Review

Died with or Died of? Development and Testing of a SARS CoV-2 Significance Score to Assess the Role of COVID-19 in the Deaths of Affected Patients

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Abstract: Since December 2019, a new form of coronavirus, SARS-CoV-2, has spread from China to the whole world, raising concerns regarding Coronavirus Disease 2019 (COVID-19) endangering public health and life. Over 1.5 million deaths related with COVID-19 have been recorded worldwide, with wide variations among countries affected by the pandemic and continuously growing numbers. The aim of this paper was to provide an overview of the literature cases of deaths involving COVID-19 and to evaluate the application of the COVID-19 Significance Score (CSS) in the classification of SARS CoV-2-related fatalities, comparing it with the Hamburg rating scale. The results obtained allowed us to highlight that CSS used after a complete accurate post-mortem examination, coupled to the retrieval of in vivo data, post-mortem radiology, histology and toxicology, as well as to additional required analyses (e.g., electronic microscopy) is a useful and concise tool in the assessment of the cause of death and the role played by this virus. A shared use of this scale might hopefully lower the inhomogeneities in forensic evaluation of SARS CoV-2-related fatalities.

Keywords: COVID-19 Significance Score (CSS); COVID-19; SARS CoV-2 related fatalities; death; cause of death

1. Introduction

In December 2019, starting from the urban area of Wuhan, a new form of coronavirus, SARS CoV-2, began to spread firstly to a national level, and rapidly to the whole world. Its diffusion was so fast that on March 11, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a pandemic [1]. At the time of the present article (December 2020), the cases of COVID-19 registered in the world have reached 68,679,195, with 47,583,441 patients completely recovered. Active cases amount to 19,530,028, 0.5% of which are in severe or critical conditions. Most affected countries include the United States, India and Brazil. Deaths related to COVID-19 amount to 1,565,726, with wide variations among countries affected by the pandemic and continuously growing numbers [2].

Global research efforts have been, since then, focused on studying the natural history of the disease, the immune responses, rapid and reliable diagnostic testing and on understanding the mechanisms underlying the clinical picture, with the aim of better treating affected patients and developing an effective vaccine as soon as possible. Although several vaccines have shown promising results in phases 2 and 3 of the experimental studies [3,4], long-term effects of COVID-19 and of related counteracting drugs and therapies might continue for years. The COVID-19 death toll is reported everyday nation by nation and is one of the main aspects of health surveillance, which guides health and social policies.

In this context, the distinction between “died from” and “died with” COVID-19 still represents an under-addressed and unsolved issue [5,6]. Often it is a difficult task for
a medical practitioner to establish into which of these categories a death falls; indeed, distinguishing between “dying with” and “dying from” COVID-19 requires more complex investigation into the cause of a death, beyond citing a positive SARS-CoV-2 test. Although some clinical conditions, as well as laboratory and imaging alterations, are known to be associated with a worse outcome [7–13], there are still difficulties in classifying COVID-19 related deaths [14], due to the lack of consensus criteria. Throwing light on what is being counted as a COVID-19 death is also essential to understand the impact of the virus and to inform the public. According to the “International guidelines for certification and classification of COVID-19 as cause of death”, published last April by the World Health organization (WHO) and based on the International Classification of Diseases (ICD), a clinical-based categorization of COVID-19 deaths can be performed by recording a pathophysiological sequence of the clinical conditions leading to death, as well as other contributing causes [15,16]. Medical certifications of death compiled for research and surveillance purposes by treating physicians have relevant consequences, e.g., they might bias scientific studies for the development of clinical risk prediction models or prevent the development of public health safety measures [17,18]. COVID-19 might be a direct cause, an underlying cause of death or a contributing condition. Even probable infections are acceptable in death certificates and do not necessarily point to the need for a judicial autopsy or a coroner intervention, even if it is a notifiable disease [15]. Though most autopsies are not necessary for laboratory-confirmed deaths [15], in the absence of a probable cause of death or when there is a suspect of medical liability, a post-mortem examination might be necessary [15,17]. It is well documented that the clinical cause of death might not coincide with the pathological one [19,20] and, notwithstanding increasingly accurate laboratory and instrumental techniques, the role of the autopsy still remains relevant [21]. Since this virus belongs to Hazard group 3, in the early stages, very few autopsies were performed on COVID-19 patients, leading to a loss of valuable information. With the aim of reducing biological risk for contagion, several guidelines have been developed [22–31]. While some authors have proposed the use of “special autopsy facilities”, others promoted a shift towards minimally invasive autopsies, performed by ultrasound-guided biopsies in different organs [32,33]. However, the latter may not provide a complete picture, making it difficult to answer questions about exact causes of death and SARS CoV-2 liability.

2. COVID-19 Significance Score (CSS)

As recently reported, a COVID-19 Significance Score (CSS) has been proposed [34]. The CSS classifies fatalities involving COVID-19 into four categories (as also suggested in other forensic disciplines, e.g., toxicology) [35,36]:

- 0: COVID-19 is merely an occasion; it has no role in the patient’s death.
- 1: A role of COVID-19 in the patient’s death cannot be excluded, although an alternative cause of death is likely.
- 2: COVID-19 likely contributed to the death, together with other factors that may have played a prominent role.
- 3: COVID-19 is the leading cause of death.
- U (unclassified or unclear), when not enough data are available, when further instrumental and laboratory tests are needed to clarify the situation or when the role of COVID-19 remains unclear despite all tests and analyses.

In the application of the CSS, the following features must be taken into consideration:

1. Presence and severity of COVID-19, considering both in vivo and postmortem data (natural history of disease, results of upper and lower airway swabs, clinical records, laboratory tests).
2. Presence and severity of comorbidities. It has been widely demonstrated that the presence of comorbidities is more frequently related to a different natural history in SARS-Cov-2 infection.
3. Circumstances of death. External traumatic events, e.g., a fatal car accident, involving a patient infected by SARS CoV-2 might rule out the responsibility of the virus in
the death. This might be less evident in suicides. Indeed, cases of Corona Suicide have been reported worldwide [37] and COVID-19 might play an indirect role, by ingenerating fear, burden and a sense of responsibility for having infected other people, especially the closest relations.

4. Post-mortem imaging. Together with the tests performed in vivo or individually, post-mortem radiology, including X-rays and post-mortem computed tomography (PMCT), may offer prominent information about the severity of the infection, as well as on any other alterations not clinically appreciable. However, due to the biological risk, these examinations should be carried out according to appropriate safety protocols and in any case should not hinder the hospital routine.

5. Macroscopic and microscopic autopsy findings. Autopsy plays a central role in the development of this score, as information that can be obtained from this examination cannot be provided by any other imaging or laboratory test.

6. Toxicological evaluation. A screening of the most common substances of abuse could be useful to exclude acute intoxications. As often happens in comorbid patients, the consumption of multiple drugs might lead to adverse events and exitus even at concentrations lower than the toxic levels, due to synergic effects. Insufficient dosages of a necessary drug might as well explain a death and these possibilities require a quantitative analysis.

7. Additional analyzes. When required by the case in question, such as bacterial culture, virological tests and other specific exams.

The aim of the present work is to provide an overview of the literature cases of deaths involving COVID-19 and to evaluate the application of the CSS in the classification of SARS CoV-2-related fatalities, comparing it with other rating scales currently available.

3. Material and Methods

3.1. Literature Review and Data Extraction

A systematic review of the available literature was performed, seeking information regarding post-mortem examinations performed on the deceased who had tested positive for SARS CoV-2, with the infection confirmed in vivo and/or after death (topic of the search and main inclusion criteria). Data was collected from May 2020 to August 2020, by performing a search on an international database (Pubmed) using the following search terms. The keyword “covid” (variably written) was linked through the Boolean operator “AND” to the following terms, alternatively: “autopsy”, “full autopsy”, “post-mortem”.

Inclusion criteria were: relevance to the topic; English, Spanish, German or Italian language; date of publication (up to 31 July 2020); retrievability of a full-text.

Papers that did not report the results of a post-mortem examination, e.g., publications dealing with the health care personnel safety or technical aspects of post-mortem examinations, cases analyzed only by post-mortem biopsies performed on a single organ and papers from which individual patient data could not be extracted, were excluded from the work (exclusion criteria).

A database with the results was created in Microsoft Excel and the following data, organized in two sections, were extracted.

- In vivo data: in addition to the patient’s personal details (age and sex), the history of the disease, any comorbidities, medications taken before and during the SARS CoV-2 infection, information about the swab, laboratory and imaging (e.g., X-rays and computed tomography or CT) data.

- Post-mortem data: death circumstances, any post-mortem imaging examinations, type of postmortem examination (full, partial, histology), macro and microscopic features emerged from the autopsy and related analyses, cause of death (when specified) and the role played by SARS CoV-2 as reported by the authors.
3.2. CSS Guiding Tool Development and Score Application

A short and easy guiding tool has been developed in order to facilitate the application of the CSS across original points 1 to 6 [34]. The features considered in this guide refer to the most frequent pictures described in literature to date. For this reason, the CSS is not to be considered as a definitive tool, but susceptible to modifications and improvements along with the progress of the state of the art.

1. in vivo and/or post mortem positivity of the swab for SARS CoV2 (YES/NO)
   - any reported symptoms compatible with COVID-19 (YES/NO) and severity of them (MILD, MODERATE = the situation required non-invasive techniques, SEVERE = the situation required invasive techniques, such as intubation)
   - any symptoms referable to other causes (YES/NO)
   - drug therapy administered during COVID-19
   - any changes in laboratory tests compatible with COVID-19 (YES/NO)
   - any alterations in the laboratory tests due to other causes (YES/NO)
   - evidence of bacterial, fungal or viral superinfection (YES/NO)
   - radiological evidence (X-ray, CT compatible with COVID-19) (YES/NO)

2. presence (YES/NO) and number of comorbidities (1, 2 OR MORE)
   - severity of comorbidities
   - drugs consumed prior to COVID-19

3. external traumatic cause of death (e.g., car accident, gunshot, electrocution, drowning) or suicidal/homicidal manner of death (YES/NO)*

4. radiological evidence (XR, CT compatible with COVID-19) (YES/NO)
   - presence of any other pathological alterations (YES/NO)

5. macroscopic and/or microscopic findings compatible with COVID-19 (YES/NO)
   - presence (YES/NO), type (as chronic obstructive pulmonary disease (COPD), cardiomyopathy, thromboembolism, coronary thrombosis) and severity of other pathological conditions

6. presence of drugs/substances of abuse (YES/NO)
   - presence and concentration of drugs taken regularly in chronic or during COVID-19.

* in case of suicide, the liability, even if indirect, for SARS CoV-2 cannot be excluded.

Any useful information, such as a history of psychiatric pathologies, should therefore be evaluated carefully.

All literature cases were classified according to the CSS by three independent blinded investigators and the inter–rater agreement was assessed by non-parametric ANOVA.

3.3. The Hamburg Score

In a recent study performed at the University of Hamburg–Eppendorf, Edler et al. also proposed a classification system for deaths involving COVID-19 [38]. In the paper, the first 80 consecutive autopsies carried out on patients positive to COVID-19, who died in Hamburg, were reported. In fact, the approach used in the federal state of Hamburg is to examine all the deceased citizens with a confirmed SARS-CoV-2 infection, subjecting the bodies to a PMCT and performing a complete autopsy (by opening the three cavities and dissection of all organs). The results of the exams are then progressively uploaded to a national register, with the purpose of collecting data from all the autopsies performed in Germany on COVID-19 patients. Based on clinical information, PMCT and autopsy findings, the researchers propose a categorization of COVID-19 positive deaths, in order to determine whether the virus was the cause of death or whether exitus occurred independently from it.

This scale, just like the CSS, ranks COVID-19 related death into 4 categories: 1—definite COVID-19 death: autopic pneumonia and/or acute respiratory distress syndrome (ARDS); 2—probable COVID-19 death: Autopic pneumonia and/or ARDS and other infectious causes of death (e.g., pulmonary embolism); 3—possible COVID-19 death: cause of death...
that cannot be determined with certainty by autopsy (e.g., cardiac arrhythmia in cardiomyopathy) OR autopic respiratory tract infection/pneumonia of other genesis (e.g., aspiration pneumonia, exacerbated COPD); 4—SARS-CoV-2 detection with cause of death not associated to COVID-19: Clear non-SARS-CoV-2-related cause of death (e.g., brain mass hemorrhage in hypertension, acute myocardial infarction in coronary thrombosis).

A death corresponding to categories 1–3 is defined as “COVID-19 death” (corresponding to CSS 3-1), therefore, COVID-19 related, while category 4 contains deaths not related to COVID-19 (corresponding to CSS = 0).

Within the post-mortem cases reported by the University of Hamburg–Eppendorf, the mean among the CSS assigned by the three raters and the Hamburg scores were compared by means of non-parametric t-test.

4. Results

4.1. Literature Review

Thirty articles were included in the present literature review, corresponding to 84 post mortem examinations. Results of the selection process are shown in Figure 1, and detailed data for each case are reported in Table 1. Fourteen studies describe multiple cases [39–52], while 16 were case reports [53–68]. The highest sample size corresponded to 14 cases.
| Author            | A | G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Course of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tox | Additional Analyses | Cause of Death | Swabs |
|-------------------|---|---|------------------------------|---------|-------|---------|-----------------------------------------------|---------|----------------------|---------------------|-----|---------------------|-----------------|-------|
| Benjamin T Bradley et al. | 57 | M | CKD, DM2, HTN, OSAS, obesity | Intubation | elevated creatinine, lymphocytopenia | Chest X-ray: bilateral multifocal perihilar airspace opacities | Hospital presentation: 4-day history of cough, fever, dyspnea, fatigue and onset of respiratory distress. Intubated, died 6 days after admission | N/D | N/D | LUNG: Interstitial fibrosis, myocyte hypertrophy. | LUNG: Interstitial fibrosis, multinucleated giant cells, reactive pneumocytes, acute bronchiolitis, background emphysematous change. | LIVER: Steatosis, peribronchial lymphocytic inflammation. | KIDNEY: Moderate to severe arteriolar hyalinosis, diastolic changes, scattered tubular casts. | TRACHEA: Edema, chronic lymphocytic tracheitis. GI: Multifocal gastric hemorrhages | (ICD-10 code) A: Coronavirus Disease 2019 (COVID-19) pneumonia. OSC: DM, end stage CKD, HTN. | Positive for SARS CoV-2 (unspecified). |
|                   | 74 | F | DM2, OSAS, AF, pulmonary hypertension, CKD, obesity | Intubation | elevated creatinine, lymphocytopenia | Chest X-ray: increased in vascular and interstitial opacities | Hospital presentation: 2-day history of AKI, delirium, cough, acute cardiomyopathy and respiratory distress. Intubated, died on the day of admission | N/D | N/D | LUNG: Organizing phase DAD, reactive pneumocytes, acute bronchiolitis, alveolar septal thickening. | LUNG: Interstitial fibrosis, myocyte hypertrophy, replacement fibrosis. | LIVER: Steatosis, congestion. | KIDNEY: Moderate-to-severe arteriolar hyalinosis, diastolic changes. | TRACHEA: Edema, chronic lymphocytic tracheitis. | (ICD-10 code) A: Cardiomyopathy. B: COVID-19. OSC: DM, pulmonary hypertension, immunosuppression. | Positive for SARS CoV-2 (unspecified). |
| 54 | M | Neurological alteration and dysphagia from previous head injury | N/D | N/D | Chest X-ray: bilateral patchy opacities | Hospital presentation: 1-day history of fever, respiratory distress and tachycardia. Refused intubation and died the day after admission | N/D | N/D | LUNG: Interstitial fibrosis, myocyte hypertrophy. | LUNG: Interstitial fibrosis, myocyte hypertrophy. | LIVER: Peribronchial lymphocytic inflammation, centrilobular necrosis. | KIDNEY: Mild arteriolar hyalinosis, scattered tubular casts | TRACHEA: Acute neutrophilic tracheitis, fibrosis and calcification. microthrombi. | (ICD-10 code) A: Aspiration pneumonia and sepsis. B: COVID-19. OSC: DM, dysphagia due to traumatic neurological damage. | Positive for SARS CoV-2 (unspecified). |
| 74 | M | Heart failure with preserved EF, frontaltemporal dementia, HTN, OSAS | Intubation | N/D | Chest X-ray: diffuse bilateral scattered opacities | Hospital presentation: cough, myalgia, respiratory distress and fever. Intubated, died on the day of admission | N/D | N/D | LUNG: Pulmonary edema, acute phase DAD, multinucleated giant cells, reactive pneumocytes, alveolar septal thickening, patchy perivascular lymphocytic inflammation. | LUNG: Interstitial fibrosis, myocyte hypertrophy, replacement fibrosis. | LIVER: Steatosis, congestion, features of toxic or metabolic disease. | KIDNEY: Mild to moderate arteriolar hyalinosis, scattered tubular casts. | TRACHEA: Acute neutrophilic tracheitis. | (ICD-10 code) A: ARDS. B: Central pneumonia. C: COVID-19. OSC: CKD. | Positive for SARS CoV-2 (unspecified). |
### Table 1. Cont.

