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PII: S1556-0864(20)30298-7

DOI: https://doi.org/10.1016/j.jtho.2020.04.003

Reference: JTHO 1783

To appear in: *Journal of Thoracic Oncology*

Received Date: 7 March 2020

Revised Date: 4 April 2020

Accepted Date: 4 April 2020

Please cite this article as: Cai Y, Hao Z, Gao Y, Ping W, Wang Q, Peng S, Zhao B, Sun W, Zhu M, Li K, Han Y, Kuang D, Chu Q, Fu X, Zhang N, COVID-19 in the perioperative period of lung resection: a brief report from a single thoracic surgery department in Wuhan, China, *Journal of Thoracic Oncology* (2020), doi: https://doi.org/10.1016/j.jtho.2020.04.003.

COVID-19 in the perioperative period of lung resection: a brief report from a single thoracic surgery department in Wuhan, China

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Conflict of Interest Disclosures: None reported

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Abstract

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and has subsequently spread worldwide. Clinical information on patients contracted with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the perioperative period is limited. Here we report seven cases who were confirmed infected with SARS-CoV-2 in the perioperative period of lung resection. Retrospective analysis suggested that one patient had been infected with the SARS-CoV-2 prior to the surgery, the other 6 patients contracted the infection after the lung resection. Fever, lymphopenia and ground-glass opacities on computerized tomography (CT) are the most common clinical manifestations of COVID-19 in patients after lung resection surgery. Pathology studies of the specimens of these 7 patients were performed. The pathological examination of Patient 1, who was infected the SARS-CoV-2 before the surgery, revealed that apart from the tumor, there was a wide range of interstitial inflammation with plasma cells and macrophages infiltration. High density of macrophages and foam cells in the alveolar cavities but no obvious proliferation of pneumocyte was found. Three out seven patients died from COVID-19 pneumonia, suggesting that lung resection surgery might be a risk factor for death in patients with COVID-19 in the perioperative period.

Introduction

As of March 5th, 2020, there have been 80565 cases of COVID-19 confirmed in China with 3015 deaths.[1] As the confirmed cases are increasing, study with large sample size has provided detailed clinical information, including the clinical characteristics, laboratory and radiographic findings, and outcomes of the COVID-19.[2] Thus far, there has been one case report by Tian and coworkers to describe the clinical course and pathological findings of two cases infected with COVID-19 before lung lobectomy surgery.[3] However, there is still lack of reports focusing on the cases of hospitalized patients infected with the novel coronavirus in the perioperative period, especially in patients underwent lung resection surgery.

From Jan 1st to Jan 22nd, 2020, the period before the human-to-human transmission of SARS-CoV-2 was declared by the national authority, the thoracic surgery department of Tongji Hospital was on schedule to perform routine operations. Total 139 patients underwent lung resection. Among these patients, 7 cases were laboratory-confirmed to be infected with SARS-CoV-2 after lung resection. The confirmation of COVID-19 was based on the positive results of patient`s oropharyngeal swabs tested for SARS-CoV-2 by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay.

In this report, we present clinical characteristics and pathological findings of the patients diagnosed with COVID-19 in perioperative period of lung resection and evaluate the influence of surgery on the progression of COVID-19.

Patient details and clinicopathological features

The 7 patients were initially hospitalized for surgical treatment for lung tumor. The median age of the patients was 60 years (25th-75th percentile, 57-66 years), and five were male. The comorbidities included chronic obstructive pulmonary disease (in 2 patients), coronary atherosclerosis (3), interstitial lung disease (1), hyperlipidemia (1). Six patients were diagnosed with non-small cell lung cancer

(NSCLC), one patient was diagnosed with pulmonary sclerosing pneumocytoma. Surgeries were successfully performed in all cases without event, including video-assisted thoracoscopic (VATS) lobectomy (4), VATS segmentectomy plus wedge resection (1), thoracotomy sleeve lobectomy (1) and lobectomy plus bronchus reconstruction (1). None of the patients had surgery related postoperative complications including air leak, hemorrhage, bronchopleural fistula, and arrhythmia (Table 1).

