Review Article

Positive airway pressure longer than 24 h is associated with histopathological volutrauma in severe COVID-19 pneumonia—an ESGFOR based narrative case-control review

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Background and Objective: A thorough understanding of the pathogenic mechanisms elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) still requires further research. Until recently, only a restricted number of autopsies have been performed, therefore limiting the accurate knowledge of the lung injury associated with SARS-CoV-2. A multidisciplinary European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group of Forensic and Post-mortem Microbiology-ESGFOR team conducted a non-systematic narrative literature review among coronavirus 2019 disease (COVID-19) pneumonia cases assessing the histopathological (HP) effects of positive airways pressure. HP lung features were recorded and compared between mechanically ventilated (>24 hours) and control (ventilation <24 hours) patients. A logistic regression analysis was performed to identify associations between mechanical ventilation (MV) and HP findings.

Methods: A PubMed and MEDLINE search was conducted in order to identify studies published between March 1st 2020 and June 30th 2021.

Key Content and Findings: Seventy patients (median age: 69 years) from 24 studies were analysed, among whom 38 (54.2%) underwent MV longer than 24 hours. Overall, main HP features were: diffuse alveolar damage (DAD) in 53 (75.7%), fibrosis (interstitial/intra-alveolar) in 43 (61.4%), vascular damage—including thrombosis/emboli- in 41 (58.5%), and endotheliitis in only 8 (11.4%) patients. Association of DAD, fibrosis and vascular damage was detected in 30 (42.8%) patients. Multivariate analysis, adjusted by age and gender, identified MV >24 hours as an independent variable associated with DAD (OR =5.40, 95% CI: 1.48–19.62), fibrosis (OR =3.88, 95% CI: 1.25–12.08), vascular damage (OR =5.49, 95% CI: 1.78–16.95) and association of DAD plus fibrosis plus vascular damage (OR =6.99, 95% CI: 2.04–23.97).

Conclusions: We identified that patients mechanically ventilated >24 hours had a significantly higher rate of pulmonary injury on histopathology independently of age and gender. Our findings emphasize the importance of maintaining a protective ventilator strategy when subjects with COVID-19 pneumonia

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undergo intubation.

Keywords: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); mechanical ventilation (MV); pathology; post-mortem microbiology; volutrauma

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Introduction

RNA viruses, such as influenza or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may be able to trigger devastating effects. They achieve this result with less than 12 genes, using strategies to evade the immune system of the host (1). In an ideal scenario, inflammatory cytokines recruit macrophages, neutrophils and dendritic cells connect with adaptive cellular immunity (lymphocytes) and humoral immunity (antibodies) and control viral replication. In the worst scenario, they can trigger an immune response that mainly harms the host (2).

Ventilator-induced lung injury (VILI) is the acute lung injury caused or aggravated by mechanical ventilation (MV) during treatment. VILI can occur during invasive ventilation and might contribute significantly to the morbidity and mortality of critically ill patients. Though MV potentially damages both normal and diseased lungs, the injury will be much more severe in the latter due to higher microscale stresses. In 1967, the term "respirator lung" was coined to describe the histopathological (HP) features encountered at post-mortem in the lungs of patients who had undergone MV and was characterized by extensive alveolar infiltrates and hyaline membrane (HM) formation. Further confirmatory evidence for VILI comes from the landmark acute respiratory distress syndrome (ARDS) Nett trial, where low tidal volume ventilation proved to be superior to high tidal volume ventilation in ARDS patients (3).

Coronavirus 2019 disease (COVID-19) affects many organs, but pulmonary disease plays a relevant role in COVID-19 mortality due to ARDS (4). A multidisciplinary European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group of Forensic and Post-mortem Microbiology-ESGFOR team conducted a non-systematic literature review with the aim to assess the key pulmonary HP findings in COVID-19, the pathological mechanisms involved and the possible implications for patient management. The focus was laid on HP findings in the lungs. Based on the timing of the HP study in COVID-19 pneumonia cases, we aimed at reconstructing different stages in the evolution of the lung damage.

The hypothesis was to confirm that MV increases lung damage in COVID-19 patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-605/rc).

Methods

Study design, population, subjects and data sources

A retrospective case-control literature review study was performed comparing HP patterns among COVID-19 patients with acute respiratory failure requiring positive airway pressure (PAP) ventilation (MV) 24 hrs or more *vs.* a control group without MV (or for less than 24 hours).

A multidisciplinary ESGFOR team, was selected among their members by AFR based on complementarity, prior publications and experience. The research team was composed of one pathologist, two microbiologists, one intensivist, one clinician, and one clinician- epidemiologist and was involved in the selection and analyses of the manuscripts.

A PubMed and MEDLINE search was conducted in order to identify studies published between March 1st 2020 and June 30th 2021 using following search terms: SARS-CoV-2 OR COVID-19 AND autopsy OR histopathology OR biopsy OR immunohistochemistry OR pathology OR post-mortem examination. Withheld publications were identified, reviewed by all authors of the multidisciplinary ESGFOR team and discussed by video conference and email before their inclusion in the analysis. Ethical Board approval was not required because data were limited to a literature search.

For the purpose of this study, all patients with hypoxemia who underwent PAP to maintain SpO_2 above 93% longer than 24 hours were considered "mechanical ventilation"

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Table 1 Search strategy summary

Items	Specification
Date of search (specified to date, month and year)	13/5/2020 until 2/6/2020, 30/6/2021
Databases and other sources searched	PubMed and MEDLINE
Search terms used (including MeSH and free text search terms and filters)	SARS-CoV-2 OR COVID-19 AND autopsy OR histopathology OR biopsy OR immunohistochemistry OR pathology OR post-mortem examination
Timeframe	March 1st 2020–June 30th 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	To evaluate possible differences between patients who underwent mechanical ventilation (MV) longer than 24 hours and controls (not-MV patients), only those articles describing individual data (per patient) about detailed HP lung features as well as the information about receiving MV or not per patient, and with an abstract in English language were included. Patients aged under 18 years were excluded
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The multidisciplinary ESGFOR (ESCMID-European Society of Clinical Microbiology and Infectious Diseases-Study Group of Forensic and Post-mortem Microbiology) team, was selected among their members by AFR (current Secretary and Past Chair) based on complementarity, prior publications and experience. The study was endorsed by the ESGFOR Executive Committee from the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) as a priority research initiative. The research team was integrated by 1 pathologist (MCC), two microbiologists (AFR & VS), one intensivist (JR), one clinician (BFG), and one clinician and epidemiologist (LA). Withheld publications were identified, reviewed by all authors of the above mentioned ESGFOR team, and discussed by video conference and email before their inclusion in the analysis
Any additional considerations, if applicable	For the purpose of this study, all patients with hypoxemia who underwent PAP to maintain SpO_2 above 93% longer than 24 hours were considered "mechanical ventilation" cases. Controls were patients with acute respiratory failure due to COVID-19 without this intervention or ventilated less than 24 hours

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus 2019 disease.

cases. Controls were patients with acute respiratory failure due to COVID-19 without this intervention or ventilated less than 24 hours.

To evaluate possible differences between patients who underwent MV longer than 24 hours and controls (not-MV patients), only those articles describing individual data (per patient) about detailed HP lung features as well as the information about receiving MV or not per patient, and with an abstract in English language were included. Patients aged under 18 years were excluded. The summary of the search strategy can be found in *Table 1*.

Variables and co-variables

Covariables including patients' demographics and comorbidities are described in *Table 2*. HP variables are described in *Table 3* and include diffuse alveolar damage (DAD), fibrosis (either interstitial or intra-alveolar), vascular damage (VD) (either thrombosis/emboli or endotheliitis), and the following associations: DAD + fibrosis; DAD or fibrosis; DAD + fibrosis + VD.

Statistical methods

Descriptive stats of patients' characteristics are expressed as mean and standard deviation or median and interquartile ranges [P25–P75] for continuous variables, while proportions are shown in the case of categorical variables. Statistical tests are performed to assess differences between main outcomes (variables) and the presence or not of MV. Continuous variables were analysed using Mann-Whitney or student's *t*-test, and discrete variables were analysed using the Chi-square test. Logistic regression analyses were run to examine the possible risk of MV on each main outcome, adjusted for patients' gender and age. Results were expressed as odds ratio (OR) with their respective 95% confidence intervals. All analyses were performed in Stata v.13 statistical software (Stata Corp., College Station, TX,

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Table 2 Comparison of patient demographics and comorbidities in cases (MV patients) and controls (not-MV patients)

Characteristic	Global (N=70)	Controls (not-MV group) (N=32)	MV group (N=38)	P value
Median age	69 [59–73]	68.5 [57–77]	69 [63–72]	0.89
Gender: men/women, n (%) (n=60)	43/17 (71.67/28.33)	19/10 (65.52/34.48)	24/7 (77.42/22.58)	0.394
Duration of symptoms (n=53)	10 [6–16]	6.5 [2.5–10]	15 [10–19]	0.0002
Duration of MV (n=20)	NA	NA	5.75 [5.5–10.5]	
Patients with comorbidities (n=56)	47 (83.93%)	22 (81.48%)	25 (86.21%)	0.63
Hypertension	24 (42.86%)	7 (25.93%)	17 (58.62%)	0.013
Cardiovascular disease (CVD)	20 (35.71%)	13 (48.15%)	7 (24.14%)	0.061
Diabetes mellitus	20 (35.71%)	9 (33.33%)	11 (37.93%)	0.720
Obesity	14 (25%)	6 (22.2%)	8 (27.59%)	0.643
Chronic renal disease (CRD)	8 (14.29%)	6 (22.22%)	2 (6.90%)	0.101
Another lung pathology	6 (10.71%)	1 (3.7%)	5 (17.24%)	0.102
Smoking	4 (7.14%)	1 (3.70%)	3 (10.34%)	0.335
Chronic obstructive pulmonary disorder (COPD)	3 (5.36%)	1 (3.70%)	2 (6.90%)	0.596
Pulmonary carcinoma	2 (3.57%)	2 (7.41%)	0 (0%)	0.0136

MV, mechanical ventilation.

