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Lung Histopathology in Coronavirus Disease 2019 as Compared With Severe Acute Respiratory Sydrome and H1N1 Influenza

A Systematic Review

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e-Appendix 1.

Supplemental Material:

COVID-19 Case Series: The Massachusetts General Hospital Experience

The following is a summary of the clinical and histopathologic findings among the first five autopsies performed on patients who died due to COVID-19 related respiratory failure at Massachusetts General Hospital. The patients' next of kin consented to autopsy at the time of death, and the use of these data for research purposes was approved by the Partners Institutional Review Board (Protocol #2020P001146). For each case, 50 sections of lung tissue were submitted for microscopic examination (10 sections each of the 5 lobes per MGH COVID-19 autopsy protocol).

Case 1:

A 76-year-old woman with a history of diabetes, hypertension, psoriasis on methotrexate, and obesity presented to the emergency department from her assisted living facility for lethargy, chills, and hypoxemia. Several residents of the facility had been recently diagnosed with COVID-19. She was found to be febrile (38.1°C) and tachypneic, and required 2 liters per minute of oxygen via nasal canula. Chest computed tomography was notable for ill-defined, peripheral ground glass opacities in the left upper lobe and bilateral perihilar regions, and a nasopharyngeal swab was positive for SARS-CoV-2 via polymerase chain reaction. She was admitted to the inpatient medical service and treated with hydroxychloroquine, ceftriaxone, and azithromycin. Her oxygenation worsened over the ensuing 24 hours, and conversations between her family and her care team confirmed that she would not want to be intubated. Comfort-focused care continued, and she passed away peacefully with family at her bedside 5 days later from progressive hypoxemic respiratory failure.

Grossly at autopsy, the lungs showed patchy foci of consolidation. On microscopic examination, both lungs exhibited a broad area of architecturally preserved alveolar parenchyma with thick hyaline membranes

(Figures 3A and 3B) and epithelial denudation. In addition, alveolar walls showed increased cellularity with spindled fibroblast-like cells in some areas. Fibromyxoid proliferation was also seen within rare alveolar spaces (Figure 3C) consistent with acute (exudative) to early organizing (proliferative) phases of diffuse alveolar damage (DAD). There were no unequivocal viral cytopathic changes in the 50 examined sections and only rare multinucleated giant cells were identified, while immunohistochemistry for SARS nucleocapsid protein highlighted numerous alveolar macrophages and pneumocytes (Figure 3D) supporting the SARS-CoV-2 infection. Inflammation was limited to perivascular chronic inflammatory aggregates and fibrin thrombi were rare. Additional features included a focus with neutrophilic infiltrates in alveolar spaces, mucus plugs, and reactive bronchial epithelial changes consistent with focal, superimposed bronchopneumonia.

Case 2:

A 76-year-old man with a history of metastatic bladder cancer status post radical cystoprostatectomy, prior pulmonary embolism, and paroxysmal atrial fibrillation on warfarin was admitted after presenting with 7-10 days of cough and nasal congestion and 3 days of fever, sore throat, myalgias and fatigue. Chest imaging was notable for bilateral hazy groundglass opacities. He was admitted to the medicine floor where he was found to be SARS-CoV-2 positive. Within 24 hours, he developed progressive hypoxemic respiratory failure necessitating intubation. He was managed with low tidal volume ventilation, treated with inhaled nitric oxide as part of a clinical trial, received hydroxychloroquine and atorvastatin, and was therapeutically anticoagulated with a heparin infusion. On hospital day 9, he developed hypothermia, bandemia, and worsening hypoxemia and was empirically treated with vancomycin and cefepime for culture negative sepsis. On hospital day 11, he developed hemodynamically significant atrial fibrillation with rapid ventricular response, worsening shock, hypoxemia, and oliguric renal insufficiency. He was started on hydrocortisone 50 mg intravenously every 6 hours and antibiotics were broadened to meropenem. Despite these interventions, his shock and hypoxemia continued to worsen. After conversations with his family, he was transitioned to comfort-focused care, and was palliatively extubated. He passed away on hospital day 12.

Grossly at autopsy, the lungs showed consolidation and hemorrhage. On microscopic examination, the majority of the parenchyma was replaced by poorly organized fibrous proliferation in alveolar walls and within airspaces (Figure 4A), consistent with an organizing (proliferative) phase of DAD. Hyaline membrane formation was limited. While no unequivocal viral cytopathic changes were seen, numerous multinucleated giant cells were present (Figure 4A) and were replacing alveolar epithelial lining focally. Multiple foci with peribronchiolar metaplasia (Figure 4B) suggested recent severe acute lung injury. In addition, both lungs exhibited numerous fibrin thrombi in small pulmonary arteries (Figure 4C) and a focus with parenchymal infarction (Figure 4D) was also noted in the left upper lobe. Large vessel thrombosis was not evident in the gross examination or microscopically examined sections.

Case 3:

A 59-year-old man with a history of hypertension, hyperlipidemia, and diabetes presented with several days of fevers and dry cough. A chest radiograph was notable for bilateral diffuse ground glass and consolidative opacities with peripheral predominance. The patient was intubated in the emergency room for hypoxemic respiratory failure secondary to COVID-19, and was ventilated with a low tidal volume strategy. His ICU course was complicated by multi-pressor shock and a bacterial pneumonia superinfection. He was treated with broad spectrum antibiotics and hydroxychloroquine, but was not enrolled in clinical trials or given other experimental therapies. He subsequently developed hemodynamically destabilizing atrial fibrillation with rapid ventricular response, non-oliguric renal failure, and worsening ARDS despite prone positioning, paralysis, and inhaled nitric oxide. He was cannulated for veno-venous extracorporeal membrane oxygenation (ECMO) following 4 days of mechanical ventilation, with in-circuit CVVH. During cannulation, the patient received an unfractionated heparin bolus of 10 units per kilogram at the time of cannulation followed by a continuous infusion per institutional ECMO protocols. On hospital day 39, ECMO day 5, he developed fixed, dilated pupils with worsening shock, concerning for intracranial hemorrhage and herniation. Following conversations with family, he was transitioned to comfort-focused care and passed away with family at the bedside.

Grossly at autopsy, the lungs were diffusely consolidated. On microscopic examination, alveolar spaces were filled with histiocytes and/or neutrophils in the vast majority of the lung parenchyma (Figure 5A), suggestive of superimposed pneumonia. A region of acute (exudative) DAD, characterized by hyaline membrane formation and edema, was limited to 1 of 50 histologic sections examined.