All 7 patients presented fever after the surgery; six patients had body temperature > 39℃. The time from surgery to onset of fever ranged from 0 day to 23 days (mean, 8.6 days). Accompany symptoms included shortness of breath (5), nonproductive cough (4), fatigue (2), productive cough (1), myalgia (2), and diarrhea (1) (Table 2).

On the first day after surgery, the number of neutrophils in the peripheral blood was increased in all 7 patients, while 4 patients had lymphopenia. At the onset of COVID-19, five patients had lymphopenia, and a decline in the lymphocyte counts was observed in all 7 cases, which is more prominent in Patient 1, 3 and 7. In terms of liver function, only 1 patient had increased concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), three patients had lower albumin level than the normal range (35-52g/L). Elevated high-sensitivity C-reactive protein and procalcitonin, the biomarkers for inflammation, were observed in all 7 patients at the onset of symptoms. The level of fibrinogen and D-dimers were increased in 5 and 7 patients respectively (Table 2).

All the patients had CT scans. After the onset of symptoms, all 7 patients presented emerging multifocal ground-glass opacities (GGOs) with (4 cases) or without (3 cases) superimposed reticulation. Bilateral involvement and progression on CT images were observed in 3 patients (Patient 1, 3 and 7) (Figure 1).

Pathological examinations of the specimens from all these patients were performed. The findings of Patient 1 have been reported in a previous study.[4] Among all the 7 patients, typical malignant pathological features of the primary tumors were identified. Hematoxylin and eosin stained sections of lung tissues away from the tumors were reviewed. For Patient 1, under the microscope, there was a wide range of lung interstitial inflammation with numerous infiltrating immune cells. The infiltrating cells were mainly composed of plasma cells and macrophages. Lymphocytes were rare. Thickened alveolar septum and fibrous connective tissue proliferation were noted. Besides that, there were a large number of macrophages and foam cells in the alveolar cavities, but no evident pneumocyte hyperplasia was observed. Moreover, no obvious viral inclusion bodies and hyaline membrane were found. The other 6 patients had no evident inflammation in their lung tissues away from the tumors (Figure 2)

Oseltamivir was initially administrated when 7 patients presented with the virus infection associated symptoms. As the symptoms were progressing, other anti-virus regimens were also used, including umifenovir in 2 patients and Lopinavir and Ritonavir in 1 patient. Four patients received systemic corticosteroid therapy. Patient 1, 3 and 7 received mechanical ventilation and eventually died from respiratory failure on the 5th, 42th, and 35th postoperative day (5, 19, and 25 days after the symptom onset), respectively. Two patients have been cured and discharged from hospital, the rest 2 patients are still hospitalized in stable condition at the time of manuscript submission with normal body temperature more than three days and objective relief of symptoms as well (Table 2).

Discussion

The incubation period of COVID-19 has been reported to be 5.2 days (95% CI, 4.1-7.0), and for some cases, the incubation period could be as long as 14 days.[5] To proper identify and screen patients with atypical symptoms during the incubation period is a big challenge. Although the laboratory confirmation of COVID-19 infection was obtained on the post-operative Day 5, the clinical course of Patient 1 revealed that the patient had been infected with SARS-CoV-2 prior to the surgery. Through retrospectively examining his clinical manifestations, we found the patient immediately developed a fever (38. 5°C) just 3 hours after the surgery and had recurrent pyrexia (>39° C) in the whole postoperative period. Chest CT scan on post-operative Day 4 showed diffused ground-glass opacities in bilateral lungs. As the pneumonia rapidly worsen, the patient died on the 5th day after the surgery. Additionally，we reviewed the patient's CT scan performed two weeks before the surgery, in addition to diffusely infiltrative opacifications in the subpleural regions of both lungs, which were previously diagnosed with interstitial lung disease, a subpleural ground-glass attenuation in the right lower lobe was noticed. At the time, there was lack of awareness of the significance of the ground-glass findings.