USA). A two-tailed P value under 0.05 was considered to indicate statistical significance.

Results

Seventy-five articles were reviewed and 24 of them met the inclusion criteria. Seventy patients with a median age of 69 years (range 59–73 years) were assessed. The main data and patient characteristics from the cases and controls analysed are presented in Table S1 (5-21) and Table S2 (6,7,11,15-17,22-28). The HP findings were obtained from 46 full autopsies (5-14,22-25), 10 minimal invasive autopsies (MIA) (15), 8 limited autopsies (16-18,26), 4 post-mortem biopsies (19,27,28) and 2 surgical biopsies (20,21).

Table 2 describes demographics and comorbidities of MV patients and controls. A significant difference between MV patients and controls was the duration of symptoms, being much longer for the MV patients. Comorbidities were available for 56 of the total of 70 patients: 47 had at least one comorbidity (22 not-MV and 25 MV), and 33 patients had more than one (15 not-MV and 18 MV) comorbidity, with a median of two. The main comorbidities reported were hypertension (HT) (42.86%), cardiovascular disease, diabetes mellitus (35.71% each), and obesity (25%). The cases and control groups were socio-demographically similar (age, gender, and comorbidities), although the prevalence of HT was higher in the MV group (P=0.013).

Nineteen of the 20 patients for which the lag time on MV was available presented with DAD or fibrosis, while 14 of them showed VD. There was no significant influence of the duration of MV for the presence of DAD or fibrosis nor for that of VD.

Among the 32 control patients (45.71%), death occurred at home in five (8-11,14), two cases were sudden deaths (7,14), one case received supplemental oxygen through a continuous PAP mask (21), two cases received oxygen via a nasal cannula (13,19) and another case only received oxygen (12) (missing data regarding supplemental oxygen therapy in the rest of patients). Of the 38 (54.29%) MV patients, 6 had received extracorporeal membrane oxygenation (ECMO) (7,11,27); and 2 patients received non-invasive MV (6,25). Information about the length of MV was available in 20 patients. In this group the lag time between start of ventilation and death was on average 10.5 days (2–42 days). Patients with HP VD in the MV group had a longer time until death from the onset of symptoms than those with VD in the control group (P=0.0016).

Table 3 shows the frequency of HP findings in all patients

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Table 3 Summary of HP findings in cases (MV patients) and controls (not-MV patients)

Histological findings	Total patients, n=70 (%)	Patients not-MV, n=32 (%)	Patients on MV, n=38 (%)	P value (Chi square)
Interstitial findings				
Interstitial lymphocytes infiltrate	43 (61.43)	20 (62.5)	23 (60.53)	0.866
Interstitial fibrous thickening	41 (58.57)	13 (40.63)	27 (71.05)	0.007
Alveolar patterns				
Macrophage clustering	12 (17.14)	8 (25.00)	4 (10.53%)	0.109
DAD	53 (75.71)	19 (59.38)	34 (89.47)	0.003
Alveolar pneumocyte hyperplasia	39 (55.71)	15 (46.88)	24 (63.16)	0.172
Multinucleated giant cells	24 (34.29)	9 (28.13)	15 (39.47)	0.319
HM	50 (71.43)	20 (62.50)	30 (78.95)	0.129
Intra-alveolar fibrin exudate	28 (40.00)	12 (37.50)	16 (42.11)	0.695
Oedema	29 (41.43)	14 (43.75)	15 (39.47)	0.717
Alveolar squamous metaplasia	13 (18.57)	1 (3.13)	12 (31.58)	0.002
Intra-alveolar fibrosis	17 (24.29)	2 (6.25)	15 (39.47)	0.001
Intra-alveolar lymphocytes	7 (10.00)	4 (12.50)	3 (7.89)	0.522
Viral cytopathic-like changes	14 (20.00)	5 (15.63)	9 (23.68)	0.401
Neutrophils/bronchopneumonia	30 (42.86)	18 (56.25)	12 (31.58)	0.038
Alveolar haemorrhage	24 (34.29)	11 (34.38)	13 (34.21)	0.988
Bronchitis	5 (7.14)	5 (15.63)	0 (0.0)	0.011
Vascular patterns				
Vascular thrombosis/emboli	38 (54.29)	12 (37.50)	26 (68.42)	0.010
Vascular endotheliitis	8 (11.43)	3 (9.38)	5 (13.16)	0.620
Associated patterns				
Fibrosis (interstitial or intra-alveolar)	43 (61.43)	14 (43.75)	29 (76.32)	0.005
DAD + fibrosis	38 (54.29)	12 (37.5)	26 (68.42)	0.010
DAD or fibrosis	58 (82.86)	21 (65.63)	37 (97.37)	0.001
Vascular damage	41 (58.57)	13 (40.63)	28 (73.68)	0.005
DAD + fibrosis + vascular damage	30 (42.86)	7 (21.88)	23 (60.53)	0.001

HP, histopathological; MV, mechanically ventilated; DAD, diffuse alveolar damage; HM, hyaline membranes.

and its distribution in the control and MV groups. DAD was the most frequent HP pattern, present in 53 patients (75.71%) according to the criteria stated by the authors. Thirty-four patients belonged to the group of MV patients, while 19 were controls. MV patients had significantly more DAD lung injury compared to not-MV patients (*Table 3*). At the multivariate regression analysis, the MV group also had more risk of DAD after adjusting for age and gender (*Table 4*).

HM were frequently described (n=50; 71.43%) as a HP lung feature, either being part of DAD or not. Interstitial lymphocytes infiltrates were more frequent (n=43; 61.43%) than intra-alveolar lymphocytes (n=7; 10%). Interstitial fibrous thickening was also frequently detected (n=41; 58.57%), while intra-alveolar fibrosis appeared only scarce (17; 24.29%).

Squamous metaplasia, another feature of DAD, was

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Table 4 Logistic regression analyses. Main outcomes: DAD, fibrosis and vascular damage comparing cases (MV patients) and controls (not-MV patients)

Main outcomes	Bivariate analysis (n=70)			Multivariate analysis (n=60)*		
	OR	95% CI	P value	OR	95% CI	P value
DAD	5.82	1.66–20.37	0.006	5.40	1.48–19.62	0.01
Fibrosis	4.14	1.49–11.53	0.006	3.88	1.25–12.08	0.019
DAD + fibrosis	3.61	1.34–9.72	0.011	3.27	1.11–9.61	0.031
DAD or fibrosis	19.38	2.34–160.82	0.006	18.20	2.09–158.29	0.009
Vascular damage	4.09	1.49–11.23	0.006	5.49	1.78–16.95	0.003
DAD + fibrosis+ vascular damage	5.48	1.89–15.82	0.002	6.99	2.04–23.97	0.002

Results were expressed as OR with their respective 95% confidence intervals. *, adjusted by age and gender. DAD, diffuse alveolar damage; MV, mechanically ventilated; OR, odds ratio.

described only in 13 patients (18.57%), 12 of which were on MV. It was first seen in this group on day 8 after the onset of symptoms, as previously described (15). The only control showing this finding had a lag time on MV of 10 days.

In general, fibrosis (either interstitial or intra-alveolar) was detected in 43 patients (61.43%), being significantly more frequent in the MV group than in controls (*Table 3*). Besides, the multivariate analysis confirmed this association between MV and fibrosis (*Table 4*). Among the 70 patients, 58 had either DAD or interstitial or intra-alveolar fibrosis (82.86%). Thirty-seven of them were on MV, whereas 21 were controls. MV patients had significantly more DAD or interstitial or intra-alveolar fibrosis compared to not-MV patients (*Table 3*). After adjusting for age and gender, there still was a clear association of DAD or interstitial or intra-alveolar fibrosis and MV (*Table 4*). An interesting association of HP findings was the presence of DAD plus interstitial or intra-alveolar fibrosis in 38 out of the 70 patients (54.29%). This pattern was significantly more frequent in MV patients (n=26) than in controls (n=12) (*Table 3*) with an OR of 3.27 after multivariate analysis (*Table 4*).

VD was a frequent pattern (41/70, 58.57%) and mostly included thrombi and emboli in pulmonary vessels (capillary, vein, or arteries), while endotheliitis was rarely described (8/70, 11.43%). In MV patients, these vascular patterns were significantly more frequent than in controls (*Table 3*), with a 4- to 5-fold higher OR when compared to the not-MV group (*Table 4*).

Finally, multivariate analysis showed a significant association between MV and the combination of DAD and fibrosis and VD (*Table 4*).

Discussion

This article adds a piece to the puzzle of previous studies reporting HP features of patients dying with or suffering from severe COVID-19 pneumonia. A unique feature of our article is that information on the specific focus of pulmonary abnormalities was correlated with specific information on MV of the patients. DAD was the predominant finding, with presence of HP features in above 50% of cases. Endotheliitis, in contrast, was unlikely. MV above 24 hours was independently associated with high OR of alveolar injury, fibrosis and VD, when controlled for age and gender.

In addition to obvious features in the overall study population of DAD (75.71%), the following were also identified in our review: HM (71.43%), fibrous thickening (58.57%), interstitial T-cell lymphoid and macrophages infiltrates (61.43%), vascular thrombosis (including pulmonary embolism, capillary fibrin thrombosis and disseminated intravascular coagulation) (54.29%), endothelial damage (11.43%) and microthrombi in capillaries in the lungs. These features suggest that T-cell immune mediated endotheliitis, and secondary thrombosis (both microthrombosis and deep vein thrombosis) are key features in COVID-19, and that the DAD and HM are likely secondary to the interstitial T-cell driven inflammation and VD.

