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

Veroniek Saegeman[1,2#], Marta C. Cohen[3#], Lydia Abasolo[4], Jordi Rello[5,6,7*], Benjamin Fernandez-Gutierrez[8*], Amparo Fernandez-Rodriguez[9]

[1]Department of Microbiology and Infection Control, Vitaz, Sint-Niklaas, Belgium; [2]Department of Infection Control, University Hospitals, Leuven, Belgium; [3]Histopathology Department, Sheffield Children's NHS FT, Sheffield, UK; [4]Rheumatology Department, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IDISSC), Hospital Clínico San Carlos, Madrid, Spain; [5]Clinical Research/Epidemiology in Pneumonia & Sepsis (CRIPS), Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain; [6]Centro de Investigación Biomédica En Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain; [7]Clinical Research, CHRU Nimes, Nimes, France; [8]Rheumatology Department, Hospital Clinico San Carlos, Madrid, Spain; [9]Microbiology Laboratory, Biology Department, Instituto Nacional de Toxicología y Ciencias Forenses, Las Rozas de Madrid, Madrid, Spain

Contributions: (I) Conception and design: J Rello, B Fernandez-Gutierrez, MC Cohen; (II) Administrative support: A Fernandez-Rodriguez, V Saegeman; (III) Provision of study materials or patients: A Fernandez-Rodriguez, V Saegeman; (IV) Collection and assembly of data: A Fernandez-Rodriguez, V Saegeman; (V) Data analysis and interpretation: A Fernandez-Rodriguez, V Saegeman, MC Cohen, B Fernandez-Gutierrez, L Abasolo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

[*]These authors contributed equally to this work as senior authors.

Correspondence to: Amparo Fernandez-Rodriguez. Microbiology Laboratory, Biology Department, Instituto Nacional de Toxicología y Ciencias Forenses, Las Rozas de Madrid, Madrid, Spain. Email: amparo.fernandezrodriguez@justicia.es.

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

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"

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,

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

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

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

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

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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