In Tian`s report,[3] pathologic examinations of the two cases who were infected with the novel coronavirus before the lobectomies revealed evident alveolar damage with alveolar edema and proteinaceous exudates. These lung injury findings were also generally observed in the severe acute respiratory syndromes (SARS) patients by autopsy.[6] In Patient 1, we did not observe typical alveolar damages and pneumocyte hyperplasia, instead, we found extensive interstitial inflammation with numerous plasma cells and macrophages infiltrating in the lung tissues. The pathology pattern of COVID-19 pneumonia in Patient 1 differs from that of the two cases reported by Tian et al. [3] Given that Patient 1 had interstitial lung disease, the pathology changes in Patient 1 may be affected by this pulmonary comorbidity. Taken together, the lesson of Patient 1 indicates that it is vitally important to perform careful preoperative examination and screening for those patients who plan to receive operation during the COVID-19 epidemic.

All 7 patients showed post-resection changes on radiographic images in the early period after surgery, including infiltration, atelectasis and pleural effusion. After the onset of symptoms, all 7 patients presented emerging multifocal ground-glass opacities which were reported the most common CT findings of COVID-19, [7] and SARS as well.[8] Although the post-resection radiographic abnormalities increased the difficulty in early detection of the viral infection, the typical radiological features and distribution pattern can facilitate the differential diagnosis. Because post-resection infiltration and effusion mostly developed in the lung on the surgery side. Thus, the presence of typical ground-glass opacity, especially in the lobe contralateral to the surgery side, could be an early radiological sign of the viral infection.

Serial CT scans showed bilateral lung involvement with evident progression in Patient 1, 3 and 7. Despite comprehensive treatment, including antivirus treatment, antibiotics, oxygenation therapy, and other supportive care, these 3 patients eventually developed respiratory failure and died. In contrast, the other 4 patients with infection predominantly involving in the lung contralateral to the surgery side had less severe symptoms and a better prognosis (2 were cured and 2 were in convalescent stage). It is consistent with the current results among the general infected population,[9] which demonstrated that bilateral involvement is corelated with the high severity and poor prognosis.

Lymphopenia is a common feature for SARS and SARS-CoV-2 infection.[10, 11] It is worth noting that lymphopenia often occurs immediately after lung surgery.[12] The results indicated that early appeared lymphopenia after lung resection was lack of specificity. At the onset of symptoms, 5 cases presented lymphopenia, and a prominent decline in the lymphocytes count was observed in Patient 1, 3 and 7, suggesting that the degree of reduction in the number of circulating lymphocytes was closely correlated with the progression of COVID-19. Thus, compared to the absolute cell count, the dynamic reduction of lymphocytes should be considered to be of more significance in the postoperative patients with COVID-19.

Patients with cancer are more susceptible to infection than individuals without cancer because of the immunosuppressive state caused by the malignancy.[13, 14] A recent nationwide analysis of COVID-19 patients，which included a cohort of 18 patients with various cancers and 1572 patients without cancer history revealed that patients with cancer are at a high risk for severe COVID-19.[15] Among the 18 cancer patients enrolled in this study, five cases were lung cancer. These five lung cancer patients showed a lower probability of severe COVID-19 compared to patients with other types of cancer (20% vs. 62%, respectively). However, the lower incidence of severe COVID-19 in lung cancer patients should be interpreted with caution because of the small sampling. In our report, 6 patients had lung cancer, 2 out of 6 died. Some considerations need to be taken into account during interpreting the findings from the present report as well. First, the effects of different surgery pattern including operation approach and lymphadenectomy on COVID-19 remain to be evaluated. Second, whether the characteristics of the cancer, such as histological type and stage, could influence the development and prognosis of COVID-19 in lung cancer patients needs to be further investigated. For now, two patients are still hospitalized, further follow-up was needed to clarify the long-term outcomes of such specific patients infected with SARS-CoV-2.