Case 4:

A 60-year-old woman with a history of diabetes, hypertension, hyperlipidemia, untreated latent tuberculosis, hypothyroidism, fibromyalgia, and several sick contacts presented to the hospital with two weeks of cough, shortness of breath, fever, and myalgias. Upon arrival to the emergency room, her chest imaging was notable for diffuse, patchy, bilateral infiltrates. A nasopharyngeal swab was positive for SARS-CoV-2, and she was intubated for hypoxemic respiratory failure. She was ventilated with a low tidal volume strategy and treated with hydroxychloroquine, atorvastatin, and empiric ceftriaxone and azithromycin for community-acquired pneumonia. She received inhaled nitric oxide as part of a clinical trial, and was ventilated in prone position on hospital day 3 and paralyzed on hospital day 4 for worsening oxygenation. Her ICU course was further complicated by fevers, ventilator-associated pneumonia, shock, acute kidney injury requiring continuous renal replacement therapy, shock liver, and disseminated intravascular coagulation. After discussion with family, in the setting of multiorgan failure, she was transitioned to comfort-focused care and passed away on hospital day 6.

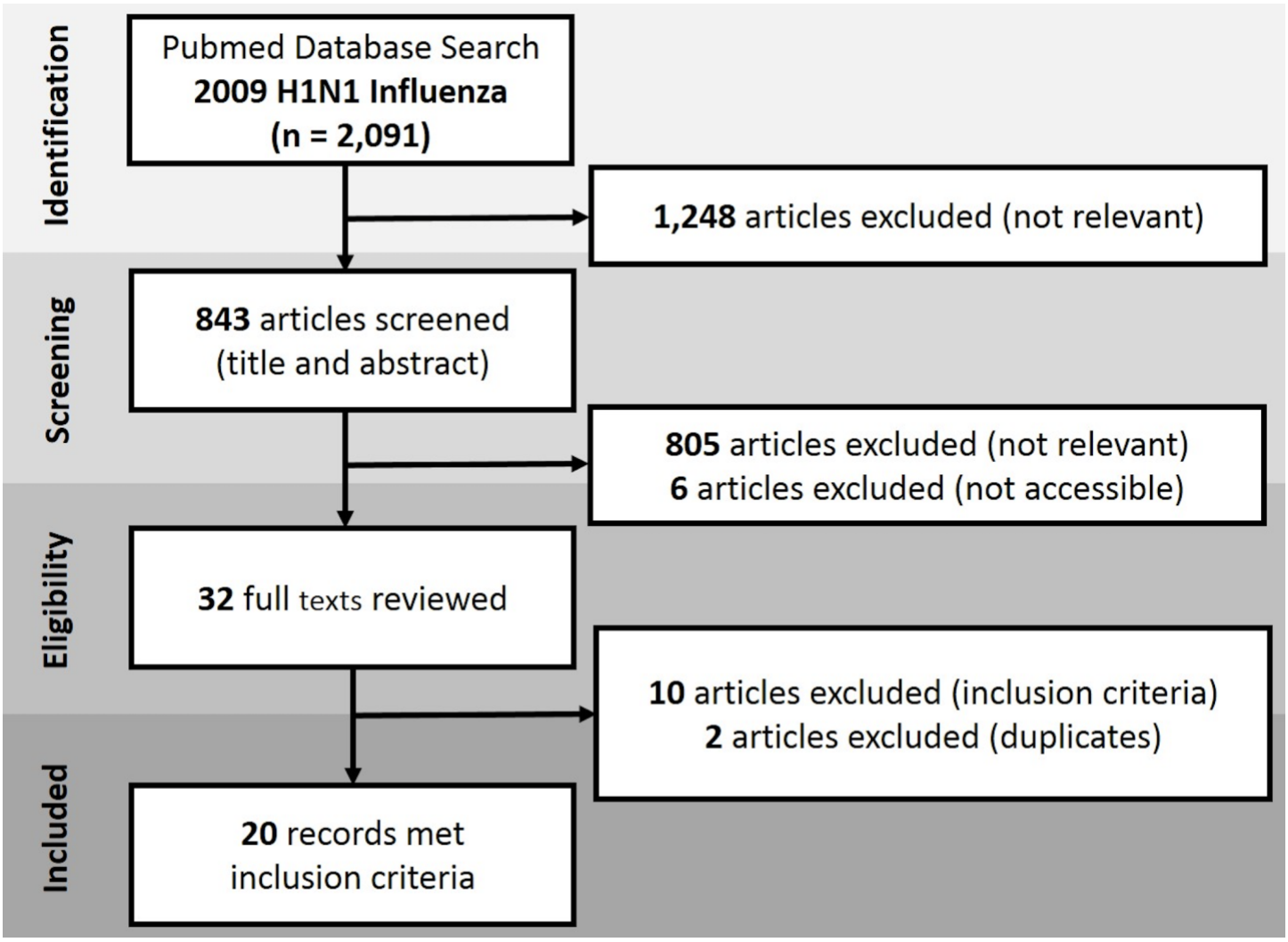
Grossly at autopsy, the lungs were consolidated. On microscopic examination, the lungs exhibited scattered foci with hyaline membranes and rare foci with fibroblast proliferation, consistent with acute (exudative) to early organizing (proliferative) phases of DAD. In some areas, alveolar spaces contained numerous macrophages and denuded pneumocytes, some of which exhibit marked reactive cytologic atypia suggestive of cytopathic changes (Figure 5B). Numerous fibrin thrombi were also identified in small pulmonary arteries. There was marked capillary congestion (Figure 5C) and megakaryocytes in capillaries were significantly increased (Figure 5D).

Case 5:

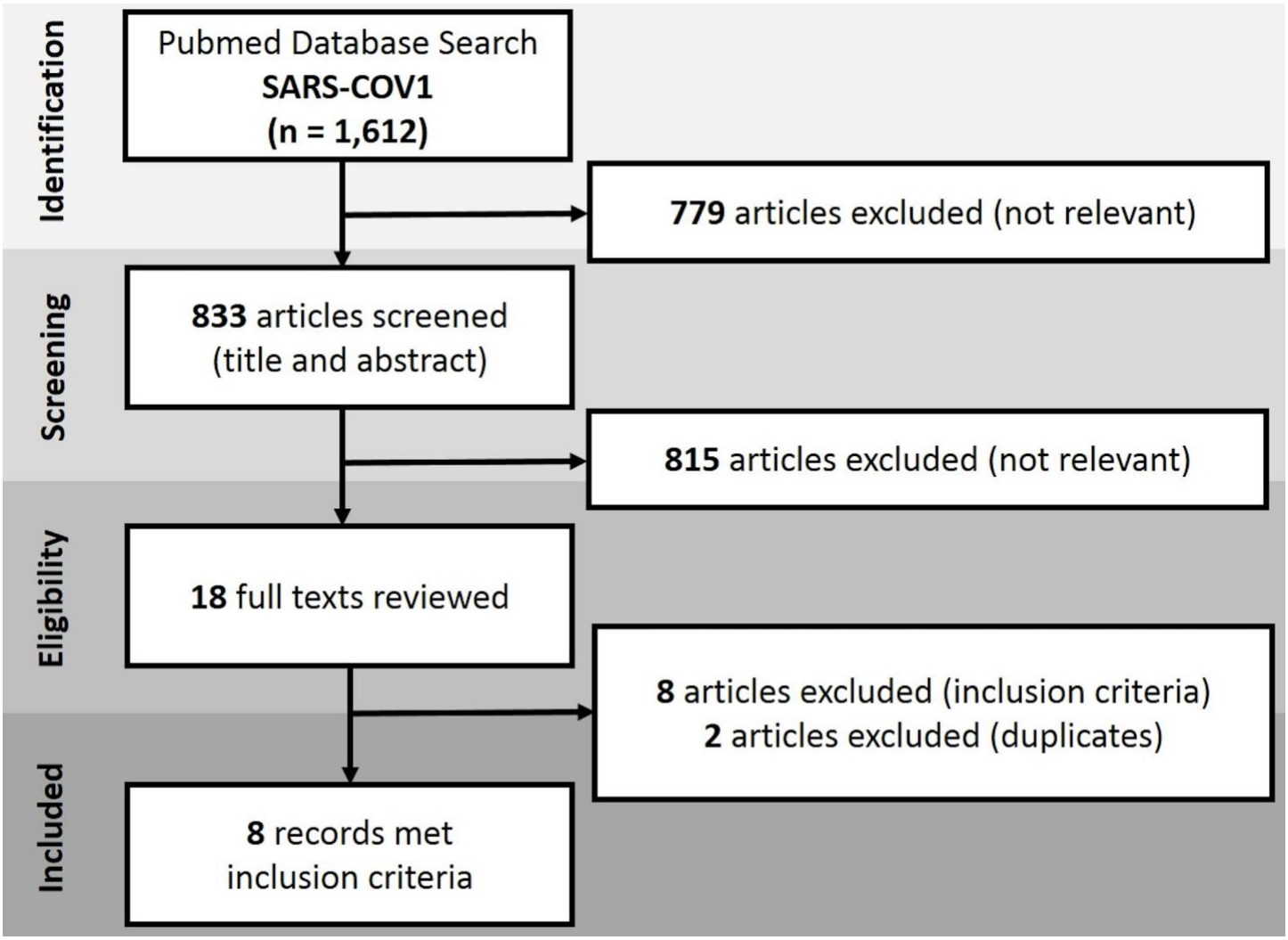
A 66-year-old man with obesity, hypertension, and diabetes presented to the hospital with one week of worsening fevers, dry cough, and dyspnea. Chest imaging was notable for bilateral diffuse hazy opacities with a retrocardiac opacity, and SARS-CoV-2 infection was confirmed by nasopharyngeal swab. He was intubated in the emergency room for hypoxemic respiratory failure secondary to COVID-19, managed with low tidal volume ventilation, and treated with broad spectrum antibiotics. He was administered hydroxychloroquine, but was not enrolled in clinical trials or given other experimental therapies. An echocardiogram was normal. On hospital day 2, he developed oliguric renal failure and CVVH was initiated. His hypoxemia continued to worsen, so he was ventilated in prone position and administered paralytics. On hospital day 4, his pressor requirement rose precipitously in the setting of ongoing refractory acidemia. After discussion with the family, the patient was transitioned to comfort-focused care, palliatively extubated, and passed away.

Grossly at autopsy, the lungs were consolidated. Microscopic examination revealed an acute (exudative) to early organizing (proliferative) phase of DAD. Other features included significant peribronchiolar metaplasia, with some mucinous metaplasia, consistent with severe acute lung injury. Numerous fibrin thrombi in small arteries and areas with parenchymal hemorrhage were present in both lungs, as was very focal neutrophilic pneumonia.

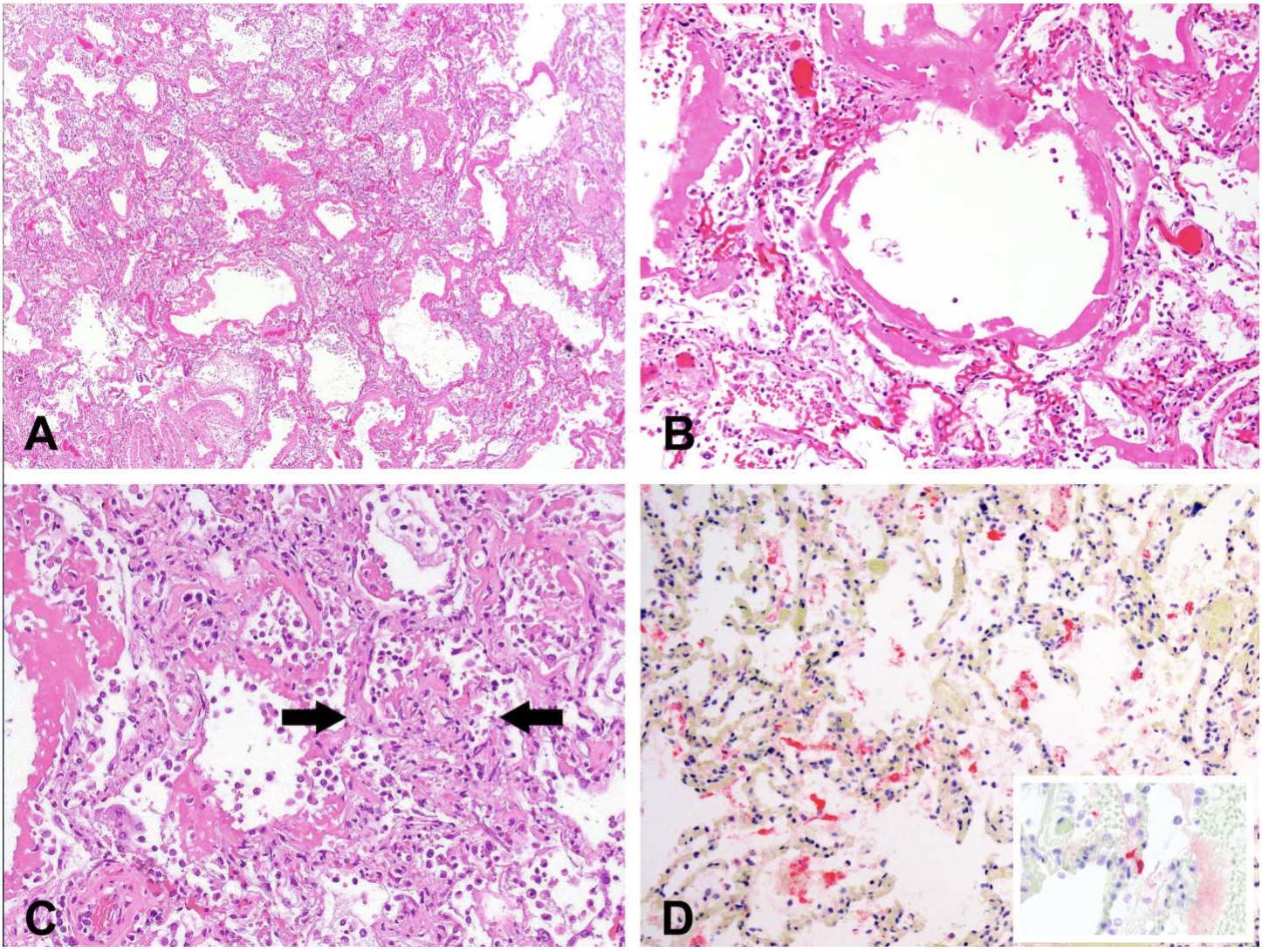
e-Figure 1.



