Caspian Journal of Internal Medicine 2024 (Autumn); 15(4): 713-728
DOI: 10.22088/cjim.15.4.713

Case Series

COVID-19 associated lung cavitary lesions: A case series

Rama Bozorgmehr (MD) [1]
Farzad Esmaili Tarki (MD) [2]
Esmat Yazdi (MD) [3]
Shahrzad Shahrokhi Nejad (MD) [2*]

1. Clinical Research Development Unit, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Internal Medicine, clinical research development Unit of Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

*** Correspondence:**
Shahrzad Shahrokhi Nejad,
Shahid Beheshti University of Medical Sciences, Tehran, Iran

E-mail: shery.1375.sh@gmail.com
Tel: +98 21 23871

Received: 14 Aug 2023
Revised: 2 Oct 2023
Accepted: 7 Nov 2023
Published: 7 Sep 2024

Abstract

Background: Our study discusses the probable etiologies and characteristics of pulmonary cavities in post-COVID-19 patients. A pulmonary cavity is a late complication of the disease, yet it has led to multiple referrals to our tertiary hospital in Tehran, Iran.

Methods: We conducted a retrospective case-series study on 20 patients who were admitted to our center between April 2020 and September 2021. They were all diagnosed with COVID-19 and concomitantly developed pulmonary cavities. We assessed their electronic medical records in 2021 and compared their characteristics with other studies based on the available literature.

Result: Of the 20 patients with cavities, 12 (60%) had been diagnosed with prior COVID-19, and 9 (45%) had type 2 diabetes mellitus. 9 patients (٤٥%) had bacterial superinfections while 4 (44%) had fungal infections. All patients received corticosteroids, but only 4 (20%) were additionally administered Tocilizumab.

Conclusion: COVID-19 patients can develop pulmonary cavities during recovery; however, this infrequent radiologic finding depends on specific risk factors.

Keywords: COVID-19, thoracic cavity, lung, Aspergillosis, pulmonary cavity, post-COVID-19 cavity, COVID-19 complications, COVID-19 rare presentations.

Citation:
Bozorgmehr R, Esmaili Tarki F, Yazdi E, Shahrokhi Nejad Sh. COVID-19 associated lung cavitary lesions: A case series. Caspian J Intern Med 2024; 15(4): 713-728.

The World Health Organization (WHO) was first alerted to a series of unexplained cases of pneumonia in Wuhan, China, on December 31, 2019. Consequently, coronavirus disease 2019 (COVID-19) became a worldwide pandemic during the first 6 months of 2020, with more than 60 million confirmed infections and a death toll surpassing 1.5 million by the end of November (1). Infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, leading to pneumonia and severe acute respiratory syndrome (2).

The typical abnormalities seen on chest computerized tomography (CT) in patients with COVID-19 have previously been well-described (3, 4), with a comprehensive review and meta-analysis of 55 studies finding peripheral ground-glass opacities(GGO) in most cases, consolidation in 44% (95% CI 1-71%), air bronchograms in 43% (95% CI 8-80%), linear opacities in 41% (95% CI 7 65%), crazy-paving pattern in 24% (95% CI 3-92%) and interlobular septal thickening in 23% (95% CI 1-80%) of the CT scans reviewed (3). The absence of cavities was notable. Although a small number of case reports have recently described pulmonary cavities (5, 6, 7), it is considered a rare event. In contrast, the experience at our tertiary care referral hospital differed significantly. Therefore, we felt the need to conduct a study assessing COVID-19 patients with cavitary lesions. Furthermore, multiple explanations have been suggested for the pathophysiology of cavitation in COVID-19 patients. Cavitary lesions can present with both symptoms and complications (8). Some might also suggest that these lesions could be incidental findings, unrelated to COVID-19 pathophysiology, which have been caused by other background conditions in patients (9).

