

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**Figure 1. Antemortem versus postmortem computed tomographic imaging (case 3).**

**Top.** Contrast medium-enhanced computed tomography scan demonstrates the antemortem findings: bilateral ground glass opacities in the lower lobes of both lungs (yellow asterisks) and a chest tube (yellow arrowheads). **Bottom.** Computed tomography scan without contrast medium enhancement demonstrates the corresponding postmortem findings. For technical reasons, the postmortem image has a lower resolution. To protect the staff from potential infection, bodies were scanned in a double-layer body bag with the arms positioned alongside the body. Although the findings correspond to the antemortem images, ground glass opacities in both lower lobes (yellow asterisks) and a chest tube (yellow arrow) are seen. In addition, a central venous line (red arrowhead) and gastric tube (red arrow) are visible.
patients. A recent report described clinical features of 85 fatal cases of COVID-19 from Wuhan (16). Besides respiratory failure, the cause of death was multiorgan failure in 16% and cardiac arrest in 9%. No autopsies were performed. The gold standard for identifying cause of death is still the autopsy (17). However, in-hospital autopsy rates have declined worldwide over the past decades. Also, because of pathologists’ potential risk for SARS-CoV-2 infection, very few autopsies have been performed worldwide (18). To our knowledge, only 3 case reports have been published on patients with COVID-19 who have undergone complete autopsy and a few more in which only lung tissue was examined (7, 8).

Other researchers have described coagulopathy as a common complication in patients with severe COVID-19 (5, 6, 19). In a recent study of 191 patients with COVID-19, 50% of those who died had coagulopathy, compared with 7% of survivors. D-dimer levels greater than 1000 μg/L were associated with a fatal outcome (6).

COVID-19 may predispose to venous thromboembolism in several ways. The coagulation system may be activated by many different viruses, including HIV, dengue virus, and Ebola virus (20, 21). In particular, coronavirus infections may be a trigger for venous thromboembolism, and several pathogenetic mechanisms are involved, including endothelial dysfunction, characterized by increased levels of von Willebrand factor; systemic inflammation, by Toll-like receptor activation; and a procoagulatory state, by tissue factor pathway activation (22). In a subgroup of patients with severe COVID-19, high plasma levels of proinflammatory cytokines were observed (23). The direct activation of the coagulation cascade by a cytokine storm is conceivable. With COVID-19, severe hypoxemia develops in some patients (24). Thrombus formation under hypoxic conditions is facilitated both in animal models of thrombosis and in humans. The vascular response to hypoxia is controlled primarily by the hypoxia-inducible transcription factors, whose target genes include several factors that regulate thrombus formation (25). Lastly, indirect causes, such as immune-mediated damage by antiphospholipid antibodies, may partially contribute, as speculated by Zhang and colleagues (26).

The macroscopic findings in our autopsy series—with rather heavy, consolidated, friable, basically air-free lungs in most of the cases—were impressive and explain the difficulties in sufficiently ventilating some of these patients. The histopathologic changes in most of our cases with diffuse alveolar damage as the main finding resemble those described by Xu and colleagues (7) and Barton and colleagues (8), who reported single cases; Zhang and colleagues (26), who reported on lung biopsy in a patient with SARS-CoV-2 positivity; and Tian and colleagues (27), who described macroscopic and histologic pulmonary findings in 2 patients with lung cancer who received positive results on SARS-CoV-2 testing. However, the full-blown picture of diffuse alveolar damage seems to be more prevalent in younger patients with fewer preexisting diseases and longer survival, whereas older patients with more co-

Figure 2. Macroscopic autopsy findings.

A. Patchy aspect of the lung surface (case 1). B. Cutting surface of the lung in case 4. C. Pulmonary embolism (case 3). D. Deep venous thrombosis (case 5).
morbid conditions tend to die in the early stages of the disease.