| Author | A | G |
|--------|---|---|
| Comorbidities and Past Drugs Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Tax | Additional Analysis | Cause of Death | Swabs |
| | | | | | | | | | |
| 73 F | DM2, HTN, congestive heart failure, hypophysialism, obesity, schizophrenia disorder, bipolar disorder | Lisinopril | N/D | Chest X-ray: widespread bilateral opacities | Hospital presentation: 5-day history of cough, respiratory distress and fever. Intubated, died 8 days after admission | N/D | N/D | LUNGS: Pulmonary edema, acute phase DAD, multinucleated giant cells, alveolar septal thickening, perivascular and interstitial lymphocytic inflammation | (ICD-10 code) A: ARDS | Positive for SARS CoV-2 (unspecified) |
| 84 F | COPD, congestive heart failure, AF, aortic stenosis, HTN, CKD, osteoporosis | N/D | Chest X-ray: bilateral atelectasis or consolidations with small pleural effusions | Hospital presentation: 1-day history of respiratory distress and delirium. Ruled intubation and died the day after admission | N/D | LUNGS: presence of intraalveolar hemorrhage | (ICD-10 code) A: ARDS | Positive for SARS CoV-2 (unspecified) |
| 71 M | HTN, dyslipidemia, coronary heart disease, AF, CKD, CRAS | elevated creatinine, lymphocytopenia | N/D | Chest X-ray: bilateral multilobar opacities | Hospital presentation: 7-day history of cough and respiratory distress. Pseudomonas aeruginosa found in the sputum. Ruled intubation and died 6 days after admission | N/D | N/D | LUNGS: Acute phase DAD, reactive pneumocytes, pulmonary hemorrhage, acute bronchopneumonia, background emphysematous changes | (ICD-10 code) A: ARDS | Positive for SARS CoV-2 (unspecified) |
| 78 F | Dyslipidemia, osteoporosis | Lisinopril, elevated creatinine, lymphocytopenia, elevated troponin | N/D | Chest X-ray: bilateral multilobar opacities | Hospital presentation: 3-day history of respiratory distress, hypotension, tachycardia and fever. Staphylococcus aureus – Viria influenza A detected. Intubated, died 4 days after admission | N/D | LUNGS: lusy and edematous, diffuse pneumonitis, splenomegaly; CNS: scattered pliculate subdural/basal hemorrhages | (ICD-10 code) A: ARDS | Positive for SARS CoV-2 (unspecified) |
| Author | A G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs |
|--------|-----|-----------------------------|---------|-------|---------|---------------------------------|---------|---------------------|---------------------|-----|---------------------|-----------------|-------|
| 75 F   | Dyslipidemia, DM2, coronary heart disease, congestive heart failure, CKD, COPD, DVT | Chest X-ray: bilateral interstitial opacities, asymmetric edema on the right | N/D | lymphocytopenia | The patient presented to the hospital with a 3-day history of delirium, fever and respiratory distress. She refused intubation and died 9 days after admission | N/D | N/D | LUNGS: Edema, acute phase DAD, reactive pneumocytes, acute bronchiolitis, microthrombi | HEART: Interstitial fibrosis, myocyte hypertrophy | LIVER: Steatosis, congestion | KIDNEY: Moderate to severe arteriomegaly | SPLEEN: White pulp depletion | TRACHEA: Edema, chronic (lymphocytic) tracheitis, microthrombi | Positive for SARS CoV-2 | (unspecified) |
| 84 M   | CKD, COPD, dyslipidemia, OSAS, mitral regurgitation, complete AI block, chronic pain, arthritis, obesity, HTN | elevated creatinine, lymphocytopenia | N/D | Chest X-ray: complete opacification of the left hemithorax, opacities in the right middle and lower lobes | Hospital presentation: 1-day history of delirium, hypotension and respiratory distress. Refused intubation and died the same day of admission | N/D | LUNGS: heavy and edematous, subsegmental emboli | HEART: Interstitial fibrosis, myocyte hypertrophy, replacement fibrosis | LIVER: Congestion | KIDNEY: Mild to moderate arteriovenous embolus | TRACHEA: Edema, chronic (lymphocytic) tracheitis | Positive for SARS CoV-2 | (unspecified) |
| 81 F   | HTN, dyslipidemia, breast cancer, CKD, demyelinating neuropathy, lacunar infarcts, recent pneumonia, Alzheimer’s disease | Intubation elevated troponin, lymphocytopenia | Chest X-ray: bilateral multifocal opacities | Hospital presentation: 1-day history of breath, cough, nausea and vomit. Intubated after 4 days, died 6 days after admission | N/D | LUNGS: heavy and edematous | LUNG: Acute and organizing diffuse DAD, reactive pneumocytes, multifocal giant cells, acute bronchopneumonia, pulmonary hemorrhage | HEART: Interstitial fibrosis, LIVER: Fatosis, congestion | KIDNEY: Mild to moderate arteriovenous embolus, scattered tubular casts | TRACHEA: Edema, acute (neutrophilic) tracheitis SUBCARINAL LYMPH NODE: Haemophagocytosis | Positive for SARS CoV-2 | (unspecified) |
| 42 F   | History of lobular breast cancer with bilateral mastectomy and neoadjuvant chemotherapy | Intubation leukocytosis, lymphocytopenia | Chest X-ray: bilateral multifocal opacities | Hospital presentation: 5-day history of fever and headache. Intubated after 7 days, died 8 days after admission | N/D | LUNGS: heavy and edematous, subsegmental emboli | LUNG: Pulmonary edema, acute and organizing diffuse DAD, reactive pneumocytes, multifocal giant cells, acute bronchopneumonia, subsegmental pulmonary emboli | HEART: Interstitial fibrosis, myocyte hypertrophy, replacement fibrosis | LIVER: Steatosis, congestion, centrilobular necrosis | KIDNEY: Mild to moderate arteriovenous embolus, scattered granular casts | SPLEEN: White pulp depletion | TRACHEA: Edema | Positive for SARS CoV-2 | (unspecified) |
| Author | A G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tox Analyses | Cause of Death | Swabs |
|--------|-----|-------------------------------|---------|-------|---------|--------------------------------|---------|----------------------|---------------------|-------------|----------------|-------|
|        |     |                               |         |       |         |                                 |         |                      |                      |             |                |       |
| 71 M   |     | Coronary heart disease, ischemic cardiomyopathy, HTN, aortic stenosis, end-stage CKD, chronic pulmonary fibrosis, history of cerebellar stroke | elevated creatinine, elevated triglycerides, lymphocytopenia | N/D    | elevated LDH and leukocytosis | Chest X-ray: reduced lung volumes, diffuse pulmonary changes, compatible with pulmonary fibrosis | Hospital presentation: 1 day-history of shortness of breath, bradycardia, new onset AV block and delirium. Worsening hypoxia, refused intubation. 4 days after hospitalization, died of cardiac arrest | N/D    | LUNGS: heavy and edematous/PLEN: splenomegaly | LUNGS: Pulmonary edema, acute phase DAD, pulmonary lymphohage, chronic fibrosis, microthrombi. HEART: Intestinal fibrosis, myocyte hypertrophy, replacement fibrosis, myocardial arrhythmia. LIVER: Congestion. KIDNEY: Severe arteriolar sclerosis, scattered tubular casts, reactive tubular epithelium, renal vein organizing thrombus. TRACHEA: Sloughed epithelium. | N/D | SARS-CoV-2 RNA detected in multiple organs. | Positive for SARS CoV-2 (unspecified) |
| 73 F   |     | HTN, asthma, DM, dyslipidemia, obesity | intubation | elevated LDH and leukocytosis | Chest X-ray: reduced lung volume, diffuse bilateral changes | Hospital presentation: 2 day-history of progressive shortness of breath and respiratory distress. Physical examination revealed hypoxia and signs of shock. Developed multilobar atelectasis, ARDS and acute respiratory failure. | N/D    | LUNGS: heavy and edematous/PLEN: splenomegaly | LUNGS: Pulmonary edema, acute bronchopneumonia, perivascular and interstitial lymphocytic infiltrate, microthrombi, reparative fibrosis and neovascularization, vascular disease. HEART: Intestinal fibrosis, myocyte hypertrophy, replacement fibrosis. LIVER: Steatosis, congestion, centrilobular necrosis, portal lymphocytic inflammation. KIDNEY: Mild to moderate arteriolar sclerosis, reactive tubular epithelium, tubular casts, chronic inflammation, focal segmental glomerulosclerosis. TRACHEA: Edema, chronic (lymphocytic) tracheitis, hemorrhage, ulceration, epithelial sloughing. SUBCARINAL LYMPH NODE: Haemophagocytosis | N/D | SARS-CoV-2 RNA detected in multiple organs. | Positive for SARS CoV-2 (unspecified) |
|        |     |                               |         |       |         |                                 |         |                      |                      |             |                |       |
|        | 52 M | Obesity (BMI 38.8 kg/m²) | N/D    | N/D    | N/D    |                                | N/D    |                      |                      |             |                |       |
|        |     |                               |         |       |         |                                 |         |                      |                      |             |                |       |
| Author | Age | Gender | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Causes of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs |
|--------|-----|--------|-----------------------------|---------|-------|--------|---------------------------------------------|--------|---------------------|---------------------|-----|---------------------|------------------|-------|
| 70 M   | 82 M | F      | Parkinson’s disease, coronary heart disease, PVD, CKD | Evacumab, piperacillin/tazobactam | Elevatad DLDs, elevated creatinine, elevated CRP | N/D | N/D | LUNGS AND AIRWAYS: pneumonia, purulent bronchitis, HEART: coronary heart disease, signs of previous AMI, cardiomyopathy, OTHERS: muscle stiffness, shock liver | LUNG: DAD, activated pneumocytes, hyaline membranes, scattered lymphocytes, focal granulocytes, acute and chronic bronchitis | N/D | N/D | PULMONARY: pneumonia with bronchiolitis | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 71 M   | 71 M | M      | HTN, smoking, granulomatous pneumonia, obesity (BMI 36.8 kg/m²) | Cefpodoxime | Elevated aPTT, Elevated LLDs, Elevated CRP, Elevated creatinine | N/D | N/D | CT: emphysema, stable reticular pattern in each lobe, consolidations in the lower right and lower left lobe | LUNG: DAD, squamous metaplasia, fibrinolysis, hyaline membranes, activated pneumocytes, thromboembolism, HEART: lymphocytic myocarditis in the right ventricle | N/D | N/D | PULMONARY: pneumonia with bronchiolitis | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 63 M   | 54 F | F      | DM2, obesity (BMI 37.5 kg/m²), asthma | Vasopressors, statins, nils, levofoxacin, enoxaparin | Elevated D-dimer, Elevated LLDs, Elevated CRP | N/D | N/D | LUNGS: pneumonia, HEART AND VESSELS: coronary heart disease, DVT, atrial fibrillation | OTHERS: anasarca | N/D | N/D | PULMONARY: pneumonia | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 66 M   | 50 M | M      | Coronary heart disease | Vasopressors, statins, nils, enoxaparin | Elevated D-dimer, Elevated LLDs, Elevated CRP | N/D | N/D | CT: consolidations in each lobe, reticular pattern in the upper and lower lobes and in both lobes | LUNG: evidence of pneumonia, HEART AND VESSELS: coronary heart disease, previous AMI, DVT | N/D | N/D | PULMONARY: pneumonia, pulmonary edema with bronchiolitis | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 54 F   | 75 F | F      | Dementia, epilepsy, trisomy 21 | Oxycodone | Elevated D-dimer, Elevated LLDs, Elevated CRP | N/D | N/D | CT: multiple right and left consolidations, ground glass opacities in the right lobe and in the upper left lobe, reticular pattern | LUNGS: pneumonia, OTHERS: renal infarction, PEG | N/D | N/D | CLINICAL: respiratory failure, parapneumonic pneumonia | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 75 F   | 82 M | M      | AE, smoking, coronary heart disease, O2, edexaban | Elevatad aPTT | Elevated D-dimer, Elevated LLDs, Elevated CRP | N/D | N/D | CT: reticular pattern in each lobe, small areas of consolidation in the lower left lobe and both lobes | LUNGS: pneumonia, pulmonary edema, HEART AND VESSELS: coronary heart disease, left heart dilation, mitral calcification, cardiac pacemaker, atelectasis | N/D | N/D | PULMONARY: pneumonia with bronchiolitis | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |

**Table 1. Cont.**
| Author | A/G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs |
|--------|-----|-----------------------------|---------|-------|---------|-------------------------------------------|---------|----------------------|---------------------|-----|---------------------|---------------|-------|
| 87     | F   | Pulmonary NET, COPD, coronary heart disease, CKD | N/D  | Elevated CRP | N/D  | N/D | CT: emphysema, spherical tumor in the lower right lobe, small areas of consolidation in the upper and lower right lobes and in the upper left lobe, reticular pattern in the upper and lower right lobes and both left lobes | LUNGS: pneumonia, purulent bronchitis, bullous emphysema, pulmonary NET HEART: coronary heart disease, previous AMI OTHERS: cachexia, atherosclerosis | LUNGS: extensive granulocytic infiltrate in alveoli and bronchi, resembling focal bacterial bronchopneumonia. Presence of emphysema, acute bronchitis, small cell NET | N/D  | N/D | CLINICAL: respiratory failure, viral pneumonia PATHOLOGICAL: suppurative bronchitis | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 84     | M   | DM2, HTN, LC | N/D  | Elevated CRP | N/D  | N/D | Leukocytosis, elevated D-dimer, elevated LDH, elevated creatinine, elevated CRP | LUNGS: pneumonia, emphysema HEART: previous MIA OTHERS: septicaemia, atrophic kidneys | LUNGS: extensive granulocytic infiltrate in alveoli and bronchi, resembling focal bacterial bronchopneumonia. Emphysema, congestion of small vessels, chronic bronchitis, fibrosis | N/D  | N/D | CLINICAL: respiratory failure, viral pneumonia PATHOLOGICAL: pulmonary, septic encephalopathy | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 85     | M   | Coronary heart disease, HTN, asthma, AF | Vasopressors, intubation, dialysis | Elevated d-dimer, elevated LDH, elevated creatinine, elevated CRP | N/D  | N/D | CT: diffuse consolidations in each lobe, reticular pattern in the middle and lower right lobes and both left lobes, ground glass opacities in the upper and middle right lobes and in the upper left lobe. Bilateral pleural effusions | LUNGS: pneumonia, minor pulmonary embolism, emphysema HEART AND VESSELS: coronary heart disease, cardiomegaly, atherosclerosis, DVT | LUNGS: DAD, scattered hyaline membranes, giant cells, activated pneumocytes, emphysema, small vessel congestion, granulocytic infiltrates | N/D  | N/D | CLINICAL: cardiac arrest due to respiratory failure PATHOLOGICAL: pneumonia | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |
| 76     | M   | Obesity (BMI 34.6 kg/m²) | Vasopressors, intubation, corticosteroids | Elevated LDH, elevated CRP | N/D  | N/D | CT: no ventilated area in both lungs, except for a small area in the upper and middle right lobes and in both the left lobes. Bilateral pleural effusions | LUNGS: pulmonary embolism with pulmonary interstitial pneumonia, emphysema, perivascular tracheobronchitis, emphysema HEART AND VESSELS: coronary heart disease, cardiomegaly, atherosclerosis, DVT | LUNGS: DAD, hyaline membranes, fibrosis, activated pneumocytes, lymphocytes, thrombus, small vessel congestion, plasma cells, humoral geometric artifacts | N/D  | N/D | CLINICAL: pulmonary embolism PATHOLOGICAL: pulmonary embolism respiratory infection | POST MORTEM: positive for SARS CoV-2 (nasopharyngeal) |

Andrey Pitalaya, et al. | 72 | M | N/D | Anthracycin, H1 blocker, intubation | N/D | N/D | Hospital presentation: a 4-day history of fever and progressive hypoxia. Initiated on 7th day, died 18 days after hospitalization | Enlarged mediastinal and lung lymph nodes | LUNGS: DAD exudative phase. Mediastinal and pulmonary lymph nodes containing clusters of haemophagocytes, marked diminution of the cortical and subcortical sinuses and local necrosis. Lymphocytic depletion in the lymph nodes SPLEEN: White pulp depletion, red pulp infarction, biconcave hyperplasia and hemosiderin-laden macrophages, suggestive of previous haemophagocytosis LIVER: mild centrilobular congestion, mild steatosis | N/D  | N/D | Immunohistochemistry for IFHV, CMV and EBV in lymph nodes with haemophagocytic negative H-score for haemophagocytic lymphohistiocytosis: 217 (HLH present) | ARDS, HLH | Positive for SARS CoV-2 (nasopharyngeal) |

Table 1. Cont.
| Author | A G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Additional Analysis | Cause of Death | Swabs |
|--------|-----|-----------------------------|---------|-------|---------|----------------------------------------|---------|---------------------|---------------------|-------------------|----------------|-------|
|        | 91  | M                            | Anthromycin, doxycycline, HCQ | elevated fibrogen, elevated ferritin, elevated CRP | N/D | Hospital presentation: 3-day history of fever and progressive hypoxia. Reunited with admission and died 8 days after admission | N/D | Enlarged mediastinal and pulmonary lymph nodes | LUNGS: signs of exudative DAD. Mediastinal and pulmonary lymph nodes. Spleen: large bleeding area in red pulp. Focal hemophagocytosis, white pulp depletion | N/D | immunohistochemistry for HHV8, CMV and EBV for EBV in lymph nodes with hemophagocytosis: negative. | ARDS | Positive for SARS CoV-2 (nasopharyngeal) |
|        | 72  | M                            | Anthromycin, sotalol, azithromycin | increase in platelets, elevated fibrogen, elevated CRP | N/D | Hospital presentation: 3-day history of fever and progressive hypoxia. Reunited with admission and died 8 days after admission | N/D | Enlarged mediastinal and lung lymph nodes | LUNGS: exudative DAD. Mediastinal and pulmonary lymph nodes containing clusters of hemophagocytes. Spleen: slightly hyperplastic white pulp, congestion of the red pulp. Liver: mild centrilobular congestion, mild steatosis | N/D | immunohistochemistry for HHV8, CMV and EBV for EBV in lymph nodes with hemophagocytosis: negative. H-score for hemophagocytic lymphohistiocytosis: 131 (HLH absent) | ARDS | Positive for SARS CoV-2 (nasopharyngeal) |
|        | 64  | F                            | Sarilumab, coltrarone, intubation | hypertriglyceridemia, elevated fibrogen, elevated ferritin, elevated CRP | N/D | Hospital presentation: 5-day history of fever and progressive hypoxia. Intubated, died 15 days after hospitalization | N/D | N/D | LUNGS: DAD in the exudative phase. Spleen: hyperplastic white pulp, congestion of the red pulp. Liver: mild centrilobular congestion, mild steatosis | N/D | H-score for hemophagocytic lymphohistiocytosis: 96 (HLH absent) | ARDS | Positive for SARS CoV-2 (nasopharyngeal) |
|        | 78  | F                            | Obesity: BMI 35.2 (pharyngeal) | elevated D-dimer, elevated ferritin, elevated CRP, elevated LDH | N/D | Death at home after 12 h of fever, cough and vomiting | N/D | LUNGS: significant pulmonary edema, slight increase in the consistency of the lower lobes. Heart: 530 g, dilation of both ventricles | LUNGS: generalized edema. Capillary endothelitis with increased neutrophils. Microthrombotal alveolar capillaries and small pulmonary vessels (including septal veins). Focal inflammatory edema with scattered neutrophils and hyaline membranes, with initial organizational changes. Liver: moderate acute congestion and activation of Kupffer cells | N/D | qRT-PCR for cytokines in lung tissue revealed a massive increase in IL-1β, IL-6 and IL-8 mRNA. SARS CoV-2 RNA detected in the lung | Early stage pneumonia with thrombotic microangiopathy, pulmonary edema and acute heart failure | Positive for SARS CoV-2 (pharyngeal) |
| Hans Bos- müller et al. | 78 | M                            | Coronary heart disease, HTN, DM, Parkinson's disease | Anticoagulants, vasopression, intubation | N/D | Hospital presentation: 3 weeks of generalized weakness, fever and dry cough, worsening in the 3 days prior to admission. Intubated. After a general improvement, massive increase of D-dimers and IL-6, thrombocytopenia, MOF and shock. Died 4 days after the peak of D-dimers | N/D | LUNGS: significant pulmonary edema and consolidation. Macroscopically visible thrombi, especially in small to medium sized pulmonary vessels (both venous and arterial), areas of recent infarction. OTHERS: moderate hypoxia–pulmonary edema | LUNGS: Diffuse DAD with massive intra-alveolar fibrin deposits and hyaline membranes. Marked hyperplasia and desquamation of the alveolar epithelium. Diffuse areas of organizing DAD with proliferation of fibroblasts and collagen. Fibrin deposition in intra-alveolar edema. Focal massive presence of kudzukyo in medium-sized vessels. Liver: signs of hemophagocytosis | N/D | ELECTRON MICROSCOPY: viral-like particles in lung endothelial cells and type 1 pneumocytes. Blood cultures for bacteria and fungi: negative. SARS CoV-2 RNA detected in the lung | ARDS, vasovagal shock and liver failure | Positive for SARS CoV-2 (pharyngeal) |
| Author A G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | IN VIVO DATA | POSTMORTEM DATA |
|-----------|-----------------------------|--------|------|--------|--------------|-----------------|
| Courtois F, Meunier X, et al. | Coronary heart disease, HTN, rheumatic polyarthritis, history of rheumatic polyarthritis, history of cardiac failure, history of diabetes | | | | Lymphopenia, elevated CRP, elevated IL-6, 6 days after admission, | LUNGS: advanced DAD, with extensive hyaline membranes and concentration of intra-alveolar macrophages, multiple giant cells and pronounced hyperplasia of the alveolar epithelium (partly atypical). Focal squamous metaplasia and areas of organizing pneumonia. Viral particles in the endothelial cells of the lung capillaries and in the interstitial spaces. |
| Louis Maximilian Buja et al. | Obesity (BMI 35.8 Kg/m²), asthma, HTN | ECMO, dialysis | Elevated D-dimer | N/D | N/D | N/D | LUNGS: ARDS in organizing phase, with extensive intra-alveolar edema and diffuse thickening of the alveolar septa. Massive hyperplasia of the alveolar and bronchial epithelium, focal squamous metaplasia and typical concentric laminated formations of loose connective tissue, with central aggregates of inflammatory cells. |
| Louis Maximilian Buja et al. | Obesity (BMI 35.8 Kg/m²) | N/D | N/D | N/D | LUNGS: heavy DAD with multiple hyaline membranes, focal mild inflammation. CD68 + macrophages in the alveolar spaces. Reactive pneumocytes with cytomegaly, nucleomegaly, prominent nucleoli and mitotic figures. Squamous metaplasia. CD3 + lymphocyte infiltrates in the epithelium of the small airways. Moderate to severe perivascular and peribronchial inflammation. CD68 + macrophages in the alveolar spaces and septum. | LUNGS: ARDS; vasogenic shock, liver failure. Positive for SARS CoV-2 (pharyngeal) | |
### Table 1. Cont.

| Author | A G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs |
|--------|-----|-----------------------------|---------|-------|---------|---------------------------------------------|---------|---------------------|---------------------|-----|---------------------|-----------------|-------|
| 34     | M   | Obesity (BMI 51.45 Kg/m²), HTN, heart failure with reduced EF (> 20%), DM2 | Antibiotics, O₂, Leukocytes, mild anemia, mildly elevated troponin, elevated creatinine | N/D   | N/D   | N/D | Hospital presentation: 4-day history of headache, shortness of breath, and productive cough with hemoptysis, 5-day of fever, Recurrent fever, hemoptysis and shortness of breath. Death 10 days after hospitalization due to respiratory failure and cardiac arrest | N/D | LUNGS: Extremely congested, with multiple hemorrhagic areas and multiple bilateral segmental thromboemboli. HEART: 1070 g, dilated hypertrophy. Mild coronary atherosclerosis | LUNGS: multiple acute segmental bilateral thromboemboli, infarcted areas and hemorrhage. Intestinal lymphocytic pneumonia. Microscopic thrombi found in some pulmonary arteries. In the alveoli, multiple fibrin deposits not organized in hyaline membranes. HEART: CD3+ epithelial lymphocytic infiltrates, myocardial hypertrophy, multifocal intestinal fibrosis, scattered damaged cardiomyocytes. OTHERS: moderate hepatic steatosis. Thrombi in glomerular capillaries and in the peritubular veins | N/D | Influenza virus and RSV test: negative | Not specified | Positive for SARS CoV-2 (nasopharyngeal) |
| 48     | M   | Obesity (BMI 35.2 Kg/m²) | N/D   | N/D   | N/D | The man was found dead in his residence | N/D | LUNGS AND AIRWAYS: 500 ml of purulent and opaque watery fluid collected in the right pleural cavity. Translucent yellowish material found focally in the visceral pleura, along the upper-mid pleural interlobar fissure. Bilateral pneumatoceles with fibrotic thickening in the parietal and visceral pleura of the lower lobe. Signs of empyema. Lungs were heavy. Tracheobronchial tree had hyperemic mucosa, without mucus plugs. | LUNGS: in the right pleura, empyema. Alveolar and interstitial edema, fibrinous intra-alveolar exudate, abundant intraalveolar macrophages and activated pneumocytes. Scattered neutrophils and intra alveolar hemorrhages. | N/D | Influenza virus test: negative | Not specified | Positive for SARS CoV-2 (nasopharyngeal) |
| Esther Youd et al. | 58  | F | Dementia | N/D   | N/D   | N/D | Died in a nursing home. No symptoms known | N/D | LUNGS AND AIRWAYS: Heavy lungs. Bilateral lobular pneumonia. Tracheobronchial inflammation with presence of mucousHEART: minimal atherosomatic plaques OTHERS: small, bilateral kidneys. Brain atrophy | LUNGS: DAD with hyaline membranes, type 2 pneumocyte hyperplasia and enlargement of the alveolar walls and interstitium, with lymphocytic infiltrate | N/D | N/D | Not specified | Positive for SARS CoV-2 (nasopharyngeal) |
Table 1. Cont.

| Author       | A   | G   | Comorbidities and Past Drugs                                                                 | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death                                                                 | Imaging | Macroscopic Features                                      | Microscopic Features                                       | Tax | Additional Analyses                                      | Cause of Death                          | Swabs                  |
|--------------|-----|-----|-----------------------------------------------------------------------------------------------|---------|-------|---------|----------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------|-----------------------------------------------------------|-----|---------------------------------------------------------|--------------------------|-----------|
| Lisa M. Barton, et al. | 77  | M   | Obesity (BMI 31.8 kg/m²), HTN, history of DVT, splenectomy, history of pancreatitis, Positivity to ANAs | N/D     | N/D   | N/D     | Chills and intermittent fever without cough for 6 days. Weakness and shortness of breath. Cardiac arrest occurred during transport to the hospital | N/D     | LUNGS: heavy, red/brown in color. Edematous parenchyma and solid consistency. Right pleural adhesion. HEART: hypertensive heart damage with microscopic signs of acute ischemia, coronary heart disease KIDNEYS: arteriosklerosis, scanty casts OTHER: RPH | LUNGS: DAD in the acute phase, with hyaline membranes. Scattered chronic interstitial inflammation, consisting mainly of lymphocytes. Thrombi in small pulmonary arterial branches. Congestion of alveolar septal capillaries and focal edema in the air spaces. Mild chronic inflammation of the bronchi and bronchioles, with edema in the bronchial mucosa. Scattered CD8+ lymphocyte infiltration in the alveolar septa, with rare CD20+ lymphocytes | N/D | Standard Panel for Respiratory Pathogens and swab for Influenza Virus: negative | POST MORTEM positive for SARS CoV-2 (nasopharynx and lower airways) |         |
| 86 M         | HTN, COPD, heart failure, dementia | N/D | N/D | Died in a nursing home. Symptoms reported before death: cough, fever, postural instability | N/D     |       |                             | LUNGS: heavy, red/brown in color, edematous, parenchyma and solid consistency. Right pleural adhesion. HEART: hypertensive heart disease with microscopic signs of acute ischemia, coronary heart disease KIDNEYS: arteriosclerosis, scanty casts OTHER: RPH | LUNGS: DAD with hyaline membranes, type 2 pneumocyte hyperplasia and enlargement of the alveolar walls and interstitium, with lymphocytic infiltrate. Bone marrow emboli. HEART: chronic ischemic changes and contraction band necrosis. SPLEEN: B-cell lymphoma undiagnosed in vivo | N/D | Not specified | POST MORTEM positive for SARS CoV-2 (trachea) |         |
| 73 F         | Obesity, DMI, asthma, heart failure | N/D | N/D | Died at home. Reported shortness of breath before death | N/D     |       |                             | LUNGS: heavy, red/brown in color. Edematous parenchyma and solid consistency. Right pleural adhesion. HEART: hypertensive heart disease with microscopic signs of acute ischemia, coronary heart disease KIDNEYS: arteriosclerosis, scanty casts OTHER: RPH | LUNGS: DAD with hyaline membranes, type 2 pneumocyte hyperplasia and enlargement of the alveolar walls and interstitium, with lymphocytic infiltrate. Bone marrow emboli. HEART: chronic ischemic changes and contraction band necrosis. SPLEEN: B-cell lymphoma undiagnosed in vivo | N/D | Not specified | POST MORTEM positive for SARS CoV-2 (trachea) |         |
Table 1. Cont.