The association of DAD with fibrosis, either interstitial or intra-alveolar in 54.29% of the patients described in this series indicates the progression of the lung injury and probably its contribution to a fatal outcome. This association of patterns was significantly more frequent

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in MV patients (68.42%, P=0.010), supporting that this can be related not only to the temporal evolution of the disease but also to the effects of MV (15,29). Likewise, interstitial fibrous thickening showed a tendency to be more prevalent among MV patients (71.05%) than among controls (40.63%). Similarly, VD, usually associated with thrombotic events, was significantly more frequent in MV patients, which suggests a contribution of MV to this injury. These two lung injury patterns—epithelial and vascular—reflect a ventilation-perfusion mismatch with hypoxemia, and lead to ARDS and respiratory failure. This has relevant implications when planning treatment (15). Contradictory to the hypothesis that MV has a role in thrombotic and epithelial damage, previous authors suggested that a primary VD caused by SARS-CoV-2 could be the initial sign of the ground-glass opacities and of the crazy-paving pattern that are observed on CT thorax early in the course of the disease (30). Our results showed that the presence of vascular events and DAD/fibrosis is significantly more frequent in MV patients than in controls, and that this effect is independent of the length of ventilation before histopathology in multivariate analysis. Observations from Coppola *et al.* demonstrated that the primary cause of oxygenation impairment in early COVID-19 related ARDS pneumonia was related to dysregulation of perfusion rather than pulmonary oedema and collapse (31).

It is possible that different mechanisms could act together to obtain the late fibrotic lesions observed in patients under MV. Although the recruitment of inflammatory monocytes and neutrophils at the site of tissue injury is important for the wound-healing process, these cells also secrete many toxic mediators, including reactive oxygen and nitrogen species harmful to the surrounding tissues (32). The rapid viral replication may cause massive epithelial and endothelial cell death/damage and vascular leakage. This triggers the production of cytokines and chemokines (33) and includes procoagulant effects together with cellular elements of acute/subacute inflammation driving to fibrosis.

SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of severe endothelial injury, intracellular presence of the virus and the host inflammatory response (16,34). In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in COVID-19. COVID-19-endotheliitis could explain the impaired systemic microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19 (34). Lungs from such patients show widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries as was previously shown (35-37).

Previous authors found that squamous metaplasia is not seen in the early phase, appearing at first around the 8th day after the onset of symptoms, similarly to SARS (15,38,39), consistently, in this study, it was first seen the 7th day of symptom onset. Moreover, in our study, pneumocytic hyperplasia was more prevalent in MV patients (63.16%) than in controls (46.88%).

Pathogenic coronaviruses are efficient replicators within ciliated cells of the respiratory tract, secreting high titres of virus after infection. Considering also the widespread ACE2 expression throughout the airways, it provides a suitable substrate for repeated cycles of virus amplification and spread through the respiratory epithelium, reaching the alveolar region. Noteworthy, ACE2 mRNA is highly expressed in renal, cardiovascular, and gastrointestinal tissues (33,40). ACE2 levels have been correlated with both men and Asian ethnicity (41-43). In this review also, men represented with 71.7% the dominant number of cases.

The novel SARS-CoV-2 virus is included as a hazard group 3 pathogen. This can be a limitation to the performance of autopsy examinations (44). HP studies among patients dying from COVID-19 were scarce during the first months of the pandemic given the worldwide paucity of available N95 respirators and other personnel protective equipment (36,45), but more autopsy studies have been performed over the last months (36,38).

Our study had some limitations. It did not identify peripheral biomarkers nor assessed specific immunological profiles in the lung. No correlation was done with the degree of hypoxemia, therapeutic interventions, ventilator settings such as tidal volume, lung compliance at intubation, steroids administration, viral load or SARS-CoV-2 variants. DAD was considered as defined by authors' criteria. On the other hand, this study has several strengths: the data included here reflect all available information in the literature on HP features in combination with clinical information about MV, which are scarce in the data sources. A sample size from a variety of geographical areas and the use of different pathological techniques yielding similar HP patterns provide uniformity of the results. A multivariate analysis adjusted by age and gender was performed.

The demonstrated widespread tissue invasion of SARS-CoV-2 lead to important lung and VD, two features exacerbated by invasive MV. Also, COVID-19 is known to cause a higher burden of thrombotic events, different

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thrombosis typologies and higher risk of thrombosis-related in-hospital mortality, also probably associated with a combined effect of COVID-19 and invasive MV (46). The longer the injury of MV, the more pulmonary and vascular injury was observed. In our view, indication of invasive MV should be carefully considered and only implemented as a last resort in the context of COVID-19 due to the demonstrated mainly pulmonary tissue and VD, including thrombosis. In any case, if MV is absolutely indicated, preventive measures against tissue damage must be applied. As in ARDS management, applying low tidal volumes (<6 mL/kg, ideal body weight) and airway pressures (plateau pressures <30 cmH_2O), limiting PEEP and respiratory driving are also highly recommended (47).

Conclusions

In this review, DAD was a predominant finding among patients suffering from severe COVID-19 pneumonia, with HP features in above 50% of cases. We identified that patients ventilated >24 hours had a significantly higher rate of pulmonary injury on histopathology independently of age and gender. Different mechanisms, such as hyperinflammation, cytokine storm, massive SARS-CoV-2 replication, tissue invasion and vascular injury may also play a role in the HP patterns observed. Our findings suggest the importance of maintaining a protective ventilator strategy when treating subjects with COVID-19 pneumonia.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-605/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Histopathological findings in lung sections from COVID-19 patients not mechanically ventilated or with MV shorter than 24 hours (5-21)