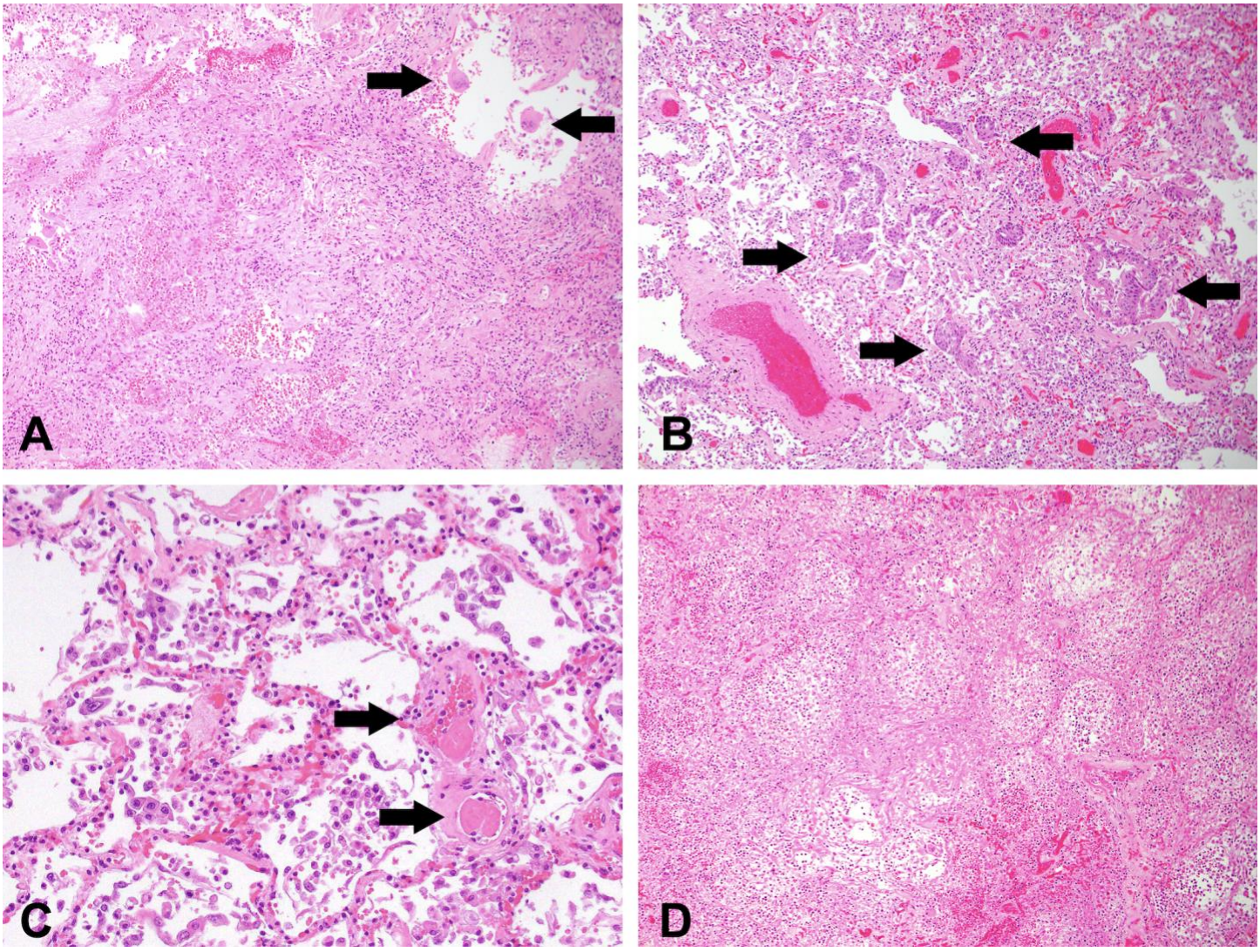
e-Figure 2.