Before the outbreak was declared by the authority, our understanding of the transmission of SARS-CoV-2 was very limited. The lack of awareness of this emerging infectious disease led to the failure of implementing appropriate protective measures in place to prevent healthcare associated infection. A comprehensive analysis of nosocomial infection of Middle East respiratory syndrome (MERS) in a tertiary hospital in South Korea revealed that the virus transmissions mainly occurred before the infected patient had been recognized.[16] In our department, nosocomial transmission could be definitively proven based on timing and patterns of exposure to infected patients and subsequent development of infection among medical staff. Based on investigation, Patient 1 was presumed to be the source of transmission in our department, because he was the first confirmed case in the ward and three health care works (HCWs) who had close contact with him were found to be infected. Subsequently, 6 patients and the other 5 HCWs were confirmed infected with COVID-19. The cross infection highlighted the high risk for SARS-CoV-2 transmission within thoracic surgery department. As there are more aerosol-generating procedures performed, such as lung suctioning, intubation and bronchoscopy in the thoracic surgery department, the medical staff carries a high risk of exposure to droplets around the patients.

The outbreak of COVID-19 imposes a major challenge in deciding and managing surgical operation on patients with lung cancer and other lung disorders. We believe it is imperative to report these cases to provide direct evidence for opting proper strategies in the thoracic department. The preliminary results from the limited cases indicate that lung resection surgery might be a risk factor for death in the patients with COVID-19 in the perioperative period. Thus, during the epidemic, any surgery related managements should be manipulated with extra caution. At the epidemic area, any negligence is unaffordable.

Acknowledgements

We thank all the patients and their families involved in the study. This study was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

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Figure 1: Representative Chest CT Images in Seven Patients with COVID-19

A: A 63-year-old male underwent VATS right lower lobe lobectomy and lymphadenectomy. CT scans performed 14 days before surgery showed bilateral infiltrative opacification in the periphery of the lung, and a subpleural ground-glass attenuation in the right lower lobe (arrow). CT images on postoperative Day 4 showed bilateral multifocal ground-glass opacities with consolidation.

B: A 57-year-old male underwent left lower lobe and segment 4+5 sleeve resection via open surgery. CT showed ground-glass shadowing in the right lung, and gradual absorption of infiltration in the left upper lobe from postoperative Day 7 to Day 20.

C: A 68-year-old male underwent right lower lobe lobectomy with reconstruction of the right bronchus intermedius and lymphadenectomy. CT images on postoperative Day 31, 38 showed a mixture appearance of ground-glass opacity with superimposed reticulation at bilateral lungs.

D: A 57-year-old male underwent VATS right upper lobe lobectomy and lymphadenectomy. CT images showed subsegmental consolidation in the right middle lobe and right encapsulated pleural effusion on postoperative Day 11 which gradually resolved on postoperative Day 18, and a progression of the ground-glass shadowing in the left lung was presented.

E: A 61-year-old male underwent VATS left upper lobectomy and lymphadenectomy. CT images showed pneumothorax and atelectasis on postoperative Day 6 which resolved on Day 10. CT images on postoperative Day 10 showed the presence of ground-glass opacities with superimposed reticulation in the periphery of the right lung.

F: A 60-year-old female underwent VATS wedge resection of left upper lobe with basal segmentectomy and lymphadenectomy. CT images showed persistent ground-glass opacities in the right middle and lower lobe on postoperative Day 10, 19.

G: A 56-year-old female underwent VATS right lower lobe lobectomy. CT images showed bilateral multifocal ground-glass opacities and pleural effusion on postoperative Day 16.

Figure 2: Histopathology of lung tissue away from the tumor

A: Diffuse lung interstitial inflammation with inflammatory cell infiltration (Patient 1, original magnification x40).

B: Thickened alveolar septum and fibrous connective tissue proliferation accompany with plasma cells and macrophages infiltrates. Macrophages and foam cell infiltrate in the alveolar cavities (Patient 1, original magnification x200).

C-H: pulmonary histology without inflammation findings (original magnification x100).