To name one probable explanation, in general, COVID-19 increases the risk of a thromboembolic state and causes hypercoagulopathy. The mechanism suggested is the hypoperfusion of the lung which is caused by vasoconstriction activated by high levels of angiotensin II after SARS-CoV-2 binds to epithelial cells of the alveoli by receptors of angiotensin-converting enzyme 2 (ACE-2) (10).

To achieve a better understanding of cavitation in COVID-19 patients, and since the clinical experience in our hospital has seemingly contradicted the rarity of cavitary lesions, we decided to carry out a case-series study evaluating twenty cases of COVID-19 patients with cavitation in their chest CT scans and discuss their characteristics, management, prognosis, possible sequelae of the condition and further comprehensively discuss our findings in light of the literature.

Methods

Our patients were referred to the emergency department of Shohada-e-Tajrish Hospital in Tehran, Iran, and were admitted between April 2020 and September 2021. In the first step, we extracted electronic data from the patients' medical records including patients' medical histories and examinations, laboratory results, CT scan reports (all performed by one skilled radiologist), and all management (based on the last update of our national guidelines) during the hospital stay. In the second step, we conducted a literature review on lung cavities in COVID-19 in Medline (PubMed) and other databases in a time-dependent manner and included all information surrounding our topic and lung cavities before the pandemic until the end of 2022. The study was approved by the Shahid Beheshti Ethics Committee (Approval No. IR.SBMU.RETECH.REC.1400.756) and was performed according to the guidelines of the Declaration of Helsinki.

Case Presentation

Case 1: A 64-year-old female was admitted with FCIII dyspnea and chest pain accompanied by other COVID-19 symptoms. Aside from usual management, prophylactic antifungal treatment with Amphotericin B was initiated due to the initial suspicion of Aspergillosis diagnosis. After a month of hospitalization, the patient's general condition worsened significantly leading to intubation and death (figure 1).

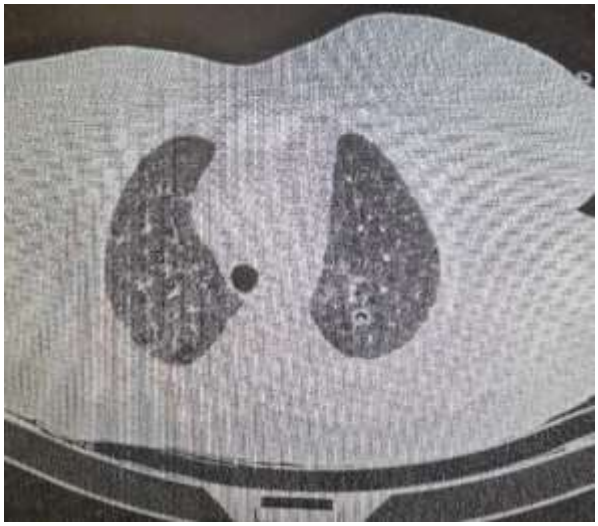

Figure 1. Bilateral cavitary lesions with thick walls

Case 2: A 56-year-old male with a positive sputum culture for E. coli and suspected fungal infection on a chest CT scan required proper testing. Due to the evidence of pulmonary emboli in CTPA, he was administered heparin infusion for four days. Unfortunately, after receiving twelve days of treatment the patient's respiratory distress worsened and he died (figure 2)

Figure 2. A prominent cavitary lesion in RLL measuring around 45mm at its largest diameter

Case 3: A 79-year-old male with poor compliance after discharge from a prior COVID-19 ICU and severe lung involvement presented with deteriorating symptoms over the past month. The pathophysiologic investigations demonstrated a mass as in figure 3 to be an inflammatory pseudotumor (IPT) of neoplastic mesenchymal origin indicative of multiple bilateral cavitary lesions, but with negative results of respiratory tract culture and serum galactomannan assay, and showing prominent signs of improvement, he was discharged after 10 days (figure 3)