| Author | Age | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Tox | Additional Analyses | Cause of Death | Studs |
|--------|-----|-----------------------------|---------|-------|---------|--------------------------------------------|---------|---------------------|----|---------------------|----------------|------|
| Miroslav Sekulic et al. | 81 M | Dementia, left lung mass, coronary artery disease, AF treated with biventricular pacemaker, congestive heart failure, PVD, DM, dyslipidemia, HTN, CKD, statin, ACE, aspirin, clopidogrel, and UTI. Surgical history of carotid endarterectomy, left inguinal hernia repair and cataract surgery. | O2 | pancytopenia, elevated creatinine, moderately elevated urea and BNP | Chest X-ray: diffuse patchy opacities in the right lung and subpleural patchy opacities in the lower lobe of the left lung. Chest X-ray: multifocal bilateral ground-glass opacities, lung mass in the left lower lobe, thin pleural effusion, moderate cardiomegaly, calcifications in the coronary arteries and in the thoracic aorta. | Hospital presentation: acute respiratory failure and fever. Cough, need for oxygen support until death, 5 days after hospitalization. | N/D | LUNG: DAD in acute/acute phase, with hyaline membranes, scattered squamous metaplasia of the distal airways and emphysema changes. Minimal chronic submucosal inflammation in the bronchi and mucus. Large cell carcinoma, with metastasis in the hilar and peribronchial lymph nodes. | N/D | Blood cultures and urine cultures: negative. Test for Legionella, pneumococcus, HSV: negative. SARS CoV-2 RNA found in the lung, bronchi and lymph nodes. | SARS CoV-2 infection in a setting of metastatic carcinoma, diabetes and ischemic cardiomyopathy, leading to respiratory failure. | Positive for SARS CoV-2 (nasopharyngeal) |
| 54 M | HTN, DM2, overweight (BMI 29.9 kg/m²) | Heparin, Oxy, nemodil, vancomycin, piperacillin/tazobactam, propofol, vasopressor, intubation | Increased D-dimer, leukocytosis, lymphocytopenia, elevated creatinine, elevated liver enzymes | Chest X-ray: diffuse bilateral opacities with areas of consolidation of the lower lobes. Chest X-ray: n.2 bilateral opacities with greater consolidation at the base of the right lung. CHEST X-ray n.3 worsening of the pulmonary picture with greater interstitial engagement. | Hospital presentation: 2-day history of shortness of breath and dry cough. Physical examination showed tachycardia and poor saturation (70%). Admitted to intensive care with acute hypoxemic respiratory failure. After performing positive blood cultures and urine cultures, antibiotic therapy was started. Initiated on day 10. Deep in blood pressure and heart rate. 12 days after the onset of symptoms, died of cardiac arrest. | N/D | LUNG: heavy and congested, with bilateral aperistaltic pleural effusion of 300 mL. Solid consistency. HEART: n.1 left ventricular hypertrophy and coronary arteriosclerosis. OTHERS: acute congestion of liver and spleen. | N/D | Influenza virus and RSV test: negative. Blood and urine cultures positive for coagulase negative Staphylococcus and Enterococcus faecalis. Viral RNA found in the lung parenchyma, bronchi, lymph nodes and spleen. | SARS CoV-2 infection in a setting of diabetes and underlying cardiovascular problems, leading to respiratory failure and MOF. | Positive for SARS CoV-2 (nasopharyngeal) |
| Author | A G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tox Additional Analyses | Cause of Death | Swabs |
|--------|-----|-------------------------------|---------|-------|---------|-----------------------------------------------|---------|----------------------|----------------------|-----------------------|----------------|--------|
| Chaofu Wang et al. | | | | | | | | | | | | | |
| 53 F | HTN, DM2 | Arbidol, O2 | severe lymphocytopenia, elevated IL-6 and CRP | Chest X-ray and Chest CT: unspecified severe lung lesions | Hospital presentation: 2-day history of cough, fever, and shortness of breath. ARDS and died of cardio-respiratory failure 8 days after admission | N/D | LUNGS: moderate bilateral pleural effusions and fibrinous pleural adhesions. Hapatization of lung tissue | N/D | | Cardio-respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |
| 62 M | N/D | Peramivir, methylprednisolone, O2 | severe lymphocytopenia, elevated IL-6 and CRP | Chest X-ray and Chest CT: unspecified severe lung lesions | Hospital presentation: 13-day history of cough, fever, and shortness of breath. ARDS and died of cardio-respiratory failure 10 days after admission | N/D | LUNGS: moderate bilateral pleural effusions and fibrinous pleural adhesions. Hapatization of lung tissue and consolidation | N/D | | Cardio-respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |
| Author | A G | IN VIVO DATA | POSTMORTEM DATA |
|--------|-----|--------------|-----------------|
| Zachary Grimes et al. | Middle age M | HTN with anti-hypertensive therapy, Ceftriaxone, azithromycin, O2 | Chest X-ray: mild trilobal lower lobe congestion, Chest X-ray n.2: new dense patchy opacities retrocardiac and in the middle of the left lung, Nebulous opacity in the lower right lobe | Hospital presentation: 9 days of fever, chills, myalgia, dry cough and dyspnea. Physical examination: temperature of 36.4°C and 90% SpO2. After starting antibiotic therapy for suspected bacterial superinfection, improvement in fever and leukocytosis. Oxygen support required. On day 9 after admission, weakness and worsening left chest pain and sudden cardiac arrest | LUNGS: pulmonary thromboembolism with right pulmonary artery occlusion. Multiple foci of solid lung parenchyma, compatible with pulmonary consolidations HEART AND VESSELS: cardiomegaly and left ventricular hypertrophy. DVT | ELECTRON MICROSCOPY: Viral-like particles (60–120 nm) in the lung, located in cytoplasmic vacuoles in pneumocytes | N/D | Pulmonary thromboembolism |
| | | | | | | Positive for SARS CoV-2 (nasopharyngeal) |
| Kristine E. Konopka et al. | Middle age M | Asthma, HTN, pharmacologically controlled HIV infection, Broad spectrum antibiotics, HCQ, piperacillin/tazobactam, vancomycin, CS, ECMO, dialysis, intubation | Chest CT: multifocal ground glass opacities | Hospital presentation: fever, cough, productive cough and worsening dyspnea. On physical examination, a temperature of 36.4°C and SpO2 95%. Despite the use of broad spectrum antibiotics, CRP and Ferritin values continued to rise. Intubation and ventilatory support required. Hemodynamic instability and, after 8 days of hospitalization, death due to cardiac arrest | LUNGS: heavy lungs, consolidation of the lung parenchyma. AIRWAYS: paucicellular mucus plugs, goblet cell metaplasia, mucous gland hyperplasia and thickening of subepithelial basement membranes LUNG: DAD, hyaline membranes, interstitial edema and reactive pneumocytes. Rare fibrin thrombi in small vessels and in a small pulmonary muscular artery. Mild fibrinous exudate in distal air spaces without involvement of bronchi or bronchioles, with prominent inflammatory mononuclear cells and scattered neutrophils | ELECTRON MICROSCOPY: Viral-like particles (60–120 nm) in the lung, located in cytoplasmic vacuoles in pneumocytes | N/D | Positive for SARS CoV-2 (not specified) |
| Author          | A | G | IN VIVO DATA | POSTMORTEM DATA | TOX Additional Analyses | Cause of Death | Swabs                          |
|-----------------|---|---|--------------|------------------|------------------------|----------------|--------------------------------|
| **Randall Craver et al.** | 17 | M | N | N/D | N/D | LUNGS: heavy and congested HEART: hypertrophic heart (500 g), soft and with mottled parenchyma 80 mL of pericardial fluid in the cavity | N/D | Tests for influenza A and R, parainfluenza and RSV: negative | Fulminant eosinophilic myocarditis | POST MORTEM positive for SARS CoV-2 (nasopharyngeal) |
| **Lei Yan et al.** | 44 | F | Obesity (BMI 41.5 Kg/m²) | LUNGS: congestion, focal acute hemorrhage and edema. Thickened bronchial membranes, mild chronic inflammation of the submucosa HEART: diffuse inflammatory infiltrates associated with multiple foci of myocyte necrosis. Minimal interstitial fibrosis LIVER: centrilobular congestion with minimal steatosis | N/D | ELECTRON MICROSCOPY: viral-like particles in altered pneumocytes (50–75 nm). Presence of fibrin microaggregates in the vessels and fibrinous exudates in the alveolar spaces. Enlarged interstitial fibroblasts and activated lymphocytes | ARDS, MOF, reverse tako Tsubo cardiomyopathy | Positive for SARS CoV-2 (nasopharyngeal) |

**Table 1. Cont.**
### Table 1. Cont.

| Author | Age | Gender | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Toxicity | Additional Analyses | Cause of Death | Swabs |
|--------|-----|--------|-------------------------------|---------|-------|---------|--------------------------------------------|---------|----------------------|---------------------|----------|----------------------|--------------|-------|
| J. Matthew Lacy et al. | 58 | F | DM2, obesity (BMI 38 kg/m²), dyslipidemia, asthma, ulceration of the lower limbs | N/D | N/D | N/D | After 7 days of fever and respiratory distress, found dead at home during quarantine | N/D | LUNGS: widespread edema, presence of lingual membranes. Mild septal mononuclear infiltrates, with hyperplasia of desquamating pneumocytes and local multinucleated cells. Acute alveolar hemorrhages and foci of reactive alveolar foamy macrophages. Intralveolar fibrin deposits. | HEART: hypertrophy of myocardium with interstitial and perivascular fibrous tissue. | LUNGS: widespread edema, presence of lingual membranes. Mild septal mononuclear infiltrates, with hyperplasia of desquamating pneumocytes and local multinucleated cells. Acute alveolar hemorrhages and foci of reactive alveolar foamy macrophages. Intralveolar fibrin deposits. | Influenza virus test: negative. Positive bacterial cultures for Staphylococcus aureus and Streptococcus viridans, interpreted as contamination or post-mortem artifacts | ARDS due to SARS CoV-2 | POST MORTEM positive for SARS CoV-2 (lower airways) |
| Evan A. Farkash et al. | 53 | M | Obesity, dyslipidemia | HCQ, O₂, furosemide, metolazone, intubation | Leukocytosis, reduced GFR | Chest X-ray: bilateral patchy opacities | Hospitalized for aortic dissection, which was surgically repaired. Re-intubation on day 6 due to hypoxemia. MOF and cardiac arrest, with death on postoperative day 12 | N/D | LUNGS: widespread signs of DAD, edema and acute bronchopneumonia | LUNGS: DAD, hyaline membranes and edema | KIDNEY: mild autolysis | Respiratory Pathogen Standard Panel with swab for Influenza Virus: Negative. ELECTRON MICROSCOPY: abundant viral-like particles (65–91 nanometers) inside tubular epithelial cells, in areas of isometric vacuolation | MOE, AKI | Positive for SARS CoV-2 (not specified) |
| Diego Aguiar et al. | 31 | F | Obesity (BMI 41.2 kg/m²) | N/D | Elevated CRP | Elevated CRP | Found dead at home, in voluntary isolation after 7 days of cough. An opial antitussive and dypirone found on the scene. Rectal temperature of 41.5 °C, 2 h after death | N/D | LUNGS: Heavy, greasy solid and rubbery lungs, with bilateral hemorrhagic edema, pleural and tracheobronchial effusions. Heterogeneous areas of consolidation. OTHERS: skin petechiae, signs of shock | LUNGS: alveolar damage and edema, DAD in the exudative phase with the presence of hyaline membranes, fibrin deposits and moderate activated and desquamated pneumocytes. Alveolar exudate, moderate increase in intra-alveolar macrophages. Focal areas of intra alveolar hemorrhage and bacterial proliferation. Abundant septal and capillaries polymorphonuclear cells OTHERS: Chronic tracheitis and microabscesses in the liver parenchyma | Panel for influenza viruses A and B, RSV A and B, adenovirus, rhinovirus, parainfluenza viruses 1–4: negative | Lung changes related to SARS CoV-2 | POST MORTEM positive for SARS CoV-2 (lower airways) |
| Author | A | G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macrophage Features | Microscopic Features | Toxic | Additional Analyses | Cause of Death | Swabs |
|--------|---|---|-------------------------------|---------|------|--------|-----------------------------------------------|---------|-----------------|-----------------|------|-----------------|------------------|------|
| Takuya Adachi et al. | 84 | F | N | Ampicillin/sulbactam, CS, leupasarin/trimethoprim, O2 | N/D | N/D | N/D | Fever, diarrhea and shortness of breath while on cruise. Admitted to the hospital with dyspnea and fever. ARDS and hypoxemia, died after 16 days. | LUNG AND ARDS: Lungs partially brown in color; consolidation. Thickening of both pleurae. HEART: dilatation of the right ventricle. CT diffuse multiple punctate hemorrhages in the mucosa of the stomach and duodenum. | LUNG: signs of DAD, both in the exudative phase and in the organization. In the exudative stages there were prominent hyaline membranes, in those in the organization phase desquamation, squamous metaplasia, hyaline membranes and inflammatory infiltrates with prominent plasma cells in the alveolar septa. Intra-alveolar hemorrhages, vascular congestion, type 2 pneumocyte hyperplasia. Also note syncytial multinucleated cells. OTHER: Hemophagocytosis in the lungs, spleen and lymph nodes. The glomeruli of both kidneys were affected by microthrombi, suggesting a picture of DIC. | Respiratory failure due to COVID-19 | Positive for SARS CoV-2 (nasopharyngeal) |
| Patrícia Kunesi et al. | 27 | F | N | Anthracyclin, ceftriaxone, leupasarin/trimethoprim, PR, levofluoxacina, vancomycin, methylprednisolone, O2, intubation | N/D | N/D | N/D | 30 weeks pregnant, presented to the hospital with a 3-day history of respiratory symptoms, fever, cough and myalgia. Physical examination: tachypnea, fever, hypoxemia. No sweat performed. MOF and death of patient and fetus. Post mortem diagnosis of COVID-19 by nPCR. | LUNG: focal hyaline membranes, pneumocytes proliferation and metaplastic changes. Cytopathic effects from viral infection. Lymphocytes and macrophages | LUNG: congestion and early stage DAD with hyaline membranes, proteinaceous exudate, alveolar hemorrhage and intra-alveolar fibrin deposition. Pathyhy distribution of intra-alveolar foamy macrophages in all lobes. Hyperplastic type II pneumocytes, with likely nuclear cytopathic effects. In the epithelium of the bronchi, similar reactive picture. Increased number of intravascular megakaryocytes and slight patchy increase in interstitial lymphocytes. Some areas of bronchial metaplasia and fibrosis of the interstitium were present. In the lower lobes, focal neutrophilic infiltration in some air spaces and bronchial walls. Hyaline microthrombi were found in the pulmonary capillaries and some fresh thrombi in the pulmonary arterial branches. In the lymph nodes found several non-caseous granulomas. LIVER: moderate macro and micronodular steatosis. Additional analyses: viral RNA in lower airways (bronchi). | MOF | Positive for SARS CoV-2 (nasopharyngeal) |
| Christine Fuso et al. | 59 | M | HTN, DM2 | Antitriose | N/D | N/D | N/D | Presented to family physician with dry cough, fever and tachycardia, quarantined. Found dead at home 5 days later. | LUNG: heavy lungs, hemorrhages in the pleural surface. Pulmonary edema and diffuse solid and rubbery pneumonia, thickened fluid-filled. Dark red pneumonia, with scattered hemorrhagic areas and filling of hilar lymph nodes. | LUNG: congestion and early stage DAD with hyaline membranes, proteinaceous exudate, alveolar hemorrhage and intra-alveolar fibrin deposition. Pathyhy distribution of intra-alveolar foamy macrophages in all lobes. Hyperplastic type II pneumocytes, with likely nuclear cytopathic effects. In the epithelium of the bronchi, similar reactive picture. Increased number of intravascular megakaryocytes and slight patchy increase in interstitial lymphocytes. Some areas of bronchial metaplasia and fibrosis of the interstitium were present. In the lower lobes, focal neutrophilic infiltration in some air spaces and bronchial walls. Hyaline microthrombi were found in the pulmonary capillaries and some fresh thrombi in the pulmonary arterial branches. In the lymph nodes found several non-caseous granulomas. LIVER: moderate macro and micro vascular stenoses, with some necrotic hepatocytes around the central vein. HEART: Fatty, non-specific pericardial effusion with inflammatory cell aggregates, including plasma cells and lymphocytes. | ARDS from severe diffuse alveolar damage due to severe SARS CoV-2 infection | Positive for SARS CoV-2 (nasopharyngeal) |
### Table 1. Cont.