Publication: reference number, country, city, publication date, type of sample, number of patients	Sex, age, risk factors/ comorbidities, outcome	Date histopathology lung after onset of symptoms	Clinical history	Ancillary methods	Main positive pathology lung findings	Findings in other organs
(20), China, Zeng *et al.*, *Histopathology* 2020 May, doi: 10.1111/his.14138. 10 April 2020, biopsy, 1 patient	F, 55 y, a benign pulmonary nodule, alive (n=1)	Day 0	Right lower lung lobe resection for pulmonary nodule. Afebrile, no respiratory symptoms. Confirmed to have preoperative SARS-CoV-2 infection	Anormal accumulation of CD4+ helper T lymphocytes and CD163+ M2 macrophages in the lung tissue	Lungs: Intra-cytoplasmatic viral-like inclusion in pneumocytes and macrophages. Exudative inflammation (lymphocytes and monocytes) surrounding the visceral pleura. Widened alveolar septa, with obvious hyperemia, dilated capillaries. Multinucleated giant cells in alveolar spaces. No HM nor fibrin. Focal pneumocyte hyperplasia. Scattered large protein globules in alveolar spaces. Alveolar spaces were filled with a large amount of light red, homogeneous, proteinaceous fluid, admixed with variable numbers of red blood cells, lymphocytes and monocytes	
(16), USA, New York, Magro *et al.*, *Transl Res* 2020 Apr 15, doi: 10.1016/ j.trsl.2020.04.007, 09 Apr 2020, limited autopsy, 1 patient	M, 62 y, CVD, DM, hepatitis C, chronic renal disease, death (n=1)	Day 0	Presented in extremis with severe hypoxemia and blood pressure of 180/100 mmHg. Placed on comfort measures and died a few hours after presentation	Chest X ray: bilateral opacities most prominent in the peri-hilar distribution. SARS-CoV-2 spike & envelope proteins demonstrated with IHC. Significant vascular deposits of C5b-9 and C4d seen with DAB technique, standard bacterial and fungal respiratory cultures: negative, no other potential pulmonary viral pathogens detected	Lungs: complement significant fibrin deposition within septal capillary lumens and walls accompanied by endothelial cell necrosis. Pattern of cutaneous and pulmonary pathology involving microvascular injury and thrombosis, consistent with activation of the alternative pathway and lectin pathway of complement. Permeation of the inter-alveolar septa by neutrophils amidst the damaged capillaries, along with intra-alveolar neutrophils	
(5), USA, Oklahoma, Barton *et al.*, *Am J Clin Pathol* 2020;153:725-33. doi: 10.1093/AJCP/AQAA062, 10 Apr 2020, full post-mortem examination, 2 patients	Case 1: M, 77 y, obesity, HT, deep venous thrombosis, splenectomy, liver cirrhosis, death (n=1)	Day 6	Case 1: fever and chills for 6 days, died while being transported for medical care, not seen by a physician, exhibited symptoms suspicious for COVID-19 at the time of death, no ante-mortem testing for COVID-19	Case 1: IHC: sparse infiltrate CD3-positive T-lymphocytes within the alveolar septa, only rare CD20-positive B-lymphocytes. CD8-positive T-cells slightly outnumbered CD4-positive T-cells. CD68 highlighted a few macrophages	Case 1: lungs: DAD with HM, interstitial lymphoid inflammation, thrombi in small pulmonary arteries, right pleural adhesions	Case 1: hypertensive heart disease with acute ischemia, coronary arteries and abdominal aorta atherosclerosis, arterio-nephrosclerosis, hepatic centrilobular steatosis, liver cirrhosis
	Case 2: M, 42 y, obesity, liver cirrhosis myotonic dystrophy, death (n=1)	Day 2	Case 2: abdominal pain, fever, shortness of breath, cough, survived only a few hours in hospital, at PM examination, evidence of intubation and chest compressions	Case 2: IHC: CD68 highlighted numerous macrophages within the areas of BN; chest CT scan: bilateral GGO; no antemortem testing for COVID-19	Case 2: lungs: acute BN with aspiration, no DAD, filling of peribronchiolar airspaces by neutrophils and histiocytes	Case 2: liver cirrhosis, right renal mass (oncocytoma), mild coronary arteries atherosclerosis, nephrosclerosis
(6) Germany, Hamburg, Wichmann *et al.*, *Annals Intern Medicine* 2020, doi: 10.7326/M20-2003, 6 May 2020, full autopsy, 7 patients (patients 1, 2, 5, 6, 8, 9, 10)	Case 1: M, 52 y, obesity Case 2: M, 70 y, Parkinson disease, CAD, peripheral artery disease, CRD Case 5: M, 66 y, CAD Case 6: F, 54 y, dementia, epilepsy, trisomy 21 Case 8: M, 82 y, Parkinson disease, type 2 DM, CAD Case 9: f, 87 y, Lung cancer, CAD, CRD Case 10: M, 84 y, type 2 DM, HT, ulcerative colitis Death (n=7)	Not mentioned	Case 1: cardiopulmonary resuscitation, sudden cardiac death Case 2: basic supportive care, respiratory failure, pneumonia Case 5: cardiopulmonary resuscitation, sudden cardiac death Case 6: basic supportive care, respiratory failure, aspiration pneumonia Case 8/9/10: basic supportive care, respiratory failure, viral pneumonia	PM RT-PCR: + in lungs in all patients (range, 1.2×10^4 to 9×10^9 copies/mL) and in the pharynx of 9 patients. Six patients showed moderate viremia ($<4\times10^4$ copies/mL). In 5 of these patients, viral RNA was also detected in other tissues (heart, liver, or kidney) in concentrations exceeding viremia. Patients without viremia showed no or a low viral load in the other tissues. Only 4 patients had detectable viral RNA in the brain and saphenous vein	3 cases with DAD: 3 activated pneumocytes; 3 HM; 1 fibroblasts; 1 granulocytic infiltration of the alveoli and bronchi, resembling bacterial focal bronchopneumonia; 2 lymphocytes, 1 fibrosis, 1 necrosis; additional findings: 1 congestion of small vessels; 2 thrombi; 1 focal neutrophils. 4 cases without DAD: 4 granulocytic infiltration of the alveoli and bronchi, resembling bacterial focal bronchopneumonia, 2 congestion of small vessels, 2 emphysema, 1 fibrosis	In the 7 cases: pharynx normal. In 1 patient with DAD: acute bronchitis & chronic bronchitis. Patients without DAD: 2 acute bronchitis, 1 chronic bronchitis. In 3 men: vein thrombosis & thrombosis in prostate. Case 1: atherosclerosis