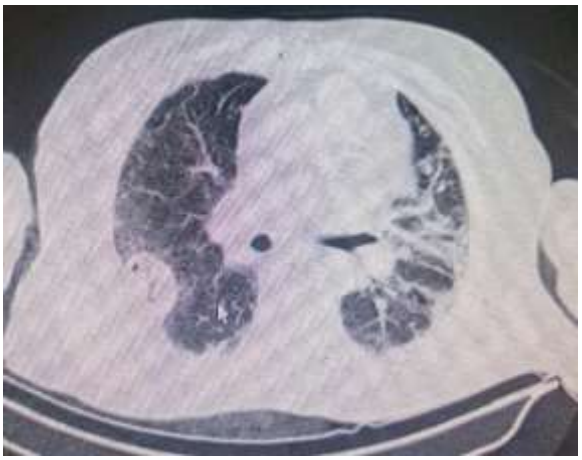

Figure 3. A mass within the RML measuring at around 30x31x24mm

Case 4: A 53-year-old male had been receiving Remdesivir for the past six days following the COVID-19 diagnosis established in another center, but his symptoms did not improve. Although his inflammatory laboratory results were high at first including an IL-6 level of 17 (decreasing to 9.1 afterward), after five days of treatment and showing signs of improvement, he was discharged (figure 4).

Figure 4. A single cavitary lesion in LUL measuring around 30mm at its greatest diameter

Case 5: A 60-year-old male with worsening symptoms and laboratory results had positive sputum culture for Klebsiella pneumoniae as well as fungi for Candida sp., nasal epithelial cell culture for Enterobacter cloacae, and positive serum galactomannan. Despite receiving two weeks of treatment with Tocilizumab and potent antibiotics, the patient's symptoms did not improve significantly and he died (figure 5).

Figure 5. A cavitary lesion in the anterior segment of LUL with left collapse consolidation

Case 6: A 58-year-old diabetic male with a history of hospitalization for a week and ongoing symptoms, presented with vertigo and an instantaneous loss of consciousness after falling. The patient required a more intense course of therapy with the addition of Voriconazole and Imipenem to the prior medications as well as diagnostic and therapeutic thoracentesis of right-sided pleural effusion. Pleural fluid cytology showed many RBCs, PMNs, and fluid ADA of 38.8 without fungal elements, but with a positive pleural culture for Klebsiella pneumoniae. Eventually, after significant improvement in his general condition, the patient was discharged (figure 6).

Figure 6. A cavitary lesion with a visible air-fluid level measuring 45x50mm in the lateral basal segment of RLL and a moderate to severe pleural effusion with septate pneumothorax on the right side

Case 7: A 56-year-old female with positive cultures for Candida albicans was administered an antifungal treatment. During hospitalization, the patient's symptoms resolved and she was discharged (figure 7).

Figure 7. A single cavitary lesion in RLL

Case 8: A 62-year-old male presented with signs of Kussmaul breathing in a severe state of respiratory distress and a GCS score of 13/15. The patient underwent CPR and was then transferred to the ICU after successful stabilization, he was then transmitted to ICU. Considering his dementia, the possibility of prior fungal and bacterial infections could not be ruled out. Subsequently, the results of the initial pathologic workups showed Mucormycosis along with a positive serum galactomannan array that eventually turned out to be falsely positive due to Nocardia asteroides. Palate mucosa biopsy showed fibrinoleukocytic exudate with colonization by septate fungal hyphae. Isavuconazole and Imipenem were added to the prior therapeutic regimen, but the patient died of cardiac arrest (figure 8).