| Author | A | G |
|--------|---|---|
| Murgue Freni Santana et al. | 71 | M |
| Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Additional Analyses | Cause of Death | Swabs |
| O₂, vasoepressors, corticosteroids, HCQ, azithromycin, omeprazole, metformin, letrozole, hypertension | Elevated area of consolidation and CRP, lymphocytes, neutrophils | Chest X-ray: infiltrates and nodular consolidation in the right lower lobe | N/D | LUNGS: focal areas of consolidation in the right lower lobe | LUNG: presence of well-defined Aspergillus structures, with hyaline and squamous metaplasia were also present. Aspergillus was also in the pulmonary vessels | N/D | blood culture: negative for bacterial growth. Detection of CM antigen in peripheral blood: positive. PCR for aspergillosis: positive |
| James R. Stone et al. | 78 | F |
| Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Additional Analyses | Cause of Death | Swabs |
| Arfina, DM, HTN, hypothyroidism, osteoporosis, posttrauma. Therapy: atorvastatin, aspirin, hydroxychloroquine, losartan, rivastigmin, glipizide, citalopram, acetaminophen, betamethasone, thioacetamide, topical fluocinonide | Hypertension, elevated creatinine kinase, elevated LDH, elevated ferritin, elevated D-dimer | Chest X-ray: patchy opacities in the upper left lobe and near the hilum Chest CT with contrain-ground glass opacities and bilateral multifocal consolidations | N/D | LUNGS: areas of pulmonary consolidation | LUNGS: large area of alveolar parenchyma with preserved architecture, with thick hyaline membranes associated with focal desquamation of pneumocytes and congested capillaries. In some areas, the alveolar walls showed increased follicularity with some fibroblast-like spindle cells. There were findings compatible with an early exudative/proliferative phase of DAD. Rare foci of neutrophil infiltrates and CD68+ macrophage and hicaes in the alveolar spaces, suggesting a focal pulmonary process. Rare multinucleated giant cells, evidence of measles and epithelial desquamation in the majority of the bronchi, with areas of squamous metaplasia. Few chronic perivascular inflammatory aggregates were also present. HEART: Diffuse CDS + macrophage infiltrate in the myocardium, along with focal infiltrates of CDS + T lymphocytes | N/D | Influenza A, B and HSV toxic negative. Immunohistochemistry for SARS CoV-1–2 (nucleocapsid protein) positive in alveolar macrophages and scattered pneumocytes |
| Scotiadi Espanolet Anatomia Patologica | 54 | M |
| Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Additional Analyses | Cause of Death | Swabs |
| HTN, post migraine, OASAS, obesity (BMI 39.9). Therapy with C-PAP | Lymphoproliferation, elevated D-dimer, elevated LDH, elevated IL-6, elevated CRP, elevated ferritin | Chest X-ray: bilateral pulmonary opacities | N/D | LUNGS: heavy, hard and congested. Red and rubbery cut surface | LUNG: reduced air spaces due to the thickening of the interstitial connective tissue. CDS + macrophages. Hyperplastic pneumocytes with cytotoxic effects. In the most affected areas of the lung, hyaline membranes compatible with DAD in the exudative stage. In 70% of the material lesions consistent with DAD in the proliferative phase and in the fibrotic phase. Intense septal thickening with an abundance of reactive fibroblasts. Abundance of thrombi in the middle and small pulmonary vessels. Some septal/alveolar calcium depositsKREYEN: cortical necrosis and crystalline calcium oxalate | N/D | Histochecmical and immunohistochemical tests for other pathogens: negative |

**Cont.**

### IN VIVO DATA

| Author | A | G |
|--------|---|---|
| M | 71 | M |
| Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Additional Analyses | Cause of Death | Swabs |
| O₂, vasoepressors, corticosteroids, HCQ, azithromycin, omeprazole, metformin, letrozole, hypertension | Elevated area of consolidation and CRP, lymphocytes, neutrophils | Chest X-ray: infiltrates and nodular consolidation in the right lower lobe | N/D | LUNGS: focal areas of consolidation in the right lower lobe | LUNG: presence of well-defined Aspergillus structures, with hyaline and squamous metaplasia were also present. Aspergillus was also in the pulmonary vessels | N/D | blood culture: negative for bacterial growth. Detection of CM antigen in peripheral blood: positive. PCR for aspergillosis: positive |
| James R. Stone et al. | 78 | F |
| Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Additional Analyses | Cause of Death | Swabs |
| Arfina, DM, HTN, hypothyroidism, osteoporosis, posttrauma. Therapy: atorvastatin, aspirin, hydroxychloroquine, losartan, rivastigmin, glipizide, citalopram, acetaminophen, betamethasone, thioacetamide, topical fluocinonide | Hypertension, elevated creatinine kinase, elevated LDH, elevated ferritin, elevated D-dimer | Chest X-ray: patchy opacities in the upper left lobe and near the hilum Chest CT with contrain-ground glass opacities and bilateral multifocal consolidations | N/D | LUNGS: areas of pulmonary consolidation | LUNGS: large area of alveolar parenchyma with preserved architecture, with thick hyaline membranes associated with focal desquamation of pneumocytes and congested capillaries. In some areas, the alveolar walls showed increased follicularity with some fibroblast-like spindle cells. There were findings compatible with an early exudative/proliferative phase of DAD. Rare foci of neutrophil infiltrates and CD68+ macrophage and hicaes in the alveolar spaces, suggesting a focal pulmonary process. Rare multinucleated giant cells, evidence of measles and epithelial desquamation in the majority of the bronchi, with areas of squamous metaplasia. Few chronic perivascular inflammatory aggregates were also present. HEART: Diffuse CDS + macrophage infiltrate in the myocardium, along with focal infiltrates of CDS + T lymphocytes | N/D | Influenza A, B and HSV toxic negative. Immunohistochemistry for SARS CoV-1–2 (nucleocapsid protein) positive in alveolar macrophages and scattered pneumocytes |ARDS due to SARS CoV-2 (nasopharyngeal) | Positive for SARS CoV-2 (nasopharyngeal) |
| Scotiadi Espanolet Anatomia Patologica | 54 | M |
| Therapy | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Additional Analyses | Cause of Death | Swabs |
| HTN, post migraine, OASAS, obesity (BMI 39.9). Therapy with C-PAP | Lymphoproliferation, elevated D-dimer, elevated LDH, elevated IL-6, elevated CRP, elevated ferritin | Chest X-ray: bilateral pulmonary opacities | N/D | LUNGS: heavy, hard and congested. Red and rubbery cut surface | LUNG: reduced air spaces due to the thickening of the interstitial connective tissue. CDS + macrophages. Hyperplastic pneumocytes with cytotoxic effects. In the most affected areas of the lung, hyaline membranes compatible with DAD in the exudative stage. In 70% of the material lesions consistent with DAD in the proliferative phase and in the fibrotic phase. Intense septal thickening with an abundance of reactive fibroblasts. Abundance of thrombi in the middle and small pulmonary vessels. Some septal/alveolar calcium depositsKREYEN: cortical necrosis and crystalline calcium oxalate | N/D | Histochecmical and immunohistochemical tests for other pathogens: negative | Positive for SARS CoV-2 (nasopharyngeal) |
### Table 1. Cont.

| Author | A | G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Course of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs |
|--------|---|---|-----------------------------|---------|-------|---------|---------------------------------------------|---------|---------------------|---------------------|-----|---------------------|---------------|-------|
| Pedro Navarro Conde et al. | 69 M | Low-grade non-invasive urothelial carcinoma of the bladder | Levofloxacin, ceftriaxone, O2 | N/D | N/D | N/D | Chest X-ray: bilateral ground glass opacities and ground glass nodules in the center of the lungs. Multifocal reticular consolidations, especially in the central areas of both lungs | CT: Moderate bilateral pleural effusion. Subpleural ground glass opacities and ground glass nodules in the center of the lungs. Multifocal reticular consolidations, especially in the central areas of both lungs | LUNG: heavy and edematous lungs. Foamy hemorrhagic fluid in the upper respiratory tract. Areas of slightly nodular, dense and hyperemic plaques. Signs of acute hemorrhage: tracheobronchial, bronchial, with patchy mucosal bleeding. HEART: congestive cardiomyopathy, dilated atria and ventricles, extensive lipomatosis of the pericardium and cardiomyopathy (600 g). Moderate arteriolar hyalinosis. | LUNG: DAD, with prominent hyaline membranes, microvascular thrombosis and activated pneumocytes, capillary congestion and protein-rich interstitial and intra-alveolar edema. Moderate mononuclear inflammatory infiltrate, mainly lymphocytes, absent granulocytes. Multinucleated syncytial cells in some alveoli. HEART: advanced interstitial and perivascular myocardial fibrosis, with biventricular lipomatosis. CNS: nonspecific immune response in the brainstem with perivascular and parenchymal CDS + infiltrates. Minimal cerebral arteriovenous | N/D | CLINICAL: severe bilateral CAP. PATHOLOGICAL: SARS-CoV-2 pneumonia. Positive for SARS-CoV-2 (nasopharyngeal) |
| Fabian Haiti-Reich et al. | 59 M | Obesity (BMI: 32.8), HTN | N/D | N/D | N/D | Systemic symptoms during a cruise, with dyspnea. Hospitalized, developed fever and productive cough. Died after 6 days of hospitalization | LUNG: dark red in color, increased in weight and density. Pleural pocket or adhesions. HEART: mild stenosis of the aortic valve, slight thickening of the left ventricle and dilation of both ventricles. OTHER: generalized congestion of other organs. | Postmortem COVID-19 diagnosis | LUNG: edema and intra-alveolar hemorrhage. DAD with desquamation of type II pneumocytes, and hyaline membranes, sometimes in the in the proliferative phase. Thrombi in the pulmonary vessels of medium caliber. Abundant intravascular macrophages. Cytopathic changes in pneumocytes and macrophages. Cells with large and hyperchromatic nuclei, similar to the smudge cells described in adenovirus pneumonia. Sanguineus metaplasia of pneumocytes. Inflammatory infiltrate with few lymphocytes and abundant macrophages. Empysematous areas. | N/D | Tests for influenza A and B, AH1N1, RSV, adenovirus, metapneumovirus, bovovirus, coronavirus NL63, coronavirus OC43, parainfluenza virus 1 and 2, rhinovirus: negative. Immunohistochemical tests for Herpes Simplex, cytomegalovirus and EBV: negative. |
| Inge-Marie Schaller et al. | 66 F | SLE, RA, Pulmonary fibrosis, CKD, interstitial lung disease, MCLS, coronary heart disease, HTN | HCQ | N/D | N/D | Chest X-ray: bilateral opacities in the airspaces, especially in the periphery. Chest CT: ground glass opacities in the lower lobes and in the periphery. Hospital presentation: 2-week history of cough and fever. Died after 7 days | LUNG: acute DAD, scattered foci in the organization phase and predominant hyaline membranes. Interstitial lung disease with bronchiolitis. Pulmonary thromboembolism. Diffuse interstitial and peribronchial lymphocytic inflammatory infiltrates, with intra-alveolar macrophages. AIRWAYS: reactive squamous metaplasia. Minimal lymphocytic infiltrate in the edematous connective tissue of the airway walls. | Post mortem immunohistochemistry for SARS-CoV-2: positive in pneumocytes (>5 cells × 4 mm²). | SARS-CoV-2 pneumonia resulting in respiratory failure. Positive for SARS-CoV-2 (nasopharyngeal) |
| Author | Age | Gender | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Toxicological Analyses | Cause of Death | Swabs |
|--------|-----|--------|-----------------------------|---------|-------|---------|---------------------------------------------|---------|-----------------------------------------------|-----------------------------------------------|----------------------------------|-----------------|-------|
| 57 M   | 66  | M      | Former smoker, UTI, acute neutropenia, relapsing B-cell acute lymphocytic leukemia | N/D   | N/D  | N/D    | Hospital presentation: diffuse bilateral opacities in the air spaces | N/D   | N/D                                           | Negative in lung and trachea (5-50 cells × 5 mm²) | Post mortem immunohistochemistry for SARS CoV-2 positive in pneumocytes (<5 cells × 4 mm²) | Positive for SARS CoV-2 pneumonia resulting in respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |
| 77 M   | 68  | F      | Former smoker, UTI, acute neutropenia | N/D   | N/D  | N/D    | Hospital presentation: diffuse bilateral opacities in the air spaces | N/D   | N/D                                           | Post mortem immunohistochemistry for SARS CoV-2 positive in pneumocytes (<5 cells × 4 mm²) | Positive for SARS CoV-2 pneumonia resulting in respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |
| 50 M   | 57  | M      | HTN, DM, neurologic impairment | N/D   | N/D  | N/D    | Hospital presentation: diffuse bilateral opacities in the air spaces | N/D   | N/D                                           | Negative in lung and trachea (5-50 cells × 5 mm²) | Positive for SARS CoV-2 pneumonia resulting in respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |
| 68 F   | 68  | M      | HTN, DM, COPD | N/D   | N/D  | N/D    | Hospital presentation: diffuse bilateral opacities in the air spaces | N/D   | N/D                                           | Negative in lung and trachea (5-50 cells × 5 mm²) | Positive for SARS CoV-2 pneumonia resulting in respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |
| 66 M   | 77  | M      | HTN, DM | N/D   | N/D  | N/D    | Hospital presentation: diffuse bilateral opacities in the air spaces | N/D   | N/D                                           | Negative in lung and trachea (5-50 cells × 5 mm²) | Positive for SARS CoV-2 pneumonia resulting in respiratory failure | Positive for SARS CoV-2 (nasopharyngeal) |