(17), USA, Boston, Prilutskiy *et al.*, *American Journal of Clinical Pathology*, doi: 10.1093/ajcp/aqaa124, Posted May 12 2020, Published 18 July 2020, limited autopsy (chest, abdomen), 2 patients	Case 2: M, 91 y; case 3: M, 72 y. comorbidities not mentioned, death (n=2)	Case 2: day 8; case 3: day 6	Progressive dyspnea. Severe ARDS. High fever, hyperferritinemia and hypertriglyceridemia. Case 2: treatment: HCQ/DOX/AZ; case 3: treatment: CRO/AZ/ sariluma	ICH CD 163 to detect haemophagocytosis. ICH for human herpesvirus-8 (HHV-8), cytomegalovirus, (CMV), and Epstein-Barr virus (EBV) by *in situ* hybridization for EBV small RNA (EBER): negative in lymph nodes with haemophagocytosis	Lungs: cases 2/3: acute exudative phase of DAD. Mediastinal and pulmonary hilar lymph nodes grossly enlarged containing multifocal clusters of hemophagocytic histiocytes localised in the subcapsular sinuses. Lymphophagocytosis was the predominant form of haemophagocytosis. Case 2: probable HLH syndrome. Case 3: follicular and interfollicular hyperplasia	Spleen (case 3): focal hemophagocytosis (areas of red pulp hemorrhage with admixed phagocytic histiocytes) and white pulp depletion
(7), Belgium, Brussels, Remmelink *et al.*, medRxiv 2020;2020.05.27.20114363, posted May 28, 2020, full autopsy, 6 patients (cases 2, 7, 8, 11, 13, 14)	Case 2: F, 91 y, HT, CAD, liver cirrhosis, CRD	Case 2: day 15	Case 2: acute kidney injury, hypoxic hepatitis, ARDS and development of respiratory failure leading to death	Case 2: CT scan: negative; SARS-CoV-2 PCR: positive	Case 2: lungs: early DAD, microthrombi, emphysema, focal lympho-plasmocytic infiltrate, atypical pneumocytes	Cases 13, 14: perivascular chronic inflammatory infiltrate
	Case 7: M, 56 y, no comorbidities	Case 7: day 7	Case 7: respiratory failure	Case 7: CT scan: bilateral consolidation; SARS-CoV-2 PCR: positive	Case 7: lungs: early DAD, late DAD, lung infarct, acute BN, bilateral invasive aspergillosis	
	Case 8: M, 66 y, HT, CAD, DM, cerebrovascular disease, renal failure	Case 8: day 14	Case 8: acute kidney injury, septic shock and multiple organ failure	Case 8: CT scan: emphysema; SARS-CoV-2 PCR: positive	Case 8: lungs: early DAD damage, acute BN, interstitial fibrosis, emphysema	
	Case 11: M, 76 y, DM, liver cirrhosis, cancer	Case 11: day 5	Case 11: ARDS, sudden death	Case 11: CT scan: bilateral consolidation; SARS-CoV-2 PCR: positive	Case 11: lungs: early DAD, hyperplasia of pneumocytes type-II, syncytial multinucleated giant cells	
	Case 13: M, 73 y, DM	Case 13: day 10	Case 13: ARDS and respiratory failure	Case 13: CT scan: ground glass opacity and bilateral consolidation; SARS-CoV-2 PCR: positive	Case 13: lungs: early DAD, acute BN	
	Case 14: F, 77 y, HT, DM Death (n=6)	Case 14: day 9	Case 14: acute kidney injury, hypoxic hepatitis, ARDS and respiratory failure	Case 14: CT scan: ground glass opacity and bilateral consolidation; SARS-CoV-2 PCR: positive	Case 14: lungs: no specific abnormalities; bilateral alveolar edema, bilateral aspiration pneumonia	
(15), Brazil, Sao Paulo, Duarte-Neto *et al.*, *Histopathology* 2020 Aug, doi: 10.1111/his.14160, epub 2020 Jul 24, ultrasound-guided MIA, 3 patients (in total 10 patients, 3 without MV). The clinical & other information not individualized is described here jointly for the 10 patients	Description of the 10 patients (n=2): 69 [33–83]. HT (n=5), DM (n=5), chronic cardiopathy (n=5), COPD (n=3), CRD (n=1), cancer (n=1). Death (n=3)	3 patients without MV: day 3–10	Description of the 10 patients: fever, dyspnoea (n=9), cough (6), diarrhoea, nausea/vomiting (n=2), myalgia, running nose, sore throat (n=1)	Description of the 10 patients: IHC: paucity of CD20+ B cells in all cases and no signs of lymphoid aggregates formation. T cell markers: CD4 and CD8 varied from scarce, especially in the cases with exudative DAD, to moderate, forming small aggregates in the patients with fibroproliferative DAD. CD57+NK cells: sparse in all cases and did not vary according to DAD patterns. CD68+ macrophages present mostly in the alveolar spaces and within areas of tissue remodelling in fibroproliferative areas. Some multinucleated atypical giant-cells were CD68+ alveolar macrophages	Definition of Exudative DAD: intense and diffuse alveolar exudates with hyaline membranes, septal edema, and mild/moderate lymphocytic infiltration. Intense pleomorphic changes on alveolar epithelial cells and also in the airways (giant cells) suggestive of virus cytopathic effects, with diffuse epithelial desquamation. Definition of proliferative DAD: poorly organised fibrous tissue within alveolar septa and alveolar lumen and was more prevalent in patients with long periods of illness and hospitalisation. Lung description in 3 not-MV patients: 3 DAD (2 exudative & proliferative; 1 exudative): 3 CE, 1 alveolar squamous metaplasia, 1 septal lymphocytic inflammation, 1 alveolar SM, 3 arteriolar microthrombi, 3 alveolar megakaryocytes, 2 alveolar haemorrhage, 3 suppurative pneumonia	Organs studied in the 10 patients: liver, heart, kidneys, spleen, brain, skin, skeletal muscle, and testis. Main systemic findings associated with comorbidities, age, and sepsis, in addition to possible tissue damage due to the viral infection. Findings attributed to shock: centrilobular congestion in the liver (10 cases) and acute tubular lesion (n=8 kidney analysed). Findings possibly due to the viral infection: dermatitis-superficial perivascular mononuclear infiltrate (n=8), myositis (n=2), orchitis (in all 2 testicle samples), mild lymphomononuclear myocarditis (n=2), endothelial changes in small vessels (cell tumefaction, vessel wall edema and fibrinoid alteration), small thrombi less frequent in glomeruli (n=6), spleen, heart (n=2), dermis (n=3), testis (n=2), and liver sinusoids (n=1)
(18), USA, New York, Barnes *et al.*, *J Exp Med* 2020, doi: 10.1084/jem.20200652, accepted: 13 April 2020, lung (limited) autopsy, 1 patient	M, 64 y, DM, end-stage renal disease on hemodialysis, heart failure and hepatitis C on ledipasvir/sofosbuvir therapy. Death (n=1)	Day 0 (not well specified). Autopsy performed within 5 h after death	He declined medical intervention, not intubated, died in the emergency room 5 h after presentation, shortly after developing fever. No sepsis. Treatment: ledipasvir/ sofosbuvir therapy	Premortem cultures negative	Extensive neutrophil infiltration in pulmonary capillaries, with acute capillaritis with fibrin deposition, and extravasation into the alveolar space. Neutrophilic mucositis of the trachea	–

Table S1 (*continued*)

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Table S1 (*continued*)