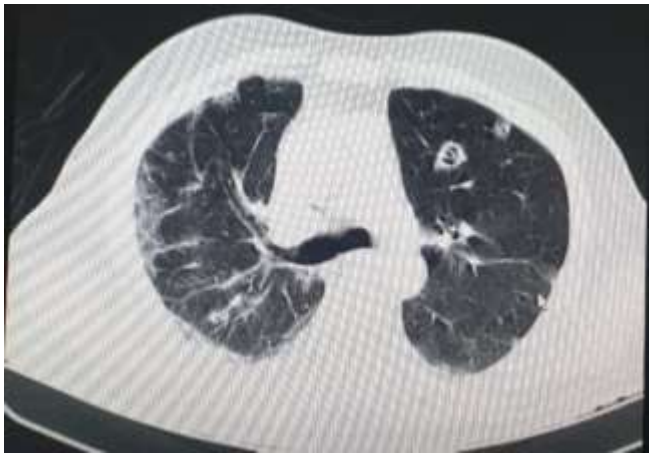

Figure 8. Multiple GGOs some of which are cavitied and filled with atelectatic bands and double-sided nodules with cavitation (especially on the left side)

Case 9: A 54-year-old addict male was admitted to our center with bilateral cavitary lesions, pneumothorax, and pleural effusion which necessitated bilateral chest tube placement. Since there were no signs of improvement in pleural effusion in about two weeks despite the chest tube, he underwent a thoracic surgeon's video-assisted thoracoscopic surgery (VATS); subsequently, his condition improved, and he was discharged (figure 9).

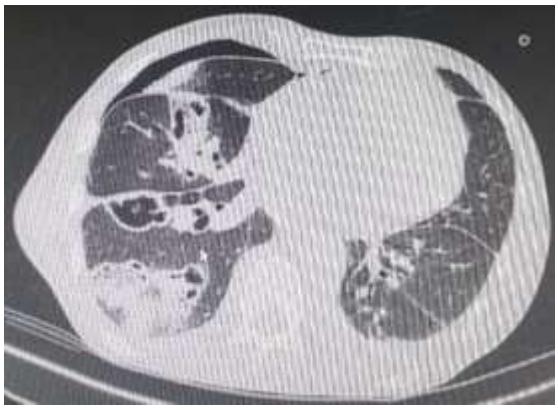

Figure 9. Fibro-bronchiectasis and fibro-cavitary in RLL, right moderate to severe hydropneumothorax, left moderate effusion with adjacent pulmonary segment collapse and mediastinal shift to the left

Case 10: A 49-year-old female was admitted with a diagnosis of spontaneous pneumothorax based on a sudden prominent increase in dyspnea. Therefore, a chest tube was immediately inserted into the patient’s right hemithorax. Owing to her positive sputum culture for Klebsiella pneumoniae and Aspergillus, positive pleural culture for Acinetobacter baumannii, and positive serum galactomannan, the patient underwent proper therapy. Eventually following the significant improvement of her symptoms, the patient was discharged (figure 10).

Figure 10. Emphysematous bullae in the left and right hemithorax measuring at the diameter of 33mm and 6mm respectively, posterobasal collapse consolidation particularly on the left, pneumothorax on the right, and hydropneumothorax on the left

Case 11: A 72-year-old female presented with a history of previous COVID-19 hospitalization. Despite suspicious cavities on her chest CT scan, the respiratory tract culture and fungal testing came out to be negative. After receiving suitable therapeutic measures for seven days, the patient's condition showed significant signs of improvement and she was discharged (figure 11).

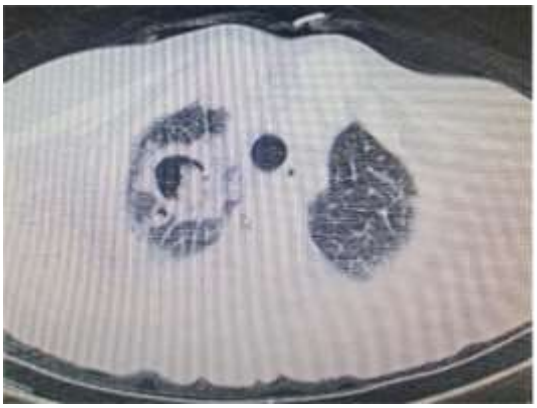

Figure 11. Numerous thick-walled cavitary lesions containing GGOs, the greatest of which measuring 39x40mm and 29x31mm present in the apex of the right lung and apicoposterior region of LUL, respectively, and several satellite cavitary lesions all around the main cavity of RUL

Case 12: A 57-year-old female was recognized with positive respiratory cultures for Staphylococcus aureus, Pseudomonas aeruginosa, and E. coli. The serum galactomannan array was recorded to be positive for Aspergillus as well. Eventually, her condition necessitated a chest tube for the patient on the right side. Although the course of improvement was found to be slow, after two months of hospitalization and care, her signs and symptoms resolved significantly, and she was eventually discharged (figure 12).