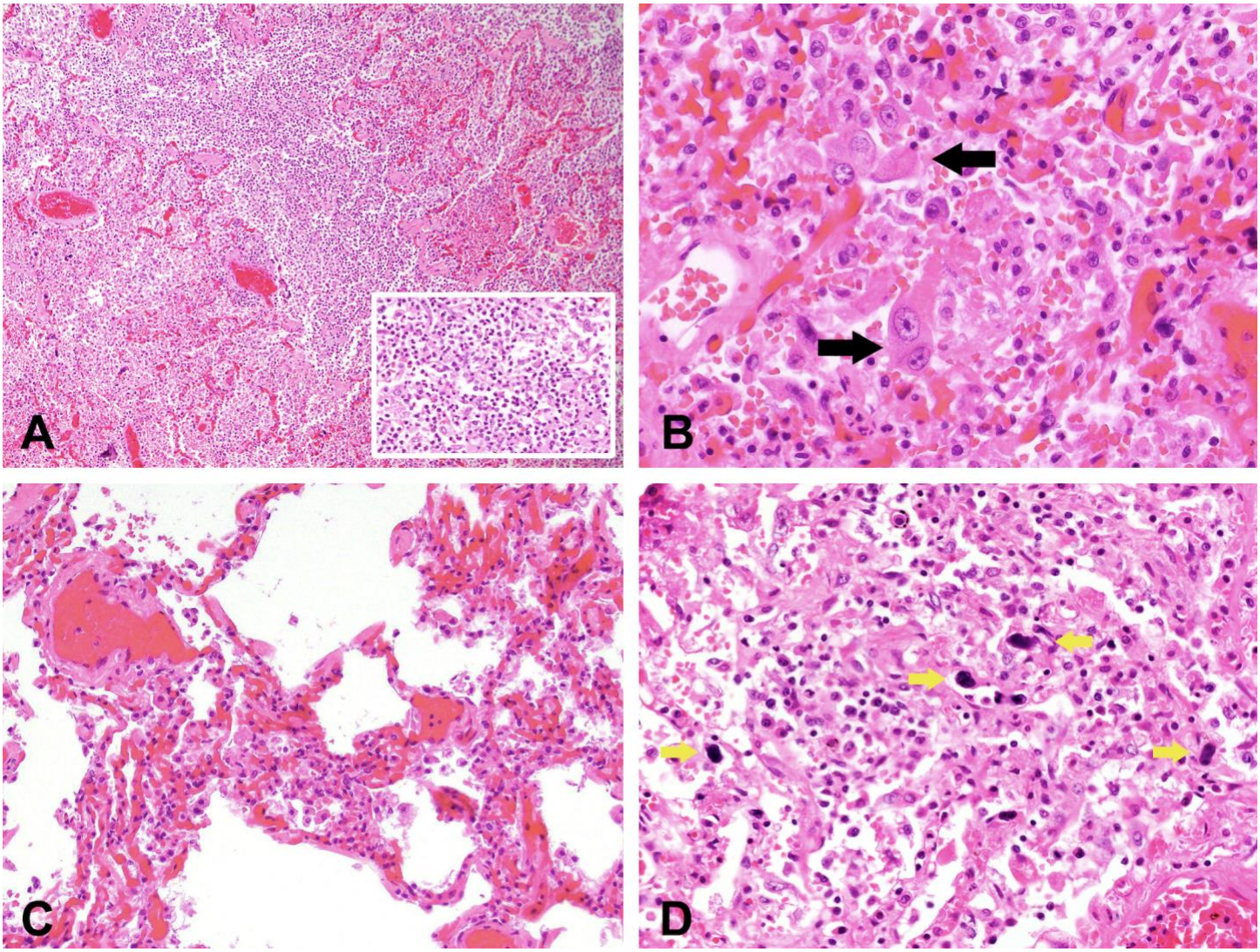
e-Figure 3.



e-Figure 4.



e-Figure 5.



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e-Table 1. Systematic review of lung histopathology features in 2009 H1N1 influenza studies. All reported numbers are the number of patients reported to have the respective finding within each respective study. No.: Number of total patients in the study; DAD: Diffuse alveolar damage; AFOP: acute fibrinous and organizing pneumonia; PNA: pneumonia; Pulmonary thrombosis: pulmonary vessel thrombosis. NIV: National Institute of Virology; CDC: Centers for Disease Control and Prevention. * Cases referred to NIV in India, which is the WHO referral center for H5N1. ** Cases referred to US CDC.

Study	Location	No. patients	Method	DAD	AFOP	Organizing fibrosis	End stage fibrosis	Superimposed PNA	Microthrombi	Pulmonary thrombosis
Ackermann et al. (2020)	Germany/ Boston, USA	7	Autopsy	7	0	3	0	0	7	4
Calore et al. (2011)	Brazil	6	Autopsy	5	0	2	0	2	2	0
Capelozzi et al. (2010)	Brazil	5	Surgical	5	0	5	0	5	0	0
Harms et al. (2010)	Michigan	8	Autopsy	8	0	7	0	6	7	5
Mauad et al. (2010)	Sao Paulo	21	Autopsy	20	0	14	0	8	6	4
Nakajima et al. (2012)	Japan	20	Autopsy	6	0	12	0	5	4	0
Rosen et al. (2010)	Houston, TX, USA	8	Autopsy	8	0	0	0	1	0	0
Shelke et al. (2012)*	Cases referred to NIV, Pune, India	44	Post-mortem biopsy	44	0	19	7	0	0	0
Shieh et al. (2010)**	Cases referred to CDC	100	Autopsy	100	0	28	0	29	17	0
Fujita et al. (2014)	Japan	4	Autopsy (3) TB biopsy (1)	4	0	2	0	0	0	0
Gill et al. (2011)	USA	34	Autopsy	25	0	9	0	19	9	0

Hajjar et al. (2010)	Brazil	5	Autopsy	4	0	0	0	4	0	2
He et al. (2010)	China	3	Autopsy	3	0	1	0	1	2	0
Marchiori et al. (2012)	Brazil	4	Post mortem biopsy	4	0	4	0	0	3	3
Mukhopadhyay et al. (2010)	New York	2	Autopsy	2	0	1	0	1	0	0
Nin et al. (2011)	Uruguay, Chile, Argentina, Spain	6	Autopsy	5	0	4	1	0	5	0
Otto et al. (2013)	Germany	1	Autopsy	0	1	1	0	0	0	0
Ru et al. (2011)	China	3	Autopsy	3	0	3	0	2	3	0
Soto-Abraham et al. (2009)	Mexico	5	Autopsy	4	0	0	0	3	5	0
Takiyama et al. (2010)	Japan	1	Autopsy	1	0	0	0	0	0	0
Total No. Patients		287		258	1	115	8	86	70	18
Proportion of Patients				90%	0.3%	40%	3%	30%	24%	6%

e-Table 2. Systematic review of lung histopathology features in SARS studies. All reported numbers are the number of patients reported to have the respective finding within each respective study. No.: Number of total patients in the study; DAD: Diffuse alveolar damage; AFOP: acute fibrinous and organizing pneumonia; PNA: pneumonia; Pulmonary thrombosis: pulmonary vessel thrombosis. * In Hwang et al. (2005), AFOP was identified as the predominant pattern in six cases that were diagnosed in the report as AFOP. However, these cases were described to have a background of hyaline membranes, and therefore, the cases were also included in the DAD category.

Study	Location	No. patients	Method	DAD	AFOP	Organizing fibrosis	End stage fibrosis	Superimposed PNA	Microthrombi	Pulmonary thrombosis
Cheung et al. (2004)	Hong Kong	10	Para-mortem biopsy (6); Autopsy (3); Pre-mortem biopsy (1)	9	0	6	3	1	1	0
Chen et al (2003)	China	7	Autopsy	7	0	5	0	7	6	1
Ding et al. (2003)	China	3	Autopsy	3	0	1	0	0	3	2
Franks et al. (2003)	Singapore	8	Autopsy	8	0	4	0	5	5	2
Hwang et al. (2005)*	Toronto, Canada	20	Autopsy	20	6*	6	0	3	17	12
Lang et al. (2003)	China	3	Autopsy	3	0	0	0	0	3	0
Nicholls et al (2003)	Kowloon	6	Autopsy	6	0	1	0	1	1	0
Tse et al. (2004)	Hong Kong	7	Autopsy	7	0	7	1	3	1	1
Total No. Patients		64		63	6*	30	4	20	37	18
Proportion of Patients				98%	9%	47%	6%	31%	58%	28%