Table 1. Summary of Clinical Characteristics of The Seven Patients with COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	63	57	68	57	61	60	56
Sex	Male	Male	Male	Male	Male	Female	Female
Smoking history	Current	Never	Ever	Current	Current	Never	Never
Resident of Wuhan	Yes	No	Yes	No	No	No	No
Comorbidity	Interstitial lung disease	Coronary atherosclerosis	COPD	COPD	None	Hyperlipidemia + Coronary atherosclerosis	Coronary atherosclerosis
FEV1 (L)	2.5	3.07	1.39	2.36	2.42	2.04	2.77
FEV1/FVC (%)	70.01	75.11	58.52	65.09	83.32	85	72.51
Tumor location	RLL	LLL	RLL	RUL	LUL	LUL(GGN) LLL(GGN)	RLL
Tumor size (cm)	3.5	5.0	1.7	1.5	3.5	LUL: 1.0 LLL: 1.7	3.5
Operation	RLL Lobectomy	LLL lobectomy + S4+5 sleeve resection	RLL lobectomy + reconstruction of the right bronchus intermedius	RUL Lobectomy	LUL Lobectomy	LUL: wedge resection LLL：basal segmentectomy	RLL Lobectomy
Lymphadenectomy	Yes	Yes	Yes	Yes	Yes	Yes	No
Approach	VATS	Open	Open	VATS	VATS	VATS	VATS
Duration of surgery (min)	200	220	280	165	150	130	110
Blood loss (ml)	130	100	200	100	50	50	100
Histological type	SCC	Ade	Ade	Ade	Ade	LUL: Ade LLL: Ade	PSP
Tumor stage	pT2aN0M0R0	pT2N2M0R0	pT1N2M0R0	pT1bN0M0R0	pT2N2M0R0	LUL: T1aN0M0R0 LLL: T1bN0M0R0	NA

Abbreviations：COVID-19, 2019 novel coronavirus disease; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; RLL, right lower lobe; LLL, left lower lobe; RUL, right upper lobe; LUL, left upper lobe; GGN, ground glass nodule; VATS, video-assisted thoracic surgery; NA, not applicable; Ade, adenocarcinoma; SCC, squamous cell carcinoma; PSP, pulmonary sclerosing pneumocytoma.

Table 2. Onset Symptoms, Laboratory Findings and Treatments of Seven Patients with COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Symptoms							
Fever	Yes, (>39°C)	Yes, (>39°C)	Yes, (>39°C)	Yes, (>39°C)	Yes, (>39°C)	Yes, (>38°C)	Yes, (>39°C)
Short of breath	+	+	+	+	+	-	-
Dry cough	-	+	-	-	+	+	+
Productive cough	+	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-
Myalgia	+	-	-	-	+	-	-
Palpitation	-	-	+	-	-	-	-
Fatigue	-	-	-	+	-	+	-
Diarrhea	-	-	-	-	-	-	+
Hospital stay prior to the operation (days)	8	10	10	3	5	7	7
Onset of symptoms (Post-op Day)	0	7	23	10	3	7	10
Laboratory findings							
First RT-PCR test for SARS-CoV-2 (Post-op Day)	4	15	34	13	12	12	15
Positive RT-PCR for SARS-CoV-2 (Post-op Day)	4	15	39	13	12	12	20
Respiratory pathogens*	NA	NA	Positive IgM to CP and MP	Negative	Negative	Negative	Negative
Leukocyte, $\times 10^9$/L	10.09	5.52	2.93	6.56	5.24	3.13	6.86
Neutrophils, $\times 10^9$/L	8.23	3.8	1.7	4.83	4.3	1.63	5.01
Lymphocytes (initial, minimum), $\times 10^9$/L	I: 0.89 M: 0.18	I:1.12 M: 0.47	I: 0.6 M: 0.29	I: 1.03 M: 0.68	I: 0.53 M: 0.39	I: 1.14 M: 1.03	I: 1.06 M: 0.26
Monocytes, $\times 10^9$/L	0.96	0.5	0.63	0.63	0.35	0.34	0.79
Haemoglobin, g/L	128	122	120	135	117	106	125
Platelet count, × 10□/L	227	225	148	220	188	191	210
Procalcitonin, ng/mL	0.22	0.06	0.08	0.09	0.09	0.06	0.05
High-sensitivity C-reactive protein, mg/L	164.9	25.5	149	67.3	55.5	11.9	46.4
Alanine transaminase	13	196	18	38	31	27	13
Aspartate aminotransferase	31	186	28	23	47	42	17
Total bilirubin, μmol/L	9.9	9.2	5.7	8.3	9.4	4.7	5
Albumin, g/L	30.8	38	31.5	38.2	35	31.8	36.2
Creatinine, μmol/L	70	54	50	63	54	61	49
Prothrombin time, s	12.7	12.1	12.3	14.8	13.5	13.4	13.7
Activated partial thromboplastin time, s	57.8	42.3	43.2	34.7	44.6	38.7	47.7
D-dimers, μg/mL	2.25	1.90	3,21	5.70	1.08	1.01	4.58
Treatments							
Intravenous antibiotics	+	+	+	+	+	+	+
Antivirus therapy	Oseltamivir	Oseltamivir	Oseltamivir	Oseltamivir Lopinavir	Oseltamivir Umifenovir	Oseltamivir	Oseltamivir Umifenovir