Figure 12. Two cavitary lesions in the upper zone of LLL, multiple nodules in the paratracheal region of the right hemithorax, the greatest of which was measured at 8mm, and a right-sided pneumothorax

Case 13: A 74-year-old female presented with loss of consciousness, nausea, and vomiting. She had multiple episodes of decrease in consciousness, she was transfused with one unit of packed cells and was intubated due to a prominent decrease in SpO2 room air. Considering her background disease, troponin was checked in serial finally reaching 1.01. After receiving 14 days of treatment and care, unfortunately, the patient's general condition aggravated and she expired (figure 13).

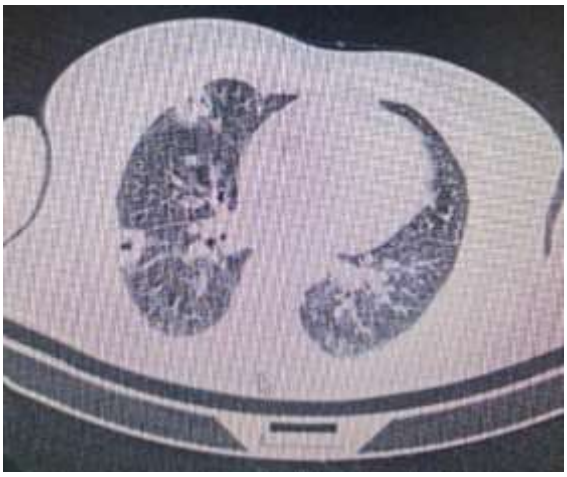

Figure 13. Multiple cavitated nodulations particularly right lung with a diameter of 7mm as the largest of them in RML, mostly in the peripheral regions of the lungs, the largest cavitary lesion was found to be 25x13mm in size, bilateral pleural effusion with adjacent collapse and mediastinal shift, particularly on the right side

Case 14: A 79-year-old female with a history of COVID-19 for two months complained of dyspnea since admission to our center. The results of respiratory tract cultures were found to be positive for Escherichia coli. After a week of stay, the patient's general condition was exacerbated and she expired following the probable diagnosis of sepsis due to a cavity in her lung (necrotizing pneumonia) (figure 14).

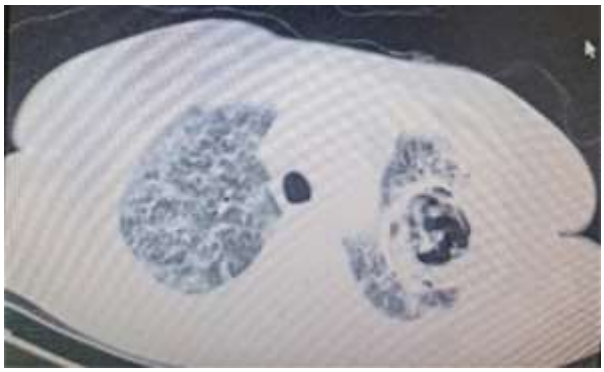

Figure 14. A single cavitary mass in LUL with a diameter of 55mm

Case 15: A 58-year-old female with a history of hospitalization for COVID-19 a week ago, presented with a decrease in SpO2 room air. She had left hemiplegia and right gaze deviation, but she was responsive. Unfortunately, after three days of stay, her condition got worse and she had a cardiac arrest and expired (figure 15).