e-Table 3. Available clinical data for included studies, part 1. All reported numbers of patients with each finding for the respective study. No.: number of patients; AF: atrial fibrillation; AIDS: Autoimmune Deficiency Syndrome; AML: Acute Myelogenous Leukemia; CVA: cerebrovascular accident; CHF: chronic heart failure; CKD: chronic kidney disease; CLL: chronic lymphocytic leukemia; COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; CVD: cardiovascular disease; DM: diabetes mellitus; DVT: deep vein thrombosis; DOAC: direct oral anticoagulant; ECMO: extracorporeal membrane oxygenation; ESRD: end stage renal disease (dialysis dependent); IVDU: intravenous drug use; IVIG: intravenous immunoglobulin; HCQ: hydroxychloroquine; HBV: hepatitis B viral infection (chronic); HCV: hepatitis C viral infection (chronic); HFNC: high flow nasal cannula; HIV: Human Immunodeficiency Virus; HLD: hyperlipidemia; HSTC: hematopoietic stem cell transplant; HTN: hypertension; MDS: myelodysplastic syndrome; MM: multiple myeloma; NIV: non-invasive ventilation; NSCLC: non-small cell lung cancer; OA: osteoarthritis; OSA: obstructive sleep apnea; PAD: peripheral arterial disease; PE: pulmonary embolism; PNA: pneumonia; PMH: past medical history; RA: rheumatoid arthritis; SUD: substance use disorder; UIP: usual interstitial pneumonia; VSD: ventricular septal defect

Study	***Location***	***Virus***	***No. Patients***	***Male*** *(no.)*	***Female*** *(no.)*	***Age*** *(yr)*	***Comorbidities***
Ackermann et al., (2020)	Germany/ Boston, MA, USA	COVID-19	7	5	2	66, 68, 74, 78, 81 86, 96	HTN (7), cigarette use (4), DM (3), Immunosuppression (1)
Adachi et al., (2020)	Japan	COVID-19	1	0	1	84	No notable PMH
Antinori et al., (2020)	Italy	COVID-19	1	1	0	73	DM (1), HTN (1), hyperthyroidism (1), AF (1), obesity (1)
Barton et al. (2020)*	Oklahoma, USA	COVID-19	1	1	0	77	HTN, (1), splenectomy for "unspecified genetic disease" (1), DVT (1), pancreatitis (1), OA (1)
Buja et al., (2020)	USA	COVID-19	3	3	0	34, 48, 62	obesity (3), HTN (1), CHF (1), DM (1), microcytic anemia (1)
Carsana et al. (2020)	Milan, Italy	COVID-19	38	33	5	Mean 62	HTN (18),CVD (11), DM (9), past malignancy (4), COPD (3)
Copin et al.	Lille, France	COVID-19	6	Not	Not	Not reported	Not reported

(2020)				reported	reported		
Craver et al (2020)	USA	COVID-19	1	1	0	17	No notable PMH
Fox et al. (2020)	New Orleans/ Louisiana, USA	COVID-19	10	Not reported	Not reported	44, 44, 53, 60, 63, 66, 68, 76, 78, 78	HTN (7), DM (5), CKD (1), OSA (1), CHF (1), COPD (1), AF (1), Polymyositis (1), RA (1)
Konopka, Wilson, and Myers (2020)	Michigan, USA	COVID-19	1	1	0	37	Asthma (1), DM2 (1)
Konopka et al (2020)	Michigan, USA	COVID-19	8	5	3	37, 46, 44, 49, 55, 63, 67, 79	DM (5), obesity (5), asthma (2), CVD (2), HTN (1), SUD (1), ESRD (1), renal transplant (1), bipolar disorder (1)
Lax et al. (2020)	Graz, Austria	COVID-19	11	8	3	Mean 80.5 (range 66-91)	HTN (9), DM2 (5), CAD (3), prior malignancy (2) COPD (2), cerebrovascular disease (4), dementia (3)
Magro et al. (2020)	New York, NY, USA	COVID-19	2	3	2	32, 40, 62, 66, 73	Obesity (2), CVD (1), CHF (1), ESRD (1), cigarette use (1), OSA (1), DM (1), prediabetes (1), treated HCV (1), anabolic steroid use (1)
Martines et al. (2020)	USA	COVID-19	8	4	4	Median 73.5	HTN (6), CKD (6), CVD (6), obesity (5), DM (4), immunocompromising condition (3), ESRD (2), CKD (2)
Menter et al. (2020)	Basel/Liestal, Switzerland	COVID-19	21	17	4	Mean 76 (range 53-96)	HTN (21), CVD (15), cigarette use (8), pre-obesity (10), obesity (6), DM2 (7), COPD (3), chronic neurologic disease (5), cancer (3), liver disease (2), CKD (4), acquired immunosuppression (1)

Nunes Duarte-Neto et al. (2020)**	São Paulo, Brazil	COVID-19	9	Data combined for PCR positive and negative			
Schaller et al. (2020)	Augberg, Germany	COVID-19	10	7	3	Median 79 (range 64-90)	HTN (7), CVD (5), AFA (4), CKD (3), COPD (2), obesity (2), DM (2), cancer (2), hypothyroidism (2), dementia (1), hyperthyroid (1), hypertrophic cardiomyopathy (1), fatty liver (1), CAD (1)
Sekulic et al. (2020)	Cleveland, OH, USA	COVID-19	2	2	0	54, 81	DM (2), HTN (2), dementia (1), lung mass (1), CVD (1), AF (1), CHF (1), PAD (1), dyslipidemia (1), CKD (1), cigarette use (1), CVA (1)
Suess et al. (2020)	Gallen, Switzerland	COVID-19	1	1	0	59	DM
Tian, Xiong, et al. (2020)	Wuhan, China	COVID-19	4	3	1	59, 74, 78, 81,	CLL (1), cirrhosis (1), variceal bleed (1), DM (1), HTN (1), renal transplant >3 mo (1)
Wichmann et al., (2020)	Hamburg, Germany	COVID-19	12	9	3	52, 54, 63, 66, 70, 71, 75, 82, 84, 87	CHF (6), obesity (3), HTN (3), DM (3), Parkinson's Disease (2), PAD (1), CKD (2), cigarette use (2), AF (2), granulomatous pneumopathy (1), dementia (1), epilepsy (1), trisomy 21 (1), NSCLC (1), COPD (1), ulcerative colitis (1), asthma
Wu et al. (2020)	China	COVID-19	10	7	3	Mean (SD) 70+/-16(49-87)	Not reported
Xu et al. (2020)	Beijing, China	COVID-19	1	1	0	50	Not reported