In line with clinical, macroscopic, and histopathologic findings, PCR detected the highest concentration of SARS-CoV-2 RNA in lung and pharyngeal tissue. Of interest, in most patients with disease, high titers of RNA were also detected in postmortem samples. The clinical relevance of this is not yet clear. Clearance of viral RNA from blood 7 days after transfusion of COVID-19 convalescent plasma was associated with substantial clinical improvement, but studies have not shown a correlation between viremia and acute respiratory distress syndrome in patients with severe COVID-19 (28, 29). As in patients with SARS-CoV-1, in whom viral replication could be detected in other organs, including the liver, kidney, spleen, and cerebrum (30), we detected viral RNA at high titers in other organs (liver, kidney, and heart) in 5 patients. These data suggest that SARS-CoV-2 may spread via the bloodstream and infect other organs. To prove this, replication intermediates must be detected.

The current study had some limitations: First, the sample size was small, possibly leading to overestimation of the rate of pulmonary embolism. However, both the clinical and postmortem observations agree well with the current knowledge about SARS-CoV-2 pathology. This includes the sex and age distribution as well as the preexisting conditions among the patients, but also the histologic findings. Second, although viral titers in swabs (pharynx) taken longitudinally up to 7 days after death remained similar, we lack data on how postmortem processes affect viral titers and dynamics in different tissues and body fluids. Moreover, the quantitative PCR assay used cannot discriminate between genomic and subgenomic RNA. As stated earlier, to prove viral replication, detection of replication intermediates or antigenomic RNA would be necessary.

In conclusion, we found a high incidence of thromboembolic events in patients with COVID-19. When hemodynamic deterioration occurs in a patient with COVID-19, pulmonary embolism should always be suspected. That patients with COVID-19 who have increased D-dimer levels, a sign of coagulopathy, may benefit from anticoagulant treatment seems plausible (31). As demonstrated in our cohort, this might be important for hospitalized patients and outpatients. In this context, some professional societies have already made recommendations for antithrombotic therapy for patients with COVID-19 (32). Robust evidence, however, remains scant, and further prospective studies are urgently needed to confirm and validate these results.

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ORIGINAL RESEARCH

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**Appendix Figure 1.** Thrombosis of the prostatic vein (case 1) (arrows).

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**Appendix Table 1.** Weights of Individual Organs, in Grams, for All Cases*

| Case Number | Brain  | Heart  | Lung (Right) | Lung (Left) | Liver  | Kidney (Right) | Kidney (Left) | Spleen |
|-------------|--------|--------|--------------|-------------|--------|----------------|---------------|--------|
| 1           | 1520   | 660    | 1135         | 940         | 3880   | 215            | 305           | 500    |
| 2           | 1430   | 515    | 1220         | 1030        | 2030   | 155            | 155           | 355    |
| 3           | 1665   | 510    | 1280         | 1445        | 1930   | 240            | 240           | 280    |
| 4           | 1435   | 605    | 1370         | 1100        | 2180   | 210            | 210           | 240    |
| 5           | 1450   | 360    | 955          | 845         | 1645   | 180            | 165           | 310    |
| 6           | 950    | 250    | 275          | 275         | 690    | 80             | 90            | 90     |
| 7           | 1210   | 415    | 690          | 655         | 1380   | 105            | 120           | 95     |
| 8           | 1170   | 575    | 1160         | 940         | 1610   | 145            | 160           | 260    |
| 9           | 1080   | 355    | 480          | 410         | 715    | 100            | 35            | 50     |
| 10          | 1350   | 390    | 730          | 630         | 945    | 115            | 145           | 135    |
| 11          | 1400   | 650    | 1880         | 1540        | 1450   | 225            | 240           | 240    |
| 12          | 1460   | 745    | 1580         | 1290        | 2265   | 270            | 220           | 360    |