Publication: reference number, country, city, publication date, type of sample, number of patients	Sex, age, risk factors/ comorbidities, outcome	Date histopathology lung after onset of symptoms	Clinical history	Ancillary methods	Main positive pathology lung findings	Findings in other organs
(8), USA, Washington, Lacy *et al.*, *Am J Forensic Med Pathol* 2020, doi: 10.1097/PAF.0000000000000567, accepted April 9, 2020, full forensic autopsy, 1 patient	F, 58 y, type 2 DM, obesity, hyperlipidemia, mild intermittent asthma, chronic lower extremity swelling with ulceration	Day 7	Fever & respiratory, difficulty, self-quarantine, found dead in her bedroom after seen alive the previous night. COD: viral pneumonia due to COVID-19	PM Dacron-tipped swabs in viral transport media from the right and left main bronchi: + PCR for SARS-CoV-2 and – testing for influenza. Bacterial cultures from abnormal lung areas (with consolidation) swabbed with amies medium: + for methicillin-sensitive Staphylococcus aureus and Streptococcus viridans. Given the lack of acute histologic inflammation in the lungs, these bacterial culture results were interpreted as being most likely contaminants or post-mortem artifact	Lung: edema and dense amphophilic concretions along alveolar septae consistent with HM. Lung architecture preserved, and septae of normal thickness, but with mild mononuclear infiltrates. Prominent desquamating pneumocyte hyperplasia with focal multinucleated cells and bizarre forms. Acute alveolar haemorrhage and collections of reactive foamy alveolar macrophages were focally present, as were collections of alveolar fibrin	Heart: myocyte hypertrophy with interstitial and perivascular fibrous tissue but no acute ischemic changes or inflammatory infiltrates. Liver: mild steatosis and central lobular pallor and congestion, but no significant portal or lobular inflammation. Kidney: arteriolosclerosis, mesangial sclerosis and hypercellularity, and focal global glomerulosclerosis. A section of medulla had no inflammatory or ischemic changes. An incidental adrenal cortical nodule and a focus of papillary adenocarcinoma of the thyroid
(9), Switzerland, Zurich, Schweitzer *et al.*, *Forensic Imaging* 2020, doi: 10.1016/j.fri.2020.200378, available online 18 April 2020, forensic autopsy, 1 patient	M, 50 y, HIV. Death (n=1)	Week 5	Absence of fever, absence of dyspnoea and of thoracic pains. In self-quarantine. Found dead at home, a day after his nasopharyngeal swab was positive for SARS-CoV-2, three days after the sample had been taken as an outpatient. The evening of this positivity called the hospital for racing heart. He didn't attend the hospital. After history revision: some mild symptoms stretching over around five weeks	PM CT: features of a severe acute respiratory distress syndrome	Lung: distorted septal and alveolar architecture: congested vessels & edematous fluid. HM. Patchy lymphocytic infiltrates, in part binuclear and trinuclear	Acute liver dystrophy and acute tubular necrosis in the kidneys were found. Coronary artery atherosclerosis
(10), Switzerland, Geneva, Aguiar *et al.*, *Int J Leg Med* 2020, doi: 10.1007/s00414-020-02318-9, accepted: 19 May 2020, full forensic autopsy, 1 patient	F, 31 y, morbid obesity. Death (n=1)	A few days (not specified)	Found dead in her flat during confinement. Cough during the previous days. High fever (rectal temperature of 41.4 ℃, 2 h after death). Only symptomatic treatment (ibuprofen & opioid antitussive sirup) found at the death scene. COVID-19 diagnosis made after death (tracheobronchial swab)	PM CT: diffuse bilateral GGO and panlobar consolidations and air bronchograms. ICH: CD3-positive T cells and megakaryocytes. PM tracheobronchial swab: + SARS-CoV-2; negative for RV. Bacteriology: mixed flora	Lung (summary: DAD and interstitial pneumonia). HP: edema, early-DAD (heterogeneous pattern, mostly affecting the central part of the lungs) with HM, and focal areas of intra-alveolar haemorrhages and bacterial proliferation. Alveolar deposit of fibrin as cotton wools, and moderate type II pneumocytes hyperplasia (mainly desquamated). Moderate intra-alveolar macrophages and only scant PMN and lymphocytes. In the interstitium: edema, vascular stasis, lympho-monocytic infiltrates. Within the alveolar septa and mainly into the capillaries, abundant PMN, indicating margination and diapedesis. Bronchi and bronchioles only minimal lymphocytic infiltrates within their walls	Other organs: chronic tracheitis. Liver: microabscesses. Not cardiac hypertrophy. Death related to COVID-19 pulmonary alterations and high fever
(11), Germany, Tübingen, Bösmuller *et al.*, *Virchows Archiv*, doi: 10.1007/s00428-020-02881-x, published online: 30 June 2020, full autopsy, 1 patient	Case 1: F, 78 y, obesity, HT, cardiac pacemaker due to atrioventricular block. Death (n=1)	Case 1: day 1. Autopsy 48 h after death	Case 1: 12 h period of symptoms: fever, cough, vomiting. Days from admission until death: 1 (home care)	Significant levels of SARS-CoV-2 RNA in the lungs (qRT-PCR), but not in the livers and hearts. qRT-PCR of cytokines in lung tissue revealed a massive increase of IL-1beta and IL-6 mRNA	Case 1: generalized edema, the lower lobes showed florid capillary endotheliitis with increased neutrophils, formation of MT in alveolar capillaries, and small pulmonary vessels, including septal veins. In addition, focal inflammatory exudate with neutrophils and sparse HM with incipient organizing changes but without hyperplasia of alveolar epithelium. COD: early pneumonitis with thrombotic micro-angiopathy resulting in inflammation-associated pulmonary edema and acute cardiac failure	Case 1: liver: moderate acute congestion and activation of Kupffer cells but lacked inflammatory infiltrates
(12), Germany, Hamburg, Fitzek *et al.*, *Rechtsmedizin*, doi: 10.1007/s00194-020-00401-4, published on line: 25 May 2020, autopsy (embalmed body), 1 patient	M, 59 y, slightly obesity, probably HT, cardiac hypertrophy and marked, cor adiposum (only identified by the autopsy)	Day 6	Infection during a journey to Egypt. Sudden flickering of his eyes. Chills and dizziness, coughing. GI symptoms. Dizziness, coughing and general exhaustion. Decompensation of the CV system. No medical documentation available, antibiotics, invasive treatment: only oxygen administration	CT scan: bilateral moderate pleural effusions and global multifocal reticular consolidation; subpleural milky glass opacities with ground-glass density nodules. Artifacts not ruled out due to embalming. PM detection of SARS-CoV-2 in lung, pharyngeal mucosa and pharyngeal swab	Lung: ubiquitous HM, vascular compressions and microthrombi, DAD. Protein-rich edema with low -grade lymphocyte infiltration	Trachea: haemorrhagic tracheobronchitis. Heart: congestive cardiomyopathy (heart weight of 600 g) a cor adiposum. GI: moderate inflammatory cells in the intestinal wall
(21), Italy, Rome, Pernazza *et al.*, *Virchows Archives* 2020, doi: 10.1007/s00428-020-02829-1, 26 Apr 2020, biopsy (lung tumor excision), 1 patient	M, 61 y, smoking. Full remission of a MALT lymphoma. Lung adenocarcinoma. Alive (n=1)	Day 0	Asymptomatic, afebrile. Elective lobectomy for lung adenocarcinoma. After surgery: cough, dyspnea, fatigue, and high fever. Treatment: meropenem and Bactrim), antiviral drugs: acyclovir, darunavir, tocilizumab; HCLOR. Supplemental oxygen through a CPAP mask	Pharyngeal swab positive for SARS-CoV-2 on PCR (during life)	Lung: early changes in parenchyma surrounding the neoplasia: diffuse hemorrhages, clusters of alveolar macrophages, occasional multinucleated cells, loss and reactive pneumonocyte hyperplasia, with nuclear inclusions. No HM or DAD. The interstitium showed edema & mild inflammatory infiltrate mainly composed of cytotoxic (CD8+) T lymphocytes. Occasional fibrous and mild fibrous thickening of subpleural alveolar septa. Scanty fibrin depositions on the alveolar surfaces	Smoking-related interstitial fibrosis
(19), China, Beijing, Xu *et al.*, *Lancet Respir Med* 2020, doi: 10.1016/S2213-2600(20)30076, 8 Apr 2020, post-mortem biopsies, 1 patient	M, 50 y, travel history to Wuhan	Day 14	Fever, chills, dried cough, fatigue, and shortness of breath 8 days before admission. He refused ventilator support in the ICU repeatedly because of claustrophobia. Therefore, he received high-flow nasal cannula (HFNC) oxygen therapy (60% concentration, flow rate 40 L/min). On day 13 of illness, symptoms had still not improved, but oxygen saturation remained above 95%. The day 14 of illness, his hypoxaemia and shortness of breath worsened. Despite receiving HFNC oxygen therapy (100% concentration, flow rate 40 L/min), oxygen saturation decreased to 60%, and he had sudden cardiac arrest with an. Rescue unsuccessful rescue. Treatment: interferon alfa-2b lopinavir + ritonavir, moxifloxacin, methylprednisolone	SARS-CoV-2 PCR +: day 9 of illness. Flow cytometry peripheral CD4 & CD8 T cells substantially reduced but hyperactivated. High proportions of HLA-DR (CD4 3·47%) and CD38 (CD8 39·4%) double-positive fractions. Increased concentration of highly pro-inflammatory CCR6+ Th17 in CD4 T cells and high cytotoxicity of CD8 T cells	Lungs: bilateral DAD (exudative phase), cellular fibromyxoid exudates, desquamation of pneumocytes & HM, indicating acute respiratory distress syndrome. Pulmonary edema. Interstitial lymphocytic infiltrates and multinucleated syncytial cells with atypical enlarged pneumocytes (with large nuclei, amphophilic granular cytoplasm, and prominent nucleoli) in the intra-alveolar spaces, showing viral cytopathic-like changes. No intranuclear or intracytoplasmic viral inclusions	Liver: moderate microvesicular steatosis and mild lobular and portal activity due to primary or secondary drug effect. Heart: few interstitial mononuclear inflammatory infiltrates
(13), China, Chongqing, Yao *et al.*, *Cell Research* 2020, doi: 10.1038/s41422-020-0318-5, published online: 28 April 2020, autopsy, 1 patient	F, 78 y, no comorbidities except contact with COVID-19 patient 2 days before admission. Death (n=1)	Day 16	Admitted to hospital due to falling-resulted trauma. Exposed to a COVID-19 patient 2 days before. Two days after admission, the patient showed pneumonia symptoms. Four days a after the onset of illness: + PCR SARS-CoV-2 confirmation (NP swab). Day 5: chest CT scan: multiple patchy shadows in both lungs, implying pulmonary infection. From day10th to 12th: 3 negative NP PCR tests. Day 15: chest CT: relief. Day 16 after the onset: When she was ready for discharge, she fell suddenly into fatal condition with cardiac arrest, and died. Leukopenia. Treatment: lopinavir, interferon alfa-1b, Ritonavir. From the 6th day after the onset of symptoms: methylprednisolone & oxygen supplementation (nasal cannula, 5 L/min) (10 days of treatment)	Digital PCR on tissue sections (lung, liver, heart, intestine, and skin): only positive SARS-CoV-2 in the lung. IHC staining (monoclonal antibody against SARS-CoV-2 nucleocapsid): + only in lung. EM: coronavirus particles in both bronchiolar epithelial cells marked by cilia and type II alveolar epithelial cells (type II AE) featured with lamellar body. ICH staining showed that the cell types of infiltrated immune cells in alveolar space and septa were predominantly infiltrating CD68+ macrophages, CD20+ B cells, and CD8+ T cells	Predominant DAD (extensive desquamation of proliferative type II AE, exudation of fibrin, monocytes, and macrophages). Some of alveolar walls were partially lined by low columnar type II AE and covered by the formation of HM in alveolar space. Thickening of alveolar septa with scattered interstitial inflammatory infiltration and hyaline thrombus in microvessels, but no pulmonary edema	Chronic respiratory disease associated changes in the lung tissues
(14), Spain, Alicante, Muñoz-Quirós *et al.*, *Gaceta Intern Cienc For* 2021, forensic autopsy, 1 patient	F, 68 y, liver cirrhosis. Death (n=1)	Day 2	Found at home death. Her husband was COVID-19 +. She refused any analysis. Sudden death		Perivascular interstitial pneumonia with HM lining alveolar spaces, few septal capillary microthrombi capillaries with the presence of lymphocytes, and scarce polymorphonuclear and macrophages with foamy appearance. Areas of type II pneumocyte hyperplasia and areas of intra-alveolar fibrin organization. Bilateral pleural and septal fibrosis, with focal chronic inflammatory infiltrate and associated areas of alveolar hyperdistension. Left lung: areas of exudates of neutrophilic polynuclear cells overlapping alveolar spaces and bronchial lumens with a basal predominance. Diagnosis: interstitial pneumonia with bilateral diffuse alveolar damage and added left pulmonary acute bronchopneumonia	Heart: moderate anterior ventricular adipose infiltration. Liver cirrhosis with marked inflammatory activity