Yan et al. (2020)	San Antonio, TX, USA	COVID-19	1	0	1	44	Obesity (!)
Yao XH et al. (2020)	Congquing, China	COVID-19	1	0	1	78	Not reported
Zhang et al. (2020)	Wuhan, China	COVID-19	1	1	0	72	DM (1), HTN (1)
Ackermann et al. (2020)	Germany/ Boston, MA	H1N1	7	5	2	Mean (male) 62.5+/-4.9 Mean (female) 55.4+/-10.9	Not reported
Calore et al. (2011)	Brazil	H1N1	6	5	1	23, 38, 41, 41, 43, 48,	No comorbidities (2), obesity (2), DM (1), cerebral palsy (1), HTN (1), long-term anabolic steroid use (1)
Capelozzi et al. (2010)	Brazil	H1N1	5	2	3	35, 35, 39, 51,81	RA (1)
Harms et al. (2010)	Michigan, USA	H1N1	8	8	0	23, 26, 28, 31, 43, 51, 57, 57	HTN (3), asthma (1), COPD (1)
Mauad et al. (2010)	São Paulo, Brazil	H1N1	21	12	9	Median 34 (range 1-68)	CVD (7), COPD (2)
Nakajima et al. (2012)	Japan	H1N1	20	14	6	25, 30, 33, 42, 45, 49, 81, 75, 2, 6, 13, 15, 24, 30, 33, 40, 41, 44, 69, 72,	HTN (4), CHF (2), COPD (2)
Rosen et al. (2010)	Houston, TX, USA	H1N1	8	8	0	1, 26, 26, 27, 27, 34, 43, 54	Obesity (3)
Shelke et al. (2012)*	Cases referred to	H1N1	44	15	29	Median 40 (range 18-60	HTN (1), DM (1)

	NIV, Prune, India						
Shieh et al. (2010)**	Cases referred to CDC	H1N1	100	51	49	Median 36 (range 1-84)	Obesity (43), CVD (23),
Fujita et al. (2014)	Japan	H1N1	4	2	2	59, 37, 97, 24	Mental retardation (1), obesity (1)
Gill et al. (2011)	Michigan, USA	H1N1	34	17	17	Median 41.5 (range 0.16 - 72)	Obesity (16), HTN (13), asthma (7), DM (5), CVD (5), IVDU (4), HIV/AIDS (3), down syndrome (1), cirrhosis (1), CHF (1), OSA (2), MM with HSCT (1), psoriasis (1), CKD (1), pregnancy (1), AML (1), hypertrophic cardiomyopathy (1), MDS (1), emphysema (1), substance use (1), home oxygen use (1)
Hajjar et al. (2010)	Graz, Austria	H1N1	8	4	4	median 41.5 (range 0.16-72)	Solid malignancy (5), hematologic malignancy (3), cardiovascular chronic disease (3), hypothyroidism (2), COPD (1), M (2),
He et al. (2010)	New York, NY, USA	H1N1	3	2	1	1, 18, 44	Not reported
Marchiori et al. (2012)	Brazil	H1N1	4	0	4	21, 21, 35, 65	HIV/AIDS (1), pregnancy (1), CHF (1), liver dysfunction (1), CKD (1), neurodevelopmental disease (1)
Mukhopadhyay et al. (2010)	New York, USA	H1N1	2	1	1	36, 46	Alcoholism (1), obesity (1), CVA (1), HCV (1), depression (1), anxiety (1)
Nin et al. (2011)	Uruguay, Chile, Argentina, Spain	H1N1	6	2	4	15, 22, 26, 32, 37, 50	Pregnancy (3), asthma (2), obesity (1)

Otto et al. (2013)	Germany	H1N1	1	0	1	66	UIP status post lung transplant
Ru et al. (2011)	China	H1N1	3	3	0	41, 72, 79	Not reported
Soto-Abraham et al. (2009)	Mexico	H1N1	5	4	1	22, 26, 28, 37, 83	Not reported
Takiyama et al. (2010)	Japan	H1N1	1	0	1	41	Obesity
Cheung et al. (2004)	Hong Kong	SARS	10	7	7	31, 39, 40, 42, 45, 50, 53, 67, 73, 78	HTN (1), VSD (1), nephrotic syndrome (1), CVD (1), HLD (1)
Chen et al (2003)	China	SARS	7	5	5	34, 40, 41, 43, 45, 47, 51	Not reported
Ding et al. (2003)	China	SARS	3	2	2	25, 57, 62	Not reported
Franks et al. (2003)	Singapore	SARS	8	6	6	18, 38, 39, 43, 50, 53, 67, 68	DM (1)
Hwang et al. (2005)*	Toronto, Canada	SARS	20	9	9	mean = 68.1 (range 43-99)	Not reported
Lange et al (2003)	China	SARS	3	1	1	64, 69, 73	DM (2), lung cancer (1), HTN (1), "heart disease" (1)
Nicholis et al (2003)	Kowloon	SARS	6	4	4	37, 39, 49, 53, 64, 77	HTN, HBV cirrhosis with portal hypertension
Tse et al (2004)	Hong Kong	SARS	7	6	6	44, 63, 69, 76, 78, 81, 81	Chronic liver disease (2), CVD(2), MDS(1), COPD (1), HTN (1)

e-Table 3. Available clinical data for included studies, part 2.

Study	***Location***	***Virus***	***No, Patients***	**Mechanical Ventilation** (no.)	**Therapy**	***Cause of death***
Ackermann et al., (2020)	Germany/ Boston, MA, USA	COVID-19	7	NIV (2)	Not reported	Respiratory failure (6), cardiorespiratory failure (1)
Adachi et al., (2020)	Japan	COVID-19	1	No	Antibiotics (1), steroids (1), lopinavir/ritonavir (1)	Respiratory failure (1)
Antinori et al., (2020)	Italy	COVID-19	1	Yes (1)	Antibiotics (1), amphotericin (1) Lopinavir/ritonavir (1),HCQ (1)	Respiratory failure, (1) shock (1)
Barton et al. (2020)*	Oklahoma, USA	COVID-19	1	Yes (1)	CPR (1)	"COVID-19"
Buja et al., (2020)	USA	COVID-19	3	No	Antibiotics (3)	Respiratory failure with PEA (1), unknown (2)
Carsana et al. (2020)	Milan, Italy	COVID-19	38	Not reported	Not reported	Not reported
Copin et al. (2020)	Lille, France	COVID-19	6	Not reported	Not reported	Not reported
Craver et al., (2020)	USA	COVID-19	1	No	CPR	Cardiac arrest (1)
Fox et al. (2020)	New Orleans/ Louisiana, USA	COVID-19	10	Yes (9)	Antibiotics (7), dexamethasone (1), HCQ (2), cisatracurium (1), amiodarone (1)	VT arrest (1), not reported (9)
Konopka,	Michigan,	COVID-19	1	Yes (1)	Antibiotics (1), HCQ (1),	Care withdrawn (1)