				Ritonavir			
Systemic corticosteroids	-	+	-	+	+	-	+
Intravenous immunoglobin	-	-	-	+	+	-	+
Oxygen therapy	+	+	+	+	+	+	+
Mechanical ventilation	BiPAP	-	IMV	-	-	-	IMV
ECMO	-	-	-	-	-	-	-
ICU	+	-	+	-	-	-	+
Clinical outcomes	Died	Discharged	Died	In hospital	In hospital	Discharged	Died
Days since the onset of symptoms to the outcome event	5	32	19	NA	NA	33	25

Abbreviations: COVID-19, 2019 novel coronavirus disease;*respiratory pathogens in our study include Respiratory syncytial virus, Adenovirus, Influenza A, Influenza B, Parainfluenza virus, Legionella pneumophila, Chlamydophila pneumoniae and Mycoplasma pneumoniae; CP, Chlamydophila pneumoniae; MP, Mycoplasma pneumoniae; NA, not available; IMV, invasive mechanical ventilation; BiPAP, bilevel positive airway pressure; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.

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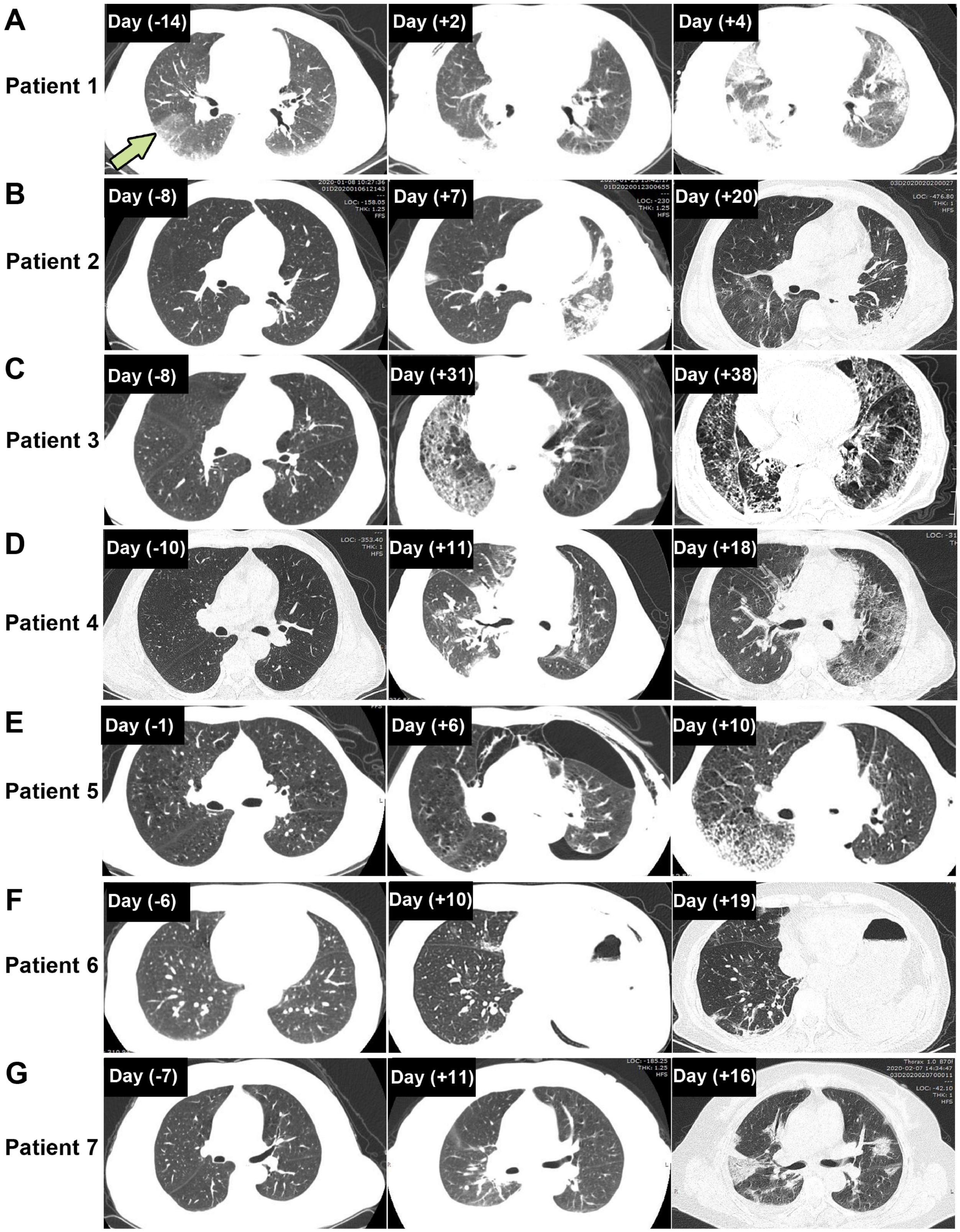
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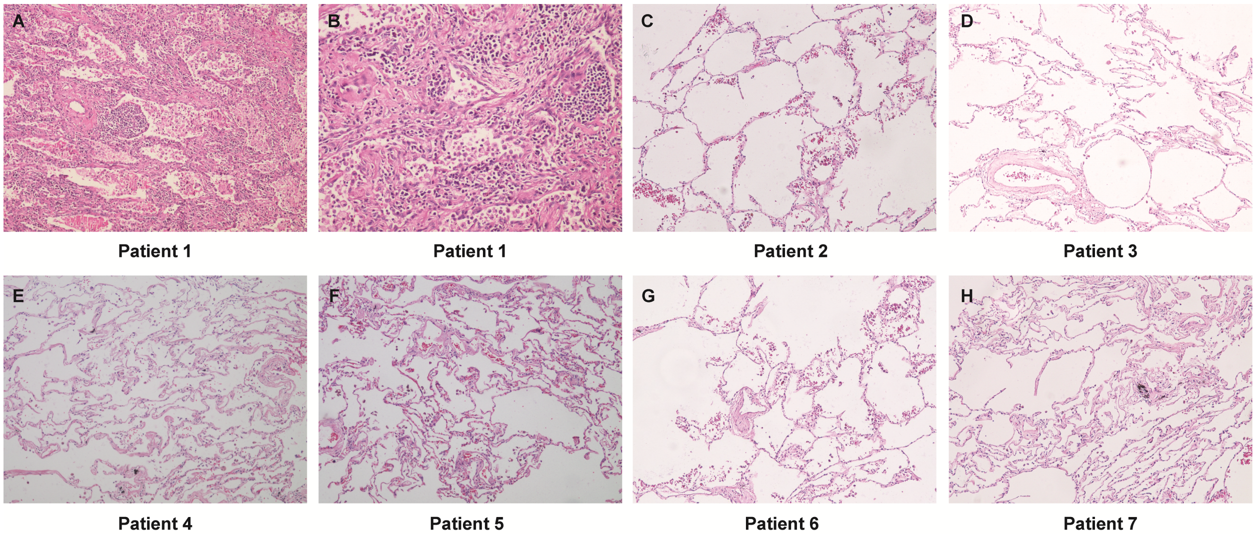
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