This table includes not mechanical ventilated patients as well as those under CPAP, HFNC, oxygen administration and oxygen supplementation. AE, alveolar epithelia; ARDS, acute respiratory distress, syndrome; AZ, azithromycin; BN, bronchopneumonia; CAD, coronary artery disease; CT, computer tomography, CPAP, continuous positive airway pressure; CRD, chronic renal disease; CRO, ceftriaxone; CVD, cardiovascular disease; DAB, diaminobenzidene; DAD, diffuse alveolar damage; DM, diabetes mellitus; DOX, doxycycline; F, female; HM, hyaline membranes; HT, hypertension; IHC, immunohistochemistry; ICU, intensive care unit; GGO, ground-glass opacity; M, male; MIA, minimally invasive autopsy; MV, mechanical ventilation; PCR, polymerase chain reaction; RV, respiratory virus; Y, years.

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Table S2 Histopathological findings in lung sections from COVID-19 patients on MV longer than 24 hours (6,7,11,15-17,22-28)

Publication: reference number, country, city, publication date type of sample, number of patients	Sex, age, risk factors/ comorbidities outcome	Date histopathology lung after onset of symptoms	Clinical history	Ancillary methods	Main positive pathology lung findings	Findings in other organs
(16), USA, New York, Magro *et al.*, *Transl Res* 2020 Apr 15. doi: 10.1016/j.trsl.2020.04.007, 09 Apr 2020, limited autopsies, 1 patient	Case 2: M, 73 y, smoker, obesity, pre-DM. Death (N=1)	Case 2: day 5	Respiratory failure (n=5) and purpuric skin rash (n=3). Case 2: evaluated at the ED by respiratory distress; fever, tachypnea, severely hypoxemic, required emergent endotracheal intubation. On day 4th of MV developed thrombocytopenia and severe hypercapnia. MV 5 weeks	Staining for SARS-CoV-2 spike & envelope proteins. (IHC) assessment for the deposition of C5b-9, C3d, and C4d via DAB technique. Significant vascular deposits of C5b-9 and C4d. Co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in the inter-alveolar septa and the cutaneous microvasculature. MASP2 staining demonstrated granular and punctate staining localized to the inter-alveolar septa. No other potential pulmonary viral, bacterial nor fungal pathogens	Lungs case 2: pauci inflammatory hemorrhagic pneumonitis, septal capillary injury (activated complement deposits), septal capillary mural and luminal fibrin deposition and permeation of the inter-alveolar septa by neutrophils. Intra-alveolar fibrin deposition. Focal HM formation and type II pneumocyte hyperplasia	
(22), Switzerland, Zurich, Varga *et al.*, *Lancet*, doi: 10.1016/S0140-6736(20)30937-5, 17 Apr 2020, full autopsy, 2 patients	Case 1: M, 71 y, CAD, renal transplant recipient, HT. Death (n=1)	Day 8	Dyspnea, fever, tachycardia, hypotension, and confusion, HT. Treatment: MV (8 days), piperacillin/tazobactam & UFH	In all cases: IHC: caspase 3	Lungs: severe DAD, mononuclear cells and neutrophils in lungs. Thickened lung septa, including a large arterial vessel with mononuclear and neutrophilic infiltration. Other organs: Prominent endotheliitis with recruitment of inflammatory cells, apoptotic bodies in many organs, especially in the pulmonary vessels but also in small bowel and heart. Virus within endothelial cells	EM analysis revealed viral inclusion structures in endothelial cells of the transplanted kidney (glomerula capillary loops)
	Case 2: F, 58 y, type 2-DM, HT, obesity. Death (n=1)	Day 19 (16 days after admission)	Cough, fever, and dyspnea for 3 days at home. Admitted directly to ICU due to progressive respiratory failure. Developed (within the first week) multi-organ failure, requiring MV renal & replacement therapy. On day 16, mesenteric ischemia prompted removal of necrotic small intestine. Circulatory failure occurred in the setting of right heart failure consequent to an ST-segment elevation myocardial infarction, and cardiac arrest resulted in death (8 days after admission). Treatment: MV (lag >8). HCL, empiric antibiotic treatment UHF		Lung: DAD, mononuclear cells, lymphocytic endotheliitis (also in heart, kidney, and liver)	Liver: necrosis. Heart: myocardial infarction but no sign of lymphocytic myocarditis. Small intestine: endotheliitis and many apoptotic bodies of the submucosal vessels with only scattered fibrin thrombi
(28), China, Zhang *et al.*, *Ann Int Med* 2020;172:629-32, doi: 10.7326/M20-0533, transthoracic needle biopsy, 1 patient	M, 72 y, DM, HT. Death (n=1)	Not mentioned	Cough and fever. Rapidly progressive respiratory failure requiring endotracheal intubation and MV (1 week after presentation)	Transthoracic lung biopsy: IHC with antibody to the Rp3 NP protein of SARS-CoV-2 revealed prominent expression on alveolar epithelial cells. In contrast, viral protein expression was minimally detectable on blood vessels or in the interstitial areas between alveoli	Lung biopsy: DAD (organizing phase), reactive type II pneumocyte hyperplasia, intra-alveolar fibrinous exudates, loose interstitial fibrosis, and chronic inflammatory infiltrates. Intra-alveolar loose fibrous plugs of organizing pneumonia, with presence of intra-alveolar organizing fibrin in most foci	
(6), Germany, Hamburg, Wichmann *et al.*, *Annals Intern Medicine* 2020, doi: 10.7326/M20-2003, 6 May 2020, full autopsy, 5 patients with MV	Case 3: M, 71 y, HT, smoker, granulomatous pneumopathy Case 4: M, 63 y, type 2 DM, obesity, bronchial asthma Case 7: F, 75 y, atrial fibrillation, CAD, smoker Case 11: M, 85 y, CAD, HT, bronchial asthma, atrial fibrillation Case 12: M, 76 y, obesity Death (n=5)	Not mentioned. PMI 4 days	Case 3: respiratory failure, pneumoniae Case 4: cardiorespiratory failure, pulmonary emboli Case 7: respiratory failure, viral pneumonia Case 11: cardiac arrest, respiratory failure Case 12: pulmonary emboli Treatment: catecholamine therapy 1 patient; AB + AC (n=1); AB (n=1); AC (n=1); 1 none. Lag of stay on MV: not mentioned. NIV (method not specified		Lungs. 5 patients with DAD: 5 activated pneumocytes, 2 fibroblasts, 1 fibrosis, 5 HM, 1 GC, 3 with SM, 1 LC and 3 with thrombi. Additional findings: 2 haemorrhagic infarctions, 2 emphysema, 2 congestion of small vessels, granulocytic infiltration, 1 plasma cells	In the 4 cases: pharynx normal and veins thrombosis; in 2 of them: thrombosis in prostate. Left cardiac dilatation, calcification of the mitral ring, cardiac pacemaker, atherosclerosis
(17), USA, Boston, Prilutskiy *et al.*, *Am J Clin Path*, doi: 10.1093/ajcp/aqaa124, posted May 12 2020, published 18 July 2020, limited autopsy (chest, abdomen), 2 patients	Comorbidities not mentioned. Case 1: M, 72 y; case 4: F, 64 y. Death (n=2)	Case 1: day 18; case 4: day 15	Progressive dyspnea. Severe ARDS. High fever, hyperferritinaemia and hypertriglyceridemia. Case 1: HCL, AZ, anakinra, intubation time: from 7 d to 18 (11 days on MV). Case 4: sarilumab, CRO. MV: from day 12 to 15	ICH CD 163 to detect haemophagocytosis. ICH for human herpesvirus-8 (HHV-8), cytomegalovirus, (CMV), and Epstein-Barr virus (EBV) by *in situ* hybridization for EBV small RNA (EBER): negative in lymph nodes with haemophagocytosis	Lung: (cases 1, 4): acute exudative phase of DAD. Case 1: mediastinal and pulmonary hilar lymph nodes grossly enlarged with multifocal clusters of hemophagocytic histiocytes. Marked distention of cortical and subcortical sinuses with focal necrosis as well as lymphocyte depletion. Lymphophagocytosis was the predominant form of haemophagocytosis. Definite HLH syndrome. Case 4: no haemophagocytosis	
(7), Belgium, Brussels, Remmelink *et al.*, posted May 28, 2020, doi: 10.1101/2020.05.27.20114363, full autopsy, 11 patients	Case 1: M, 77 y, CAD, cerebrovascular disease, DM	Median time from admission to death was 13 days. Case 1: day 3	Case 1: ARDS, acute kidney injury, multiple organ failure, cardiogenic shock	8 patients with viral presence in all tested organs (lung, heart, spleen, liver, colon, kidney and brain). Case 1: CT thorax: negative; SARS-CoV-2 PCR: positive	Case 1: lung: early DAD, lung microthrombi, acute BN, atypical pneumocytes	No specific SARS-CoV-2 lesions were observed in any organ using RT-PCR, SARS-CoV-2 could be detected in all organs, even those without evident microscopic lesions. As some patients died outside the ICU without undergoing mechanical ventilation, we could not estimate lung compliance before death
	Case 3: M, 68 y, cancer, COPD	Case 3: day 15	Case 3: ARDS, acute kidney injury, respiratory failure	Case 3: CT thorax: GGO; SARS-CoV-2 PCR: positive	Case 3: lung: early DAD, lung microthrombi, emphysema	
	Case 4: F, 64 y, HT, cerebrovascular disease, cancer	Case 4: day 8	Case 4: ARDS, respiratory failure	Case 4: CT thorax: minor abnormalities; SARS-CoV-2 PCR: positive	Case 4: lung: early DAD, lung microthrombi, emphysema, atypical pneumocytes	
	Case 5: M, 56 y, COPD, cancer	Case 5: day 14	Case 5: ARDS, acute kidney injury, hypoxic hepatitis, multiple organ failure, mesenteric ischemia. ECMO	Case 5: CT thorax: GGO; SARS-CoV-2 PCR: positive	Case 5: lung: early DAD, lung microthrombi, lung infarct, acute BN	
	Case 6: M, 73 y, HT, CRD	Case 6: day 11	Case 6: ARDS, acute kidney injury, respiratory failure ECMO	Case 6: CT thorax: bilateral consolidation; SARS-CoV-2 PCR: positive	Case 6: lung: early DAD, late DAD, lung microthrombi, acute BN, atypical pneumocytes	
	Case 9: F, 49 y, HT, DM	Case 9: day 17	Case 9: ARDS, acute kidney injury, respiratory failure	Case 9: CT thorax: GGO; SARS-CoV-2 PCR: positive	Case 9: lung: early DAD, lung microthrombi, late DAD	
	Case 10: M, 63 y, HT, DM	Case 10: day 16	Case 10: ARDS, acute kidney injury, respiratory failure. ECMO	Case 10: CT thorax: GGO; bilateral consolidation, SARS-CoV-2 PCR: positive	Case 10: lung: early DAD, lung microthrombi, hyperplasia of pneumocytes type-II, syncytial multinucleated giant cells	
	Case 12: M, 75 y, HT, CAD, DM	Case 12: day 5	Case 12: ARDS, acute kidney injury, hypoxic hepatitis, multiple organ failure	Case 12: CT thorax: GGO; SARS-CoV-2 PCR: positive	Case 12: lung: early DAD, lung microthrombi, acute BN, late DAD, syncytial multinucleated giant cells	
	Case 15: M, 61 y, no comorbidities	Case 15: day 31	Case 15: ARDS, acute kidney injury, pulmonary embolism, multiple organ failure, septic shock	Case 15: CT thorax: GGO; lobar pneumonia, SARS-CoV-2 PCR: positive	Case 15: lung: early DAD, lung microthrombi, lung infarct, late DAD	
	Case 16: F, 70 y, HT, DM, liver tx	Case 16: day 19	Case 16: ARDS, acute kidney injury, pulmonary embolism, multiple organ failure, septic shock	Case 16: CT thorax: GGO; bilateral consolidation, SARS-CoV-2 PCR: positive	Case 16: lung: early DAD, lung microthrombi, late DAD, hyperplasia of pneumocytes type-II	
	Case 17: M, 53 y, HT, cerebrovascular disease	Case 17: day 13	Case 17: ARDS, acute kidney injury, pulmonary embolism, multiple organ failure, septic shock. ECMO	Case 17: CT thorax: GGO bilateral consolidation, lobar pneumonia; SARS-CoV-2 PCR: positive	Case 17: lung: acute BN, late DAD	
	Death (n=11)					
(15), Brazil, Sao Paulo, Duarte-Neto *et al.*, *Histopathology* 2020 Aug. doi: 10.1111/his.14160, epub 2020 Jul 24, ultrasound-guided MIA, 7 patients MV (of a total of 10 patients)	Description of the 10 patients (n=2): 69 [33–83], HT (n=5), DM (n=5), chronic cardiopathy (n=5), COPD (n=3), CRD (n=1), cancer (n=1). Death (n=7)	7 patients: ICU with MV. Onset symptoms-death: day 5–16. Three patients died within 24 hours of hospitalisation	Information in Table 1	Information in Table 1	Definitions in Table 1. Lungs: 7 patients: 6 with exudative/proliferative DAD; 1 exudative DAD. 7 cytopathic effects, 5 alveolar squamous metaplasia, 7 septal lymphocytic inflammation, 5 arteriolar MT, 1 with a high density of alveolar megakaryocytes, 1 alveolar haemorrhage, 3 suppurative pneumonia. 5 alveolar SM	Information in Table 1

Table S2 (*continued*)

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Table S2 (*continued*)