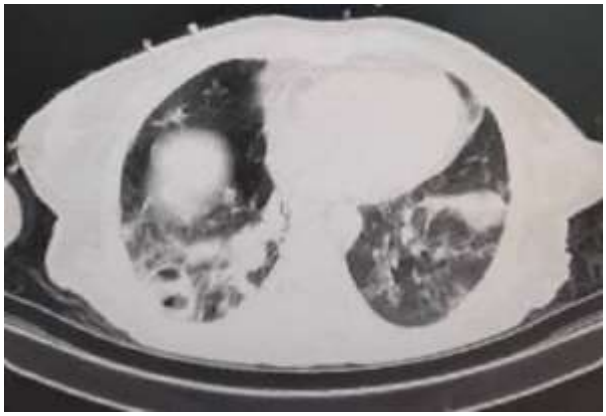

Figure 15. A cavitary lesion in RLL measuring ~~at~~ around 25mm in its largest diameter

Case 16: A 38-year-old male was admitted with the diagnosis of necrotizing pneumonia. He had symptoms of progressive FC II-III dyspnea from three days ago and loss of weight from 3 months ago. He has been a 12-pack-year smoker and a consumer of hookah. After nine days of receiving treatment, although the patient was not in a condition to be discharged, he decided to leave the hospital with his consent (figure 16).

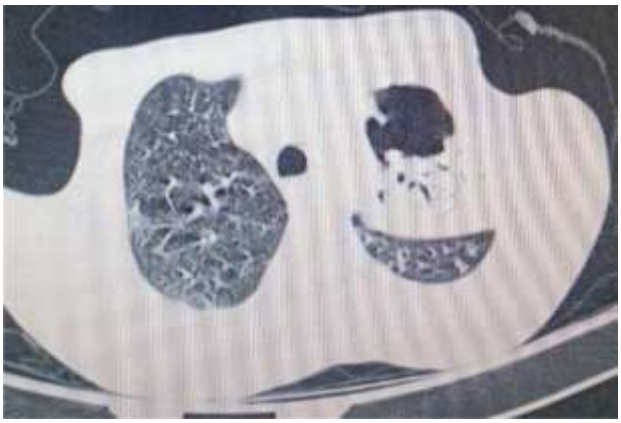

Figure 16. A single cavitary lesion in LUL and multiple foci of consolidations

Case 17: A 79-year-old male was admitted to the ICU ward. Lower respiratory tract sputum culture was positive for Enterococcus, coagulase-negative staphylococci, and E. coli. After 20 days of receiving treatment, the patient's symptoms resolved significantly (figure 17).

Figure 17. Two cavities, one of which was 40mm and located in the medial RLL and the other 16mm in the posterior RUL

Case 18: A 70-year-old male case of Parkinson's disease presented to our emergency with a decrease in the level of consciousness from three days ago which has aggravated since. Respiratory tract specimen cultures were positive for Klebsiella pneumoniae. The PPD test was measured at 20 mm. The patient went through assessments to rule out TB including an interferon-gamma release assay (IGRA) test and smear BK which were both negative. It is fair to mention, he did not receive Tocilizumab during his stay. He was discharged after 17 days with proper medications and recommendations to refer to specialized clinics weeks after (figure 18).

Figure 18. A cavitary lesion in RLL

Case 19: A 22-year-old woman living in a rehabilitation center and incapable of walking was admitted. After 11 days of stay, with a probable diagnosis of aspiration pneumonia and administration of antibiotics, her condition got better, and was discharged (figure 19).

Figure 19. A cavitary lesion of 22mm in the base of the left lung with some scattered GGOs

Case 20: A 48-year-old with a history of sinusitis presented with an ill condition. Voriconazole was administered due to multiple cavitary lesions in the chest CT scan and amphotericin B starting from two days after the stay. Eventually, after 12 days of hospitalization, his signs and symptoms resolved significantly and he was discharged (figure 20).