*Weights are rounded to 5 g. Standard weights for men and women (adopted from Molina and DiMaio [13, 14]), respectively, are as follows: brain, 1401 g and 1233 g; heart, 331 g and 245 g; lung (right), 445 g and 340 g; lung (left), 395 g and 299 g; liver, 1561 g and 1288 g; kidney (right), 129 g and 108 g; kidney (left), 137 g and 116 g; and spleen, 139 g and 115 g.*
### Appendix Table 2. Macroscopic Autopsy Findings in Organs Other Than the Lung in Patients Dying of COVID-19*

| Case Number | Heart | Liver | Kidneys | Spleen | Prostate | Veins | Bowel | Pharynx | Adrenal Glands | Arteries | Miscellaneous |
|-------------|-------|-------|---------|--------|----------|-------|-------|---------|---------------|----------|---------------|
| 1           | Excentric hypertrophy of both ventricles | Hepatomegaly | Shock kidneys | Splenomegaly | Thrombosis | Thrombosis | Ischemic enterocolitis | Normal | Normal | Atherosclerosis | – |
| 2           | CHD with stenting, status post MI, cardiac aneurysm, hypertrophy | Shock liver | Normal | Enlarged | Status post prostatectomy | Normal | Normal | Normal | Normal | Normal | Atherosclerosis | – |
| 3           | Biventricular hypertrophy, moderate CHD | Shock liver | Normal | Normal | Thrombosis, benign hypertrophy | Thrombosis, phlebosclerosis | Diverticulosis, ischemic enterocolitis | Normal | Micronodular hyperplasia | Atherosclerosis | Status post VATS (resection of right upper lung lobe) | – |
| 4           | Left ventricular hypertrophy | Shock liver | Normal | Normal | Thrombosis | Thrombosis | Ischemic colitis | Normal | Normal | Slight atherosclerosis | Struma olllaries nodosa |
| 5           | CHD, status post MI | Normal | Normal | Normal | Normal | Thrombosis | Thrombosis | Status post abdominal surgery | Normal | Normal | Slight atherosclerosis | – |
| 6           | CHD, moderate hypertrophy, calcification of the mitral ring, status post MI, pancreatic lipomatosis cords | Normal | Normal | Normal | Normal | Normal | Normal | Adenoma | Normal | Adenoma | Normal | Trisomy 21, PEG tube, cholelithiasis, small brain, umbilical hernia, cholelithiasis |
| 7           | CHD, status post bypass surgery, status post MI, cardiac aneurysm, global hypertrophy | Chronic congestion | Cysts | Chronic congestion | Thrombosis, benign hypertrophy | Thrombosis | Diverticulosis of the small bowel | Normal | Normal | Atherosclerosis | Cerebral sclerosis, status post cholecystectomy |
| 8           | CHD, status post MI | Fatty change | Shrinkage (left kidney) | Nonspecific acute splenitis | – | Normal | Pseudomembranous colitis | Normal | Normal | Atherosclerosis | NET of the lung, osteoporosis |
| 9           | Left atrial dilatation, CHD, status post MI | Normal | Arteriosclerosis, atrophy, cysts | Nonspecific acute splenitis | Benign hypertrophy | Normal | Normal | Normal | Slight atherosclerosis | Suspected septic encephalomalacia (brain dissection pending), pancreatic fibrosis, cholelithiasis |
| 10          | CHD, status post MI | Normal | Normal | Normal | Normal | Status post prostatectomy | Thrombosis | Normal | Normal | Micronodular hyperplasia | Atherosclerosis | – |
| 11          | CHD, status post aortic valve replacement, biventricular hypertrophy | Normal | Normal | Normal | Normal | Status post prostatectomy | Thrombosis | Normal | Normal | Micronodular hyperplasia | Atherosclerosis | – |
| 12          | CHD, hypertrophy | Chronic congestion, fatty changes | Multiple cysts | Chronic congestion | Benign hypertrophy, thrombosis | Thrombosis | Normal | Normal | Micronodular hyperplasia | Atherosclerosis | Cerebral sclerosis, hemorrhagic cysts |

CHD = coronary heart disease; MI = myocardial infarction; NET = neuroendocrine tumor; PEG = percutaneous endoscopic gastrostomy; VATS = video-assisted thoracoscopic surgery.

* No abnormal findings were present in the testes or ovaries of any patient.
Appendix Figure 2. Mononuclear infiltrations consisting of lymphocytes (arrows) in the myocardium of the right ventricle (case 3) (hematoxylin-eosin stain; original magnification, × 100).