**Table 1. Cont.**

| Author | Age | Gender | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Toxicological Analyses | Cause of Death | Swabs |
|--------|-----|--------|-----------------------------|---------|-------|---------|---------------------------------------------|---------|-----------------------------------------------|-----------------------------------------------|----------------------------------|-----------------|-------|
|        |     |        |                             |         |       |         |                                             |         |                                |                                |                                |                 |       |

**IN VIVO DATA**

- **Author**: The name of the patient.
- **Age**: The age of the patient.
- **Gender**: The gender of the patient.
- **Comorbidities and Past Drugs**: A list of the patient's comorbidities and past drugs.
- **Therapy**: The therapy received by the patient.
- **Labor**: The labor performed on the patient.
- **Imaging**: The imaging performed on the patient.
- **Cause of the Disease/Circumstances of Death**: The cause of the disease or circumstances of death.
- **Imaging**: The imaging performed on the patient.
- **Macroscopic Features**: The macroscopic features observed.
- **Microscopic Features**: The microscopic features observed.
- **Toxicological Analyses**: The toxicological analyses performed.
- **Cause of Death**: The cause of death.
- **Swabs**: The swabs performed.

**POSTMORTEM DATA**

- **Author**: The name of the patient.
- **Age**: The age of the patient.
- **Gender**: The gender of the patient.
- **Comorbidities and Past Drugs**: A list of the patient's comorbidities and past drugs.
- **Therapy**: The therapy received by the patient.
- **Labor**: The labor performed on the patient.
- **Imaging**: The imaging performed on the patient.
- **Cause of the Disease/Circumstances of Death**: The cause of the disease or circumstances of death.
- **Imaging**: The imaging performed on the patient.
- **Macroscopic Features**: The macroscopic features observed.
- **Microscopic Features**: The microscopic features observed.
- **Toxicological Analyses**: The toxicological analyses performed.
- **Cause of Death**: The cause of death.
- **Swabs**: The swabs performed.
| Author | Age | Gender | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Course of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs |
|--------|-----|--------|-----------------------------|---------|-------|---------|---------------------------------------------|---------|---------------------|---------------------|-----|---------------------|--------------|-------|
| 53 M   | 53  | M      | HTN, DM, CKD, NASH          | Remdesivir | N/D   | Chest X-ray: diffuse bilateral opacities in the pulmonary air spaces. Pneumothorax. | Hospital presentation: 8-day history of cough, fever, and dyspnea. Died after 21 days | N/D | N/D | LUNGS: DAD and organizing lung injury. Superimposed bacterial lobar pneumonia. Pulmonary thrombembolism. Diffuse interstitial and peribronchial lymphocytic inflammatory infiltrates, with intra-alveolar macrophages. ARDS: active squamous metaplasia. Minimal lymphocytic infiltrate in the edematous connective tissue of the airway walls | N/D | post mortem immunohistochemistry for SARS-CoV-2: negative in lung and trachea | SARS-CoV-2 pneumonia resulting in respiratory failure | Positive for SARS-CoV-2 (nasopharyngeal) |
| 58 M   | 58  | M      | HTN, Therapy: losartan, aspirin | HCQ, atovaquone, trimethoprim | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially in the basal segments | Hospital presentation: fever, dyspnea and vomiting. Intubation, died 7 days after hospitalization | N/D | N/D | LUNGS: pulmonary edema, hyaline membranes, inflammation in the alveolar walls, alveolar macrophages, hemorrhagic areas, fibrinous material in the walls of the vessels. HEART: local interstitial inflammation. LIVER: mild portal inflammation, interface hepatitis, congestion, mild macrovesicular changes | N/D | Not specified | Positive for SARS-CoV-2 (not specified) |
| 84 F   | 84  | F      | HTN, Therapy: amlodipine, aspirin, citalopram | HCQ, levetiracetam/ceftaricin, trimethoprim | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially along the basal segments | Hospital presentation: fever, dyspnea and myalgia. Intubation, died 3 days after hospitalization | N/D | N/D | LUNGS: pulmonary edema, hyaline membranes, fibrinous exudate, inflammation in the alveolar walls, alveolar macrophages, fibrinous material in the walls of the vessels. LIVER: minimal portal inflammation, severe congestion, mild macrovesicular and microvesicular steatosis, mild ballooning degeneration. | N/D | Not specified | Positive for SARS-CoV-2 (not specified) |
| 72 F   | 72  | F      | RA, Therapy: sulfasalazine, prednisolone, MTX | HCQ, levetiracetam, levothioiracin | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially along the basal segments | Hospital presentation: fever, headache, nausea and vomiting. Intubated, died 15 days after hospitalization | N/D | N/D | LUNGS: pulmonary edema, fibroin exudate, inflammation in the alveolar walls, alveolar macrophages, fibrinous material in the walls of the vessels. HEART: mild-moderate interstitial inflammation with LCA+ and CD68+ cells. LIVER: mild portal inflammation, mild interface hepatitis, mild fibrosis, moderate congestion, minimal macrovesicular steatosis, scattered biliary plugs | N/D | Not specified | Positive for SARS-CoV-2 (not specified) |
| 72 M   | 72  | M      | HTN, DM with insulin treatment | HCQ, oxacillin, atovaquone, levothioiracin | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially along the basal segments | Hospital presentation: fever, dyspnea and diarrhea. Intubation, died 4 days after hospitalization | N/D | N/D | LUNGS: pulmonary edema, hyaline membranes, inflammation in the alveolar walls. LIVER: mild portal inflammation, mild congestion, minimal macrovesicular and microvesicular steatosis | N/D | Not specified | Positive for SARS-CoV-2 (not specified) |
| Author          | A G    | Comorbidities and Past Drugs | Therapy       | Labor | Imaging | Course of the Disease/Circumstances of Death | Imaging | Macroscopic Features | Microscopic Features | Tax | Additional Analyses | Cause of Death | Swabs                  |
|-----------------|--------|-----------------------------|---------------|-------|---------|---------------------------------------------|---------|----------------------|----------------------|-----|----------------------|---------------------|------------------------|
|                 | 68 M   | HTN, valvular regurgitation |
|                 |        | Therapy: losartan, propranolol | HCQ, oseltamivir, intubation | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially along the basal segments | Hospital presentation: fever and dyspnea. Endocarditis and valve surgery. Development of respiratory symptoms, intubated, died after 19 days of hospitalization | N/D   | N/D                 | Not specified          | N/D | Positive for SARS CoV-2 (nasopharyngeal) |
|                 | 46 M   | Peptic ulcer disease, Therapy: chlordiazepoxide, clindamycin | HCQ, nontoxic, nontoxic, azithromycin, intubation | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially along the basal segments | Hospital presentation: fever, chills, myalgia, and pharyngodynia. Intubation, died after 16 days | N/D   | N/D                 | Not specified          | N/D | Positive for SARS CoV-2 (not specified) |
|                 | 75 M   | N                            | HCQ, oseltamivir, intubation | N/D   | Chest CT: bilateral peripheral ground glass opacities, especially along the basal segments | Hospital presentation: fever, chills, myalgia, and pharyngodynia. Intubation, died after 6 days | N/D   | N/D                 | Not specified          | N/D | Positive for SARS CoV-2 (nasopharyngeal) |
| Sufang Tian et al. | 78 F   | Chronic lymphocytic leukemia | Antibiotics, antivirals, O2, elevated pro-BNP, elevated troponin, elevated LDH, leukocytosis | N/D   | Chest CT 1: multiple bilateral ground glass opacities in the upper lobes, mostly on the right; Chest CT 2: similar to the first CT, with thickening of the bronchi and vessels | Hospitalized for COVID-19 pneumonia at Wuhan University Zhongnan Hospital. Died after 21 days | N/D   | N/D                 | SARS CoV-2 pneumonia   | N/D | Positive for SARS CoV-2 (nasopharyngeal) |
### Table 1. Cont.

| Author            | Age | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Course of the Disease/Circumstances of Death | Imaging | Microscopic Features | Toxicological Analysis | Cause of Death | Swabs |
|-------------------|-----|------------------------------|---------|-------|---------|---------------------------------------------|---------|----------------------|------------------------|----------------|-------|
| Zsuzsanna Varga et al. | 71 M | Kidney transplant, coronary heart disease, HTN | Inhination | N/D   | N/D     | Hospitalized with a diagnosis of COVID-19, mechanical ventilation. 8 days later died due to MOF | N/D   | N/D                 | ELECTRONE MICROSCOPY: in the transplanted kidney, viral inclusions in endothelial cells | MOF             | Positive for SARS CoV-2 (not specified) |
| 74 M              | Cirrhosis, variceal bleeding | Antibiotics, antivirals, O₂ | Elevated troponin, elevated LDE, leukocytosis, lymphocytopenia | Chest CT 1: patchy ground glass opacities, consolidations, air bronchogram. Chest CT 2: additional consolidation in the left upper lobe | Hospitalized for COVID-19 pneumonia at Wuhan University Zhongnan Hospital. Died after 15 days | N/D   | N/D                 | RT-PCR for viral RNA in lung samples: positive | SARS CoV-2 pneumonia | Positive for SARS CoV-2 (nasopharyngeal) |
| 51 M              | DM, HTN | Antibiotics, antivirals, O₂ | Elevated troponin, elevated LDE, leukocytosis, lymphocytopenia | Chest CT 1: patchy opacities in both lungs, especially in the lower lobes. Chest CT 2: worsening of the previous picture | Hospitalized for COVID-19 pneumonia at Wuhan University Zhongnan Hospital. Died after 23 days | N/D   | N/D                 | RT-PCR for viral RNA in lung samples: negative | SARS CoV-2 pneumonia | Positive for SARS CoV-2 (nasopharyngeal) |
| 59 M              | Kidney transplant performed 3 months earlier | Antibiotics, antivirals, O₂ | Elevated pre-BNP, elevated troponin, mildly elevated LDE, elevated LDF, elevated gamma-GT, leukocytosis, lymphocytopenia | Chest CT 1: diffuse ground glass opacities, consolidation in the posterior segment. Chest CT 2: additional visible air bronchogram | Hospitalized for COVID-19 pneumonia at Wuhan University Zhongnan Hospital. Died after 52 days | N/D   | N/D                 | RT-PCR for viral RNA in lung and liver samples: negative | SARS CoV-2 pneumonia | Positive for SARS CoV-2 (nasopharyngeal) |
Christine et al. 50 M N/D N/D

Ox, interferon alfa-2b, lenalidomide, mepiprin, methylprednisolone

lymphocytopenia

Chest X-ray on admission: multiple bilateral patchy opacities. Chest X-ray 2: progressive infiltrate and diffuse bilateral molar opacities.

Hospital presentation: fever, chills, cough, fatigue and shortness of breath, recent trip to Wuhan. On day 14 after the onset, hypoxemia and worsened dyspnea died due to cardiac arrest.

Table 1. Cont.

| Author | A | G | Comorbidities and Past Drugs | Therapy | Labor | Imaging | Cause of the Disease/Circumstances of Death | Imaging | Microscopic Features | Toxicity Microscopic Features | Tox Additional Analyses | Cause of Death | Swabs |
|--------|---|---|-------------------------------|---------|-------|---------|---------------------------------------------|---------|---------------------|-------------------------------|-----------------------------|----------------|--------|
| Zhe Xu et al. 50 M | N/D | DM, HTN, obesity, Dialysis | N/D | N/D | Progressive respiratory failure due to COVID-19, MOF, dialysis required. On day 36 of admission, mesenteric ischemia requiring surgery. STEMI intubation, circulatory failure and cardiac arrest. | N/D | N/D | LUNGS: lymphocytic endothelitis. KIDNEY: lymphocytic endothelitis. LIVER: hepatitis necrosis, lymphocytic endothelitis. HEART: myocarditis infiltration, lymphocytic endothelitis. GI: endothelitis of the submucosal vessels. | N/D | Cardiac arrest | Positive for SARS-CoV-2 (nasal gastric) |
| Christine M. Lowy et al. 56 M | N/D | DML, smoker, COPD, small cell lung cancer. Therapy: dosoxycline for possible pneumonitis before diagnosis of carcinoma, then carboplatin, etoposide, pemetrexed, platinum. | Methyldoxorubicin, ifosfamide, Ox vancomycin and piperacillin/tazobactam, vancomycin, methylprednisolone, methotrexate, melphalan, and carboplatin | CT: speculated mass in the lingula, 5 cm in diameter. Mediastinal lymphadenopathy and multiple liver masses. CT 2: bilateral ground glass opacities with thickening of the interlobular septa, more pronounced in the right upper lobe. CT 3: progression of bilateral ground glass opacities, reduction in the size of the previously detected tumor. | High fever, high LDH | N/D | LUNGS: widespread DAD, especially in the organizing phase, with greater involvement of the right lung. Thickened alveolar septa, alveolar foamy macrophages, desquamating epithelial cells, organizing thrombotic exudate, fibrin, hemorrhages and edema. Areas of fibrosis and fibrotic nodules in the alveolar spaces. Reactive epithelial cells, immunohistochemistry revealed the presence of CD8+ cells in the interstitium, with some CD8+ and CD20+ cells. | N/D | Serum antibodies to SARS-CoV-2: positive for IgG and IgM (low positivity) | IN SITU HYBRIDIZATION FOR VIRAL RNA SARS-CoV-2 RNA identified in the submucosal glands of the large airways, in the macrophages of a paratracheal lymph node and in the pulmonary interstitium. In the lungs, positive within the intra alveolar macrophages, in the alveolar walls and in desquamating cells. | Shock | Positive for SARS-CoV-2 (nasal gastric) |
Victims were mostly male (58 cases), with a mean age of 65.3 years (median: 70.5, lower limit: 17, 25% percentile: 55.5; 75% percentile: 76.0; upper limit: 91). Since the exact age was not reported in two cases, defined as “middle aged”, in the mean calculation they were both considered to be 55 years old. All the cases tested positive for SARS CoV-2 RNA, with swabs performed in vivo and/or post-mortem. Seventy-four victims had comorbidities, though no information was reported in 5 cases, and of these, the majority (56 cases) had 2 or more diseases, up to a maximum of 14. The most frequently reported were: arterial hypertension (in 41 cases, 55%), diabetes mellitus (in 28 cases, 37.8%) and obesity (in 24 cases, 32.4%).