Wilson, and Myers (2020)	USA				steroids (1), ECMO (1)	
Konopka et al (2020)	Michigan, USA	COVID-19	8	Yes (3)	Antibiotics (3), HCQ (2), sarilumab (1) steroids (1), tocilizumab (1),	Not reported
Lax et al. (2020)	Graz, Austria	COVID-19	11	Yes (2)	prophylactic enoxaparin (9), antibiotics (8), antiplatelet (7), therapeutic DOAC (1), steroids (1)	Not reported
Magro et al. (2020)	New York, NY, USA	COVID-19	2	Yes (1)	No therapy (1), not reported (1)	Not reported
Martines et al. (2020)	USA	COVID-19	8	Yes (6)	Not reported	Not reported
Menter et al. (2020)	Basel/ Liestal, Switzerland	COVID-19	21	Yes (6)	Anticoagulation (11)	"Multifactorial"
Nunes Duarte-Neto et al. (2020)**	São Paulo, Brazil	COVID-19	9	Yes (7)	Not reported	Not reported
Schaller et al. (2020)	Augberg, Germany	COVID-19	10	Yes (4)	Not reported	Not reported
Sekulic et al. (2020)	Cleveland, OH, USA	COVID-19	2	Yes (1)	Antibiotics (1), therapeutic anticoagulation (1) remdesivir (1)	Respiratory failure (1), multi-organ failure (1)
Suess et al. (2020)	Gallen, Switzerland	COVID-19	1	No	Pain medication (1), cough suppressant (1)	Unknown (found dead at home)
Tian, Xiong, et al. (2020)	Wuhan, China	COVID-19	4	Not reported	Antibiotics (4), "antiviral therapy" (4), oxygen (4)	Not reported

Wichmann et al., (2020)	Hamburg, Germany	COVID-19	12	Yes (4), NIV (1)	Not reported	respiratory failure/PNA (7), cardiac arrest (3), PE (2)
Wu et al. (2020)	China	COVID-19	10	Not reported	Not reported	Not reported
Xu et al. (2020)	Beijing, China	COVID-19	1	No (HFNC)	Not reported	Cardiac arrest (1)
Yan et al. (2020)	San Antonio, TX, USA	COVID-19	1	Yes (1)	HCQ (1), azithromycin (1), tocilizumab (1), prone positioning (1)	Multi-organ failure (1)
Yao XH et al. (2020)	Congquing, China	COVID-19	1	No	Not reported	Cardiac arrest (1)
Zhang et al. (2020)	Wuhan, China	COVID-19	1	Yes (1)	Not reported	Not reported
Ackermann et al. (2020)	Germany/ Boston, MA	H1N1	7	Yes (5)	Not reported	Respiratory failure (7)
Calore et al. (2011)	Brazil	H1N1	6	Yes (6)	Not reported	Respiratory failure (6), PE (2)
Capelozzi et al. (2010)	Brazil	H1N1	5	Yes (5)	Oseltamivir (5), steroids (5)	Multi-organ failure (2)
Harms et al. (2010)	Michigan, USA	H1N1	8	Yes (8)	Not reported	Not reported
Mauad et al. (2010)	São Paulo, Brazil	H1N1	21	Yes (21)	Oseltamivir (16), steroids (12)	Not reported
Nakajima et al. (2012)	Japan	H1N1	20	Yes (20)	Oseltamivir (14), antibiotics (10)	Not reported
Rosen et al. (2010)	Houston, TX, USA	H1N1	8	Not reported	Not reported	Not reported

Shelke et al. (2012)*	Cases referred to NIV, Prune, India	H1N1	44	Yes (17)	Oseltamivir (26)	Not reported
Shieh et al. (2010)**	Cases referred to CDC	H1N1	100	Yes (42)	Oseltamivir (44)	Not reported
Fujita et al. (2014)	Japan	H1N1	4	Yes (4)	ECMO (3), oseltamivir (2), peramivir (1), laninamivir (1)	Respiratory failure (3)
Gill et al. (2011)	Michigan, USA	H1N1	34	Yes (12)	Oseltamivir (22)	Not reported
Hajjar et al. (2010)	Graz, Austria	H1N1	8	Yes (5), NIV (3)	Steroids (8), oseltamivir (8), antibiotics (8)	Not reported (5)
He et al. (2010)	New York, NY, USA	H1N1	3	Not reported	Not reported	Not reported
Marchiori et al. (2012)	Brazil	H1N1	4	Yes (4)	Oseltamivir (4), antibiotics (4), steroids (4)	Respiratory failure (4)
Mukhopadhyay et al. (2010)	New York, USA	H1N1	2	Yes (2)	Oseltamivir (2), antibiotics (2)	Respiratory failure (2)
Nin et al. (2011)	Uruguay, Chile, Argentina, Spain	H1N1	6	Yes (6)	Oseltamivir (6), antibiotics (6), steroids (3)	Respiratory failure (5), multi-organ failure (1)
Otto et al. (2013)	Germany	H1N1	1	Yes	Steroids (1), oseltamivir (1), zanamivir (1), antibiotics (1), ECMO (1)	Respiratory failure
Ru et al. (2011)	China	H1N1	3	Not reported	Not reported	Not reported

Soto-Abraham et al. (2009)	Mexico	H1N1	5	Not reported	Antibiotics (4)	Respiratory failure (4), CVA (1)
Takiyama et al. (2010)	Japan	H1N1	1	No	None	Unknown (found dead)
Cheung et al. (2004)	Hong Kong	SARS	10	Yes (9)	Antibiotics (10), steroids (9), ribavirin (9)	Respiratory failure (10)
Chen et al (2003)	China	SARS	7	Not reported	Steroids (5)	Respiratory failure (7)
Ding et al. (2003)	China	SARS	3	Not reported	Not reported	Not reported
Franks et al. (2003)	Singapore	SARS	8	Not reported	Not reported	Not reported
Hwang et al. (2005)*	Toronto, Canada	SARS	20	Not reported	Not reported	Not reported
Lange et al (2003)	China	SARS	3	Not reported	Steroids (1), not reported (2)	Not reported
Nicholis et al (2003)	Kowloon	SARS	6	Yes (6)	Antibiotics (6), ribavirin (3), , oseltamivir (1), foscarnet (1), IVIG (1), steroids (3), amantadine (1)	Respiratory failure (6), cardiac arrests (1), multiorgan failure (1)
Tse et al (2004)	Hong Kong	SARS	7	Yes (6)	Ribavirin (6), hydrocortisone (5)	Respiratory failure (7)