Publication: reference number, country, city, publication date type of sample, number of patients	Sex, age, risk factors/ comorbidities outcome	Date histopathology lung after onset of symptoms	Clinical history	Ancillary methods	Main positive pathology lung findings	Findings in other organs
(11), Germany, Tübingen, Bösmuller *et al.*, *Virchows Archiv*, doi: 10.1007/s00428-020-02881-x, published online: 30 June 2020, full autopsy, 3 patients (1 one of them on ECMO)	Case 2: M, 79 y, CAD, HT, type 2-DM, obesity and Parkinson's disease	Case 2: 3 weeks. Autopsy within 24 after death	Case 2: general weakness for 3 weeks, fever, & dry cough; worsening symptoms during the last 3 days before admission. Intubated due to respiratory failure. Neg. blood cultures for bacteria or fungi. Despite improvement in the next 2 days, then, IL-6 and D-dimer concentrations peaked, whereas thrombocytopenia worsened despite AC. Within 24 h, multi-organ failure & vasoplegic shock and death (4 days after peak of D-dimer concentration). Treatment: vasopressor, ORT & AC. 8 days MV (days in ICU). Days from admission until death: 9	EM: in both patients: viral particles in pulmonary endothelial cells; in patient 2: also in pneumocytes type 1. In patient 3: also in vacuoles within the interstitial space IL-1 beta and IL-6 mRNA were not increased in lung tissue in any patient. All patients: significant levels of SARS-CoV-2 RNA in the lungs (qRT-PCR), but not in the livers and hearts (in fresh samples-unfixed)	Case 2: edema. DAD with extensive intra-alveolar fibrin deposits with formation of HM, marked hyperplasia and desquamation of alveolar epithelium, and accumulation of macrophages with frequent multinuclear GC. Areas of organized DAD especially in lower lobes, with proliferation of fibroblasts and early collagen fibre deposits within the intra-alveolar exudate. Macroscopically visible thrombi mainly in small to medium-sized pulmonary vessels, both arteries and veins. Focally massive accumulation of leukocytes in medium-sized vessels, but florid neutrophilic capillaritis was absent	Case 2: liver: significant activation of macrophages with signs of, but no necrosis or inflammatory infiltrates
	Case 3: M, 72 y, CAD, HT, Merkel cell carcinoma under radiotherapy, obesity, polymyalgia rheumatica	Case 3: no specification of the lag from onset until death. Autopsy within 24 after death	Case 3: syncope, fever, cough, and emesis. Transferred to the ICU and intubated 4 days after admission with worsening respiratory symptoms and recurrent fever. Despite improving of oxygenation, the day 6 after ICU admission, acute hypercapnia & pulmonary superinfection with Klebsiella oxytoca. Treatment: meropenem therapy was started. Renal and liver failure, ORT (renal) was initiated, but he died 10 days after admission to ICU due to liver failure. Days from admission until death: 16; 11 days with MV		Case 3: macroscopically identifiable thrombi in pulmonary vessels. Advanced DAD, with extensive HM and intra-alveolar macrophage accumulations with multiple GC and pronounced, in part atypical hyperplasia of alveolar epithelium with focal squamous metaplasia and areas of organizing pneumonia. Neutrophils were infrequent arguing against bacterial superinfection	Case 3: no HP description of other organs
	Patient 4: M, 59 y, HT, intrinsic asthma, obesity	Case 4: day 14. Autopsy within 24 after death	Case 4: respiratory symptoms 2 weeks prior admission. Admitted to the ICU of a peripheral hospital and transferred to a big hospital 6 days later for his respiratory failure and started on ECMO. Dialysis. Two episodes with marked increase in D-dimer levels, the second 4 days before his death.35 days in the ICU. 24 days on ECMO. He expired due to terminal ARDS and multi-organ failure 6 weeks since the beginning of his symptoms. Days at ICU: 35 (24 on ECMO). Days from admission until death: 35		Case 4: longstanding ARDS in organizing stage with extensive fibrinous exudates, diffuse thickening of alveolar septae, massive hyperplasia of alveolar and bronchial epithelium with focal squamous metaplasia, and typical concentrically layered plugs of loose connective tissue with concentrically arranged fibroblasts and central accumulation of inflammatory cells (lymphocytes) filling alveolar spaces	Case 4: cardiomegaly; signs of liver damage; intestinal mucositis and haemorrhage
	Death (n=3)					
(23), USA, Michigan, Ann Arbor, *Konopka Chest* 2020;158:e99-e101.28, doi: 10.1016/j.chest.2020.04.032, Published online 2020 Apr, autopsy, 1 patient	M, 37 y, type-2 DM, asthma. Death (1)	Day 9	Admitted to hospital after 1-day history of fever, non-productive cough, and myalgias. On admission: CT chest with multifocal GGO. Progressive hypoxemia and ARDS. Treatment: Intubation and MV on hospital day 4. HCL, piperacillin/tazobactam, vancomycin, CRR. Lag MV: 6		Lung: DAD in distal alveolated lung tissue, with patchy mild interstitial thickening by edema, focal pneumocyte hyperplasia, and scattered HM. Rare fibrin thrombi within small vessels and a small muscular pulmonary artery (endothelial injury). This was accompanied by a mild patchy fibrinous airspace exudate in which mononuclear inflammatory cells predominated with scattered neutrophils. The inflammatory infiltrate was limited to distal airspaces without involvement of bronchi or bronchioles (probably early BN). Proximal airways: paucicellular mucus plugs, but without tissue eosinophilia	Findings probably due to the patient's history of asthma: Goblet cell metaplasia, mucus gland hyperplasia, and thickening of subepithelial basement membranes in cartilaginous and non-cartilaginous airways (mucus plugs) no evidence of hyperinflation/air trapping, the anticipated finding in patients who die of status asthmaticus
(26), USA, Texas, San Antonio, Yan *et al.*, *Arch Pathol Lab Med* 2020, doi: 10.5858/arpa.2020-0217-SA, "Minimalistic" (limited) autopsy (brain not extracted, except the heart, organs biopsied *in situ*), 1 patient	F, 44 y, obesity. Additional history: probable undiagnosed immunological disorder such as systemic lupus erythematosus. Death (n=1)	Day 13	One week history of fever, cough & dyspnoea. Invasive MV with endotracheal intubation due to worsening hypoxia, ARDS, severe multi-organ failure. Treatment: HCL, azithromycin, tozilizumab (one dose) (6 days of hospitalization and MV). Initial 12-lead ECG: sinus tachycardia along with slow R wave progression from V2 and V3; no ST-segment elevation. Transthoracic echocardiogram: severe septal, mid and mid-inferior hypokinesis; apical and infero-lateral wall motion was preserved. Mildly to moderately depressed left ventricular systolic function with an estimated left ventricular ejection fraction of 40–45%. Dx: reverse Takotsubo cardiomyopathy with clinical suspicion of viral myocarditis	Chest Rx: patchy bilateral airspace peripheral opacities that progressively worsened over the course of her admission. EM lung: structures consistent with viral capsids. Positive ANA result though with a very low titre of 1:40	Lung: extensive and markedly severe acute lung injury consistent with viral pneumonia (diffuse interstitial lymphocytic infiltrates and fibrinous exudates, DAD with HM, pulmonary infarction, severe edema, extensive desquamation of pneumocytes with intra-alveolar aggregation (resembling multinucleated giant cells), and pneumocyte morphological alterations suspicious for viral cytopathic, though marked reactive pneumocyte hyperplasia couldn't be entirely excluded. No microthrombi in lungs. Pulmonary blood vessels: extensive and widespread perivascular lymphocytic cuffing with a few foci of lymphocytic infiltration within vessel walls without fibrinoid necrosis, consistent with non-necrotizing lymphocytic vasculitis	Heart: myxoid edema, mild myocyte hypertrophy, and focal nuclear pyknosis. Notably, rare foci with few scattered CD45+ lymphocytes were identified in the left ventricular papillary muscle, though no definitive findings of acute or chronic myocyte necrosis. Kidney: unremarkable
(27), China, Jiangsu, Chen *et al.*, *Chin Med J*, 10.1097/CM9.0000000000000839, biopsy of lung explant (patient alive), 2 patients (from a total of 3 patients)*. *, a third case not included here as HP findings not detailed in the paper	Case 1 (also described at Luo WR): M, 66 y, HT. Case 2: M, 58 y, HBV infection. Alive (case 2), death (case 1)	Case 1: day 42; case 2: day 37 (until LT)	Post-COVID-19 patients with pulmonary fibrosis-related ARDS leading to an irreversible pulmonary injury undergoing LT. Pre-LT chest imaging confirmed pulmonary consolidation with fibrotic change. Anti-viral drugs. Tracheostomies previously performed time under MV pre-LT: 27 & 22 days. ECMO days pre-LT: 15 & 7. Case 1: high fever and cough after coming back from Wuhan on January 4, 2020. He developed respiratory failure and septic shock during the treatment and was done with transplant. Case 2: survival	Case 1: virus-negative in: nasopharynx, BAL, and sputum. Case 2: nasopharynx BAL, sputum, and serum. Explanted lung virology. Mild positive in both patients	Case 1: parenchyma: extensive pulmonary interstitial fibrosis with hyaline degeneration. Intrapulmonary vessels: occluded vessel lumen with microthrombosis (vascular and fibrotic patterns). Interstitial infiltration of inflammatory cells including lymphocytes, plasma cells and mononuclear cells (focal monocytes). Alveolitis with edema, proliferation, atrophy, desquamation and squamous metaplasia of epithelial cells (mainly type II). Atrophy, vacuolar degeneration, proliferation, multinucleate giant cells and intracytoplasmic viral inclusion bodies. Case 2: parenchyma: extensive pulmonary interstitial fibrosis and alveolar haemorrhage. Intrapulmonary vessels: Intravascular organized thrombosis and vasculitis (vascular & fibrotic patterns)	
(24), China, Beijing, Shao *et al.*, *Human Pathol* 2020, doi: 10.1016/j.humpath.2020.04.015, available online 11 May 2020, autopsy, 1 patient, 65 y, no comorbidity, visited Wuhan 8 days ago. Death (n=1)	Day 21	Fever (38.6 ℃) and dry cough since 4 days. On day 9, after admission, the chest computed tomography scan showed diffuse GGO in the patient's bilateral lungs. On day 11, worsening of respiratory symptoms & diagnosis of type I respiratory failure, coinciding with kidney injury, and type II respiratory failure occurred, coupled with multiorgan failure including the heart and liver. Day 12: intubation & ventilation support (9 days on MV). He died on day 21 with the diagnosis of septic shock. Treatment: methyl prednisolone, biapenem	On admission: NSP swab + SARS-CoV-2 tests were negative since day 13. IHC in lung for SARS-CoV-2 N protein negative. PAS, GMS, and CMV IHC staining was negative, excluding secondary fungi or CMV infection	Lung: DAD in the early organizing phase with focal HM, intra-alveolar edema, reactive type II pneumocyte hyperplasia, and focal intra-alveolar fibrosis. Extensive acute alveolitis with numerous intra-alveolar neutrophils, lymphocyte, and macrophage infiltrations. Multinucleated giant cells. Microthrombi in the dilated pulmonary capillaries. Purulent discharge in most of the areas of the alveolar spaces (probably due to a secondary bacterial infection, but, unfortunately, respiratory and blood cultures for bacteria and other organisms were not performed	
(25), Spain, Valencia, Navarro Conde *et al.*, *Rev Esp Patol* 2020;53:188-92, doi: 10.1016/j.patol.2020.04.002, accepted: 29 April 2020, available online 11 May 2020, autopsy, 1 patient	M, 69 y, non-invasive urothelial carcinoma of the bladder. Death (n=1)	Undetermined time with symptoms (but with a previous visit to an ED) previous admission. 2 days from admission to death	Fever (38 ℃), dyspnoea, cough and hypoxia without acidosis. Previous diagnosis: common cold &discharged with symptomatic treatment. Antibiotic treatment with levofloxacin and ceftriaxone. Non-invasive MV up to 90% FiO_2 since admission. Poor evolution, he was transferred to the ICU 2 days after admission, where he died four hours later in shock with renal failure	Chest-X-ray: bilateral interstitial infiltrate with a ground glass appearance involving the inferior lobes. CT angiogram: no pulmonary thromboembolism. COVID-19 diagnosis confirmed by RT-PCR assay on a throat swab sample taken during the patient's admission. The positive result was reported fifteen days subsequent to autopsy. PCR respiratory viruses: negative. IHC neg for: herpes simplex virus, cytomegalovirus and Epstein-Barr virus	Lung: pathological changes in 80% of the parenchyma. Large areas of DAD: edema and intra-alveolar haemorrhage, desquamation of type II pneumocytes and HM & thrombi in the medium sized vessels. Abundant intra-alveolar macrophages and occasional multinucleated giant cells. Vesicular nuclei with prominent nucleoli suggestive of viral cytopathic involvement in both pneumocytes and macrophages. Cells with large, hyperchromatic nuclei, similar to smudge cells described in adenovirus related pneumonitis. No intra-alveolar organized fibrin similar to that found in acute pneumonia was seen. 30% of the pulmonary parenchyma findings were consistent with the proliferative phase of DAD. Pneumocytic hyperplasia and myofibroblastic proliferations contributed to widening of alveolar septa. No collagen fibrosis; squamous pneumocytic metaplasia was evident. The inflammatory component consisted of a mild lymphoid infiltrate with abundant macrophages. Areas of emphysema	

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