Signs and symptoms of SARS Cov-2 infection were reported in 65 out of 84 cases. Respiratory symptoms were described in 50 cases, fever in 47, cough in 34. Fatigue/myalgia (11 times), gastrointestinal symptoms (10 times), alterations of consciousness, e.g., delirium/confusion/syncope (8 times), chills (6 times), tachycardia (5 times) and headache (4 times) were less common. Even more rarely hypotension, incontinence, chest pain and balance disorders (like dizziness/postural instability), described each in 2 cases, were reported. Acute kidney injury, acute cardiomyopathy, bradycardia, atrioventricular block, cardiac arrest, hemoptysis, hematuria, sore throat, sinusitis and anorexia were reported only one 1 time. In one case, unspecified systemic symptoms were described. Among the 49 cases whose laboratory abnormalities were reported, the most frequently encountered changes were elevated c-reactive protein (CRP) (51%), lymphocytopenia (46.9%), elevated lactate dehydrogenase (LDH) (38.7%), elevated creatinine (26.5%), elevated D-dimer (24.4%), leukocytosis (22.4%). Other alterations, such as in the values of fibrinogen, troponins, ferritin and IL-6, were rarely found.

Data on medications were available in 13 patients, 12 of whom were taking therapy for their previous conditions, while drugs administered during COVID-19 were reported in 55 out of 84 cases. The most common drugs included antibiotics (52.7%), antivirals (34.5%), hydroxychloroquine (32.7%), vasopressors (10, 18.1%), corticosteroids (12.7%), anticoagulants and heparins (12.7%) and biologics (10.9%). Other medications, such as diuretics, pain relievers and other medications were used in less than 5 patients (9%). The use of non-invasive ventilatory support was specified in 21 patients (38.1%), while 33 cases (60%) required intubation during hospitalization for COVID-19. Finally, 6 patients underwent hemodialysis (10.9%), while extracorporeal membrane oxygenation (ECMO) was used in 2 of them (3.6%).

The majority (73) of the deaths occurred in a hospital setting, i.e., intensive care or other wards, while among the 11 out of the hospital cases, 3 occurred in nursing homes, 5 patients were found dead in their homes, 1 in his car, while in 2 cases the data were not extractable. Post mortem examinations performed included complete autopsies (29 cases), partial autopsies (33 cases) and post mortem histology (22 cases). The histological samples involved the lung in all the 22 cases, heart in 10 cases, liver in 13, airways in 7, kidney in 2 and gastrointestinal tract in 2.

Imaging studies have been reported in 65 cases. Of these, in vivo imaging was performed in 50, post mortem in 14, both in 1. On in vivo radiographs, the most commonly reported features were bilateral patchy opacities and/or consolidations (60.7%), and 39.2% of chest CT showed ground glass opacity and/or consolidations. Post-mortem chest X-ray was performed in 2 cases and displayed bilateral opacities, while by PMCT, various degrees of pulmonary consolidation (80%), presence of reticular pattern (60%), pleural and/or pericardial effusions (40%) were described, as well as less represented features, e.g., emphysema, ground glass opacities and evidence of neoplastic lesions.

As for the autopsy room, macroscopic changes were described in several organs, although with a variable frequency, also caused by pre-existing pathologies. The most affected organs were lungs/airways in 51 of 54 cases, heart and vascular system in 33, liver in 12, kidneys in 11, spleen in 9, lymph nodes in 6 and CNS in 5 cases. Lungs were commonly described as heavy and edematous, with or without intraparenchymal hemorrhages or emboli. A macroscopic feature of pneumonia was also quite frequent, while purulent infections, empyema or green exudate were rarer. Extra-pulmonary common
features included heart hypertrophy, though this is unlikely connected with COVID-19, enlargement of the spleen and of the lymph nodes. Alterations found in the gastrointestinal tract, prostate, skin, testis and other anatomical parts were much rarer. A similar picture was found in microscopic examinations of tissues, with lung/airways affected in all the 84 cases, liver in 40, heart and vascular system in 37, kidney in 25, spleen in 13, lymph nodes in 7, gastrointestinal tract in 3. Alterations reported in the CNS, bone marrow, testis and thyroid had lower frequencies. The most described finding within lung tissues was represented by diffuse alveolar damage (DAD) in exudative or organizing phases, coupled to pulmonary edema, hemorrhages and microthrombi. Less commonly, slight fibrosis, atypical pneumocytes or acute inflammatory infiltrates were noted. Microthrombi, together with signs of acute or chronic inflammation, were also reported in the trachea. Haemophagocytosis was occasionally noted in lymph nodes. In the heart, fibrosis and myocardiocyte hypertrophy have been mostly observed. In the liver, the dominant microscopic picture found was mild to severe hepatic steatosis, though portal/periportal inflammation, hepatocyte necrosis and hepatic congestion have been also described. The spleen commonly showed hyperplasia of the white pulp. In the kidney, arteriolosclerosis was the most frequently encountered finding, often related to chronic hypertensive damage and diabetes.

Regarding other examinations carried out, 9 electron microscopy tests were performed. In 8 of these 9 cases, the authors found viral-like particles within cells of different tissues (such as tracheal epithelial cells, pneumocytes, enterocytes, renal tubular cells). In the remaining case, no viral-like particles were found, but neutrophils in the alveolar capillaries and fibrin deposits in the alveolar spaces were documented. Moreover, the presence of bacteria, fungi or viruses in addition to SARS CoV-2 was documented in 7 of the patients by using cultural tests, rt-PCR and other laboratory tests. In 2 cases, toxicological investigations were also carried out, finding dextromethorphan in one patient (part of the antitussive therapy taken during COVID-19) and in another patient caffeine and naloxone. Causes of death were reported in 71 decedents, while the role of COVID-19 was specified in 51 of them, being considered “cause of death” in 37 cases (72.5%), “contributing factor” in 12 (23.5%) and “significant factor” in 2 (3.9%).

A summary of the results is shown in Figure 2.

4.2. CSS Application

The COVID-19 Significance Score was applied to each case found in the literature review. The non-parametric ANOVA comparing the CSS assigned by three independent blinded investigators did not show significant differences (p > 0.05). Complete agreement was found in 68 cases. As shown in Table 2, 57 of the 84 reported deaths fell into CSS category 3 for at least 2 raters, which means that “COVID-19 was the leading cause of death”.

Twenty-two of the deaths fell into category 2 for at least two raters. In these cases, “COVID-19 likely contributed to the patient’s death, together with other factors that may have played a prominent role”. Four deaths were included in category 1, where “an alternative cause of death was likely”, by at least two raters. In one case, CSS was classified as U by two raters, further specific investigation being necessary, and as 0 for the third one.

4.3. Hamburg Score

The two classifications of deaths were compared in the cases reported in this work also described in the study by Edler et al., specifically in 13 of the 84 deaths collected in this paper (Table 2). Considering the Hamburg category 1 (defined COVID-19 death) equivalent to the CSS category 3, and the Hamburg category 2 (probable COVID-19 death) equivalent to the CSS category 2, the results of the two classification systems agreed in 8 out of the 13 cases. In the remaining 5 cases, differences in assessment emerged. Particularly:
- in cases 1, 3, 4, 12 by Wichmann et al. [40], CSS classified COVID-19 as the cause of death (CSS = 3), while the Hamburg score revealed a probable COVID-19 death (corresponding to CSS = 2);
- in case 2 by Wichmann et al. [40], CSS classified COVID-19 as the cause of death (CSS = 3), while Hamburg scored the fatality as possible COVID-19 death (corresponding to CSS = 1).

The t-test between the average CSS score and the Hamburg score, converted into CSS, did not yield a statistical significant difference.

**Figure 2.** Summary of the main in vivo and post-mortem data emerged from literature cases.
Table 2. Type of post-mortem examination, role of SARS CoV-2, comparison between scores and inter-raters agreement.

| Author                   | Age | Gender | Type of Examination | Role of SARS CoV-2       | CSS R1 | CSS R2 | CSS R3 | H Score |
|--------------------------|-----|--------|---------------------|--------------------------|--------|--------|--------|---------|
| Benjamin T Bradley et al.| 57  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | -       |
|                         | 74  | F      | Partial autopsy     | Contributing factor      | 2      | 2      | 2      | -       |
|                         | 54  | M      | Partial autopsy     | Contributing factor      | 2      | 3      | 3      | -       |
|                         | 74  | M      | Partial autopsy     | Contributing factor      | 3      | 3      | 3      | -       |
|                         | 73  | F      | Partial autopsy     | Contributing factor      | 3      | 3      | 3      | -       |
|                         | 84  | F      | Partial autopsy     | Contributing factor      | 3      | 3      | 3      | -       |
|                         | 71  | M      | Partial autopsy     | Contributing factor      | 2      | 3      | 2      | -       |
|                         | 76  | F      | Complete autopsy    | Contributing factor      | 2      | 2      | 2      | -       |
|                         | 75  | F      | Partial autopsy     | Contributing factor      | 3      | 3      | 3      | -       |
|                         | 84  | M      | Complete autopsy    | Significant factor       | 2      | 2      | 2      | -       |
|                         | 81  | F      | Complete autopsy    | Contributing factor      | 3      | 3      | 3      | -       |
|                         | 42  | F      | Complete autopsy    | Contributing factor      | 3      | 3      | 3      | -       |
|                         | 71  | M      | Complete autopsy    | contributing factor      | 1      | 1      | 1      | -       |
|                         | 73  | F      | Partial autopsy     | Contributing factor      | 3      | 3      | 3      | -       |
| Dominic Wichmann et al. | 52  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 2       |
|                         | 70  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 3       |
|                         | 71  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 2       |
|                         | 63  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 2       |
|                         | 66  | M      | Complete autopsy    | Cause of death           | 2      | 2      | 2      | 1       |
|                         | 54  | F      | Complete autopsy    | Cause of death           | 2      | 1      | 1      | 1       |
|                         | 75  | F      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 1       |
|                         | 82  | M      | Complete autopsy    | Cause of death           | 2      | 2      | 2      | 1       |
|                         | 87  | F      | Complete autopsy    | Cause of death           | 1      | 2      | 2      | 3       |
|                         | 84  | M      | Complete autopsy    | Cause of death           | 2      | 2      | 2      | 2       |
|                         | 85  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 1       |
|                         | 76  | M      | Complete autopsy    | Cause of death           | 3      | 3      | 3      | 2       |
| Andrey Prilutskiy et al.| 72  | M      | Complete autopsy    | Not specified            | 2      | 3      | 3      | -       |
|                         | 91  | M      | Complete autopsy    | Not specified            | 2      | 3      | 3      | -       |
|                         | 72  | M      | Complete autopsy    | Not specified            | 3      | 3      | 3      | -       |
|                         | 64  | F      | Complete autopsy    | Not specified            | 3      | 3      | 3      | -       |
| Hans Bösmüller et al.   | 78  | F      | Partial autopsy     | Not specified            | 2      | 2      | 3      | -       |
|                         | 78  | M      | Partial autopsy     | Not specified            | 3      | 3      | 3      | -       |
| Author                        | Age | Gender | Type of Examination | Role of SARS CoV-2 | CSS R1 | CSS R2 | CSS R3 | H Score |
|------------------------------|-----|--------|---------------------|-------------------|-------|-------|-------|--------|
| Louis Maximilian Buja et al. |     |        | Partial autopsy (no cranial cavity) | Not specified      | 2     | 2     | 2     | -      |
|                             | 59  | M      | Partial autopsy (no cranial cavity) | Not specified      | 3     | 3     | 3     | -      |
|                             | 62  | M      | Partial autopsy (no cranial cavity) | Not specified      | 3     | 3     | 3     | -      |
| Louis Maximilian Buja et al. |     |        | Partial autopsy (no cranial cavity) | Not specified      | 2     | 2     | 2     | -      |
| Louis Maximilian Buja et al. | 88  | F      | Complete autopsy | Not specified      | 3     | 3     | 3     | -      |
| Louis Maximilian Buja et al. | 86  | M      | Complete autopsy | Not specified      | 3     | 2     | 2     | -      |
| Esther Youd et al.           | 77  | M      | Complete autopsy | Cause of death     | 3     | 3     | 3     | -      |
| Lisa M. Barton et al.        | 42  | M      | Complete autopsy | Significant factor | 1     | 1     | 1     | -      |
| Miroslav Sekulic et al.      | 81  | M      | Partial autopsy (no cranial cavity) | Cause of death     | 2     | 2     | 2     | -      |
| Miroslav Sekulic et al.      | 54  | M      | Partial autopsy (no cranial cavity) | Cause of death     | 2     | 2     | 2     | -      |
| Chaofu Wang et al.           | 53  | F      | Complete autopsy | Not specified      | 3     | 3     | 3     | -      |
| Zachary Grimes et al.        |     |        | Complete autopsy | Not specified      | 3     | 3     | 3     | -      |
| Kristine E. Konopka et al.   | 37  | M      | Complete autopsy | Cause of death     | 3     | 3     | 3     | -      |
| Randall Craver et al.        | 17  | M      | Complete autopsy | Not specified      | U     | U     | 0     | -      |
| Lei Yan et al.               | 44  | F      | Partial autopsy (no cranial cavity, internal organs left in situ) | Not specified | 2     | 3     | 3     | -      |
| J. Matthew Lacy et al.       | 58  | F      | Complete autopsy | Cause of death     | 3     | 3     | 3     | -      |
| Evan A. Farkash et al.       | 53  | M      | Partial autopsy (no cranial cavity) | Cause of death     | 1     | 2     | 2     | -      |
| Diego Aguiar et al.          | 31  | F      | Complete autopsy | Cause of death     | 3     | 3     | 3     | -      |
| Takuya Adachi et al.         | 84  | F      | Partial autopsy (no cranial cavity) | Cause of death     | 2     | 2     | 2     | -      |
| Author                        | Age | Gender | Type of Examination                                      | Role of SARS CoV-2 | CSS R1 | CSS R2 | CSS R3 | H Score |
|-------------------------------|-----|--------|----------------------------------------------------------|--------------------|--------|--------|--------|---------|
| Parisa Karami et al.          | 27  | F      | Partial autopsy (only lungs reported)                    | Not specified      | 3      | 3      | 3      | -       |
| Christine Suess et al.        | 59  | M      | Complete autopsy                                         | Cause of death     | 3      | 3      | 3      | -       |
| Monique Freire Santana et al. | 71  | M      | Complete autopsy                                         | Not specified      | 1      | 1      | 1      | -       |
| James R. Stone et al.         | 76  | F      | Partial autopsy (only heart and lungs examined macroscopically) | Cause of death     | 3      | 3      | 3      | -       |
| Sociedad Espanola de Anatomia Patologica | 54  | M      | Partial autopsy (no cranial cavity, internal organs left in situ) | Not specified     | 3      | 3      | 3      | -       |
| Pedro Navarro Conde et al.    | 69  | M      | Partial autopsy (no cranial cavity)                      | Cause of death     | 3      | 3      | 3      | -       |
| Fabian Heinrich et al.        | 59  | M      | Complete autopsy                                         | Cause of death     | 3      | 3      | 3      | 1       |
| Inga-Marie Schaefer et al.    | 66  | F      | Post mortem histological samples (lung, airways)         | Cause of death     | 3      | 3      | 3      | -       |
|                               | 57  | M      | Post mortem histological samples (lung, airways)         | Cause of death     | 3      | 3      | 3      | -       |
|                               | 77  | M      | Post mortem histological samples (lung, airways)         | Cause of death     | 2      | 2      | 2      | -       |
|                               | 50  | M      | post mortem histological samples (lung, airways)         | Cause of death     | 2      | 2      | 2      | -       |
|                               | 68  | F      | Post mortem histological samples (lung, airways)         | Cause of death     | 3      | 3      | 3      | -       |
|                               | 66  | M      | Post mortem histological samples (lung, airways)         | Cause of death     | 3      | 3      | 3      | -       |
|                               | 53  | M      | Post mortem histological samples (lung, airways)         | Cause of death     | 2      | 2      | 2      | -       |
Table 2. Cont.

| Author                       | Age | Gender | Type of Examination | Role of SARS CoV-2 | CSS R1 | CSS R2 | CSS R3 | H Score |
|------------------------------|-----|--------|---------------------|--------------------|-------|-------|-------|---------|
| Mohammad Taghi Beigmohammadi et al. | 58  | M      | Post mortem histological samples (lung, airways) | Not specified      | 3     | 3     | 3     | -       |
|                              | 84  | F      | Post mortem histological samples (lung, airways) | Not specified      | 3     | 3     | 3     | -       |
|                              | 72  | F      | Post mortem histological samples (lung, airways) | Not specified      | 3     | 3     | 3     | -       |
| Sufang Tian et al.           | 72  | M      | Post mortem histological samples (lung, airways) | Not specified      | 3     | 3     | 3     | -       |
|                              | 68  | M      | Post mortem histological samples (lung, airways) | Not specified      | 2     | 3     | 3     | -       |
|                              | 46  | M      | Post mortem histological samples (lung, airways) | Not specified      | 3     | 3     | 3     | -       |
| Zsuzsanna Varga et al.       | 75  | M      | Post mortem histological samples (lung, airways) | Not specified      | 3     | 3     | 3     | -       |
|                              | 78  | F      | Post mortem histological samples (lung, airways) | Cause of death     | 3     | 3     | 3     | -       |
|                              | 74  | M      | Post mortem histological samples (lung, airways) | Cause of death     | 3     | 3     | 3     | -       |
|                              | 81  | M      | Post mortem histological samples (lung, airways) | Cause of death     | 3     | 3     | 3     | -       |
| Zhe Xu et al.                | 59  | M      | Post mortem histological samples (lung, airways) | Cause of death     | 2     | 3     | 3     | -       |
| Christine M. Lovly, M.D. et al. | 71  | M      | Post mortem histological samples (lung, airways) | Not specified      | 2     | 2     | 2     | -       |
|                              | 58  | F      | Post mortem histological samples (lung, airways) | Not specified      | 2     | 2     | 2     | -       |
|                              | 50  | M      | Post mortem histological samples (lung, airways) | Cause of death     | 3     | 3     | 3     | -       |
|                              | 56  | M      | Post mortem histological samples (lung, airways) | Not specified      | 1     | 3     | 3     | -       |

CSS: COVID-19 Significance Score. F: female. H: Hamburg. M: male. R: rater.
5. Discussion

Information about 84 deaths involving SARS CoV-2 positiveness or infection have been collected in the present study, showing the growing interest of the literature with respect to post-mortem findings in COVID-19 pandemic.

So far, several tests have been developed in order to confirm a patient’s positivity to the virus, none of them free from issues of sensitivity [31]. The most used is certainly rt-PCR performed on swabs collected from the upper airways. All patients included in this study tested positive for airway swabs, performed in vivo or post-mortem. However, the accuracy of post-mortem swabs is yet to be clearly defined and false negative are theoretically possible [69]. Indeed, even though different studies report positive swabs even after several days, the influence of post-mortem interval and bacterial superimposition is unknown. One study suggested it might be reliable until 5 days [70]. C. Edler et al. verified the post-mortem sensitivity of the nasopharyngeal and oropharyngeal swabs by performing the test on 30 deceased at the time of dissection, finding a positive swab in 100% of cases, with a maximum time elapsed from death to the test of 12 days [38]. Furthermore, a study by Marco Dell’Aquila et al. highlighted the importance of performing multiple swabs in the post-mortem examination [71]. COVID-19 has been detected by nasopharyngeal and oropharyngeal swabs up to 27 h after death [72], while in another study the positivity of throat swabs lasted up to 128 h [73]. By performing rhino-pharyngeal, tracheal and lung swabs in 12 autopsy cases of patients with a clinical diagnosis of Sars-CoV-2 related pneumonia, 9 out of 12 cases had at least one post-mortem swab positive for Sars-CoV-2, with the virus found in samples up to 310 h from the post mortem sampling [71]. Moreover, a paper by Prema Seetulsingh et al. described the case of a patient who died of respiratory failure during transport to the hospital, with a negative upper airway swab, but with SARS CoV-2 found in the lung at an analysis performed 27 days following the death [74]. However, a correlation between the negativity of the lung swabs and the number of days elapsed from the ante mortem swabs was also found, as well as a negative correlation between the positivity of the other swabs and the number of days passed from the ante mortem swabs [71]. Thus, results of swabs should be interpreted with caution and never taken as an evidence of COVID-19 when singularly considered.

As a matter of fact, despite multiple reports allowed to assess the vitality of SARS CoV-2, scientific evidence regarding the risk of becoming infected for health care personnel arising from human dead hosts is lacking. Notwithstanding this, the risk of contagion involved in the post-mortem examination led some countries to discourage the performance of autopsies, as happened in Italy [75]. This might explain why the number of cases here considered, although significant, is rather low when compared to the high worldwide mortality for COVID-19. An additional possible explanation for the decline of the autopsy rate might be connected to the guidance for the safe management of a dead body, published by the World Health Organization and by the Center for Disease Control and Prevention [76,77]. Indeed, not all the autopsy facilities could be equipped with the required safety measures (e.g., negative pressure rooms) and the lack of “safe” autopsy rooms might have additionally led to a reduction in postmortem examinations [69,76].

The epidemiology of the victims, and the rate of comorbidities (absent in 28% of the cases), do not allow to confirm that SARS-CoV-2 is only affecting the elderly or patients who bear in already critical conditions. Rather, this is a confirmation that COVID-19 can be lethal even in healthy people and this should be taken in mind by forensic pathologists, who might incur in an otherwise unexplained death. As for the history of the disease, reported symptoms, laboratory alterations and macro as well as microscopic findings of the cases collected in this study were in line with those reported by other works, showing a prevalence of lung damage with edema, acute and late phase of DAD, presence of microthrombi in the pulmonary vessels or pneumonia [78–83], but also involvement of other organs, such as kidneys, heart and liver [84–87]. This also highlights that investigations limited to the lungs might not be enough to obtain a clear clinical post-mortem picture. Moreover, the
complexity of the histological features shown even within the lungs might suggest that a biopsy-based approach might not be representative of the whole parenchyma.

As for the type of analyses performed, in vivo imaging was far more common than in the post-mortem setting (only 15 cases). Particularly, post-mortem imaging was performed when in vivo instrumental analysis was missing, e.g., cases 1,3,5,7–12 by Dominic Wichmann et al. [40], and its concordance or discordance with pathological findings allowed a high inter-rater agreement in the assignment of the CSS. Its application is strongly encouraged, especially when other info might be missing. Toxicology was extremely rarely applied. However, several drugs were administered before and during COVID-19 in most cases and, in this condition, it would appear reasonable to confirm the effectiveness of the administration, e.g., by excluding under- as well as over-doses.

A rather worrying picture emerged from the type of post-mortem examination performed, since the majority of cases (55 in total, out of 84) were not complete, nor performed with respect to the international guidelines [88,89]. Indeed, even though micro-invasive autopsies, especially if coupled to post-mortem imaging and extensive sampling of tissues for histology and electronic microscope-based analyses, might represent a viable alternative to reduce the risk of infection for health care personnel, the exclusion of some organs (most often, the brain) or the loss of a global view on the health status of the victim might lead to false conclusions. Especially in the case of such a widespread and systemic infection as COVID-19, which might affect multiple organs and lead to an unpredictable and severe immune response, the careful dissection of each organ appears of paramount importance. Indeed, a full autopsy is the only chance to observe the systemic changes and take optimal samples to identify the cause of death [28].

As already emerged for some toxicological issues, when the scientific data are scarce [35,36], a multidisciplinary evaluation is necessary and shared criteria might aid forensic pathologists in their delicate task, which has many consequences.

By observing the CSS applied to the collected cases, it can be noted that most of the deceased fall into the category “deaths from COVID-19”. A similar result is reported by an interesting study by Francesco Grippo et al. [5] By analyzing more than 5000 death certificates compiled according to the ICD, it was observed that COVID-19 was reported as the leading cause of death in 88% of cases. Sefer Elezkurtaj also confirms, by performing autopsies on 26 patients, that in the majority of decedents, the causes of death were directly related to SARS CoV-2 [90]. According to this study, the majority of patients had “died of COVID-19”, with only a contributory implication of pre-existing health conditions to the mechanism of death. However, the influence of a publication bias should be considered.

The very good agreement found by three blind and independent raters allows to hypothesize that the CSS is an easy tool which could be applied in the everyday routine of post-mortem examination on SARS-CoV-2 positive deceased, even by less experienced pathologists. Regarding the comparison with the Hamburg score by Edler et al. [38], as previously mentioned, it was not possible to apply that categorization in all cases, but only in the autopsies performed in Hamburg which were also reported in the studies by Wichmann et al. [40] and Heinrich et al. [57]. The study of the University of Hamburg, in fact, collected the key points of the first 80 consecutive autopsies carried out in the federal state of Hamburg, then applied a categorization of deaths on the basis of the causes of death reported, making this scale not usable in different studies. Furthermore, the 80 cases described by Edler et al. do not contain extractable information, particularly regarding post-mortem findings [38]. Therefore, they could not be included in our database of literature cases. The Hamburg score mostly considered the findings of “pneumonia”, “ARDS” and “pulmonary embolism” as indicators for a COVID-19-related death. Even if these findings are certainly fundamental in the evaluation of the role of SARS-CoV-2, we believe that a more comprehensive overview, as well as a valorization of past history and of the status of the other organs and functions (e.g., of coagulation), are needed. For example, findings of aspiration pneumonia in a patient with neurological comorbidities might be misinterpreted as SARS-CoV-2-related, when they might have occurred even...
in the absence of this pathogen and in any moment of the patient’s life (e.g., case 6 by Wichmann et al. [40], assigned CSS = 1). This further underlies the importance of collecting in vivo data when performing a post-mortem assessment. Clinical risk prediction models (e.g., QCOVID) have already been developed and validated on large population sets, to estimate the risk of becoming infected and then of dying of COVID-19, or of dying when admitted to hospital with COVID-19 [18,91,92].

The quantification of such risks might be certainly useful even in the postmortem setting, and might give forensic pathologists strong indications on the most important clinical predictors of death. However, these statistical ex ante tools do not allow one to assess ex post the cause of death and the role of the virus in the specific evaluated case. Thus, in the post-mortem evaluation, clinical stratification risk models or image-based outcome models should be always integrated with the CSS [93].

Even though the results, by comparing the converted Hamburg score and the CSS, were not significantly different, this type of analysis has been made possible only in a minority of cases and further studies would be needed to establish whether they are interchangeable. Nevertheless, we agree that, when the cause of death is difficult to be ascertained, a high degree of suspicion for COVID-19 should be maintained, and this probably had a reflection in the above-mentioned high degree of CSS 3 and 2 assigned.

Beside the difference in numbers among cases classified by Hamburg score and by CSS, the study has several limitations. Until July 31, only a few reports of complete autopsies had been published. The early publication of the present study has the aim to provide a quick overview and practical instruments which might be helpful for further cases evaluation. Despite the diffusion of safety protocols, very often these were not applied due to the infectious risk, preferring minimally invasive approaches such as ultrasound guided biopsies or partial autopsies, by opening of the thoracic and abdominal cavity, but leaving the organs in situ. Additionally, not all the articles reported information such as laboratory tests performed, comorbidities, circumstances of death and radiology. Regarding the swabs, all cases found were positive for the virus, but it has not always been reported whether the swab was performed in vivo or post mortem and, when performed post mortem, when with respect to the post-mortem interval. This information could be important in understanding how long the virus remains detectable in the patient’s airways after death, with implications in CSS, built to evaluate SARS CoV-2 positive patients. The lack of one or some of the CSS key points could make the score less accurate. A possible solution could consist in the creation of a register that contains all the autopsies performed on patients affected by COVID-19, with findings organized in a systematic way.

6. Limitations

The present systematic review has several limits. Firstly, the time of publication chosen was quite narrow, from the early months of 2020 to 31 July 2020. However, this was necessary due to the urgency of the matter. A broader period of observation would certainly provide more relevant data. Secondly, only papers at least providing some results of a post-mortem examination were included. This was motivated by the will of obtaining stronger evidence, even though we are aware that this might have resulted in a lower number of cases. Indeed, the total number of cases herein reported is certainly low, when compared to the worldwide mortality from Covid-19. This might be due to the limitations in performing autopsies which have been established, due to the infective risk for health care personnel and forensic pathologists, in many countries. Thirdly, the comparison between the CSS and the Hamburg score was only limited to a few cases. Finally, all relevant studies were included, with no distinction on the basis of the adherence to ethical standards and of the conflicts of interest, neither selecting only high-impact journal. This was done in order to offer a broad collection of cases, though it has resulted in the inclusion of a withdrawn article. However, the corresponding paper only provided a single case; thus, statistics were only minimally affected.
7. Conclusions

As the pandemic continues to claim victims, it is fundamental to distinguish those patients who have died “from COVID-19” from those who have died “with COVID-19”. The SARS CoV-2 Significance Score (CSS) used after a complete accurate post-mortem examination, coupled to the retrieval of in vivo data, post-mortem radiology, histology and toxicology, as well as to additional required analyses (e.g., electronic microscopy) aims to be a useful, concise tool helping in the assessment of the cause of death and the role played by this virus. A shared use of this scale might hopefully lower the inhomogeneities in forensic evaluation of SARS-CoV-2.

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