Figure 20. Multiple cavitary lesions, a fungus ball, and multifocal GGOs predominantly developing in the peripheral and subpleural of both lungs

Results

The demographics, initial vital signs, and symptoms of the twenty patients mentioned are illustrated in table 1. Most of the patients were above 50 years old and had comorbidities. The onset of symptoms including fever, cough, dyspnea, chest pain, and weight loss varied from 2 months to a day prior to referral. Laboratory tests including BS, CBC, inflammatory markers, and COVID-19 RT PCR as well as direct smear, serum galactomannan, and culture test results are shown in table 2. Based on table 2, most of the patients with positive COVID-19 RT PCR had positive sputum cultures for different organisms including bacteria and fungus.

However, only two patients had positive blood cultures. The third table provides details about the prior COVID state, characteristics of the cavities on CT, treatment choices, and outcome i.e., ICU admission, LOHS, intubation, and final condition. The most prevalent drugs used were Cephalosporins, Vancomycin, Meropenem, Amphotericin B, and Voriconazole. Only one patient suffered from concomitant pulmonary embolism, and the LOHS varied from 3 days to 2 months (table 1, 2, 3).

Table 1. Demographics, initial vital signs, and symptoms of patients

	Demographics			On admission vital signs					Symptoms					
Case	Age	Sex	Comorbidity	Room air SpO2	Blood Pressure	Pulse Rate	Respiratory Rate	Temperature	Fever	Cough	Dyspnea	Chest Pain	Weight Loss	Onset day
1)	51	F	Asthma HBS DLP IHD	78%	130/80	86	15	36.1	+	+	+	+	-	7d prior
2)	56	M	Prediabetic HTN	74%	120/80	90	20	36.5	+	-	+	-	-	14d prior

Case	Demographics			On admission vital signs					Symptoms					
	Age	Sex	Comorbidity	Room air SpO2	Blood Pressure	Pulse Rate	Respiratory Rate	Temperature	Fever	Cough	Dyspnea	Chest Pain	Weight Loss	Onset day
3)	79	M	T2DM HTN CHF BPH CABG	93%	95/70	88	20	37	-	-	+	-	-	2m prior
4)	53	M	-	82%	130/80	96	18	37.6	+	-	+	-	-	10d prior
5)	60	M	-	73%	110/70	96	15	38.2	+	+	+	-	-	12d prior
6)	58	M	T2DM	81%	110/80	86	20	36.8	-	-	+	+	-	1m prior
7)	56	F	Asthma	85%	100/70	94	18	37	+	+	+	-	-	14d prior
8)	62	M	Prediabetic	70%	100/60	95	30	37	-	-	+	-	-	2d prior
9)	54	M	Moderate to Severe MR CHF CABG	90%	90/70	75	19	37.2	+	+	+	+	+	1d prior
10)	49	F	HTN Asthma	95%	134/97	120	20	37.1	-	-	+	-	-	1d prior
11)	72	F	T2DM HTN IHD	86%	130/80	81	16	36.8	-	+	-	-	-	14d prior
12)	57	F	KT	93%	100/70	83	18	36	+	+	+	-	-	15d prior
13)	74	F	T2DM MI IHD	79%	95/70	88	20	36.8	+	-	-	-	-	4d prior
14)	79	F	T2DM CKD HTN hypothyroid -ism	70%	125/70	108	24	36	-	+	+	-	-	1m prior
15)	58	F	T2DM CKD HTN HLP	76%	117/81	80	24	36.8	-	-	-	-	-	2d prior
16)	38	M	-	83%	120/80	80	13	36.8	-	+	+	-	+	3d prior

Case	Demographics			On admission vital signs					Symptoms					
	Age	Sex	Comorbidity	Room air SpO2	Blood Pressure	Pulse Rate	Respiratory Rate	Temperature	Fever	Cough	Dyspnea	Chest Pain	Weight Loss	Onset day
17)	79	M	-	86%	90/58	170	16	37	-	+	+	-	-	3d prior
18)	70	M	Parkinson's disease	85%	100/60	60	17	36.2	-	+	+	-	-	3d prior
19)	22	F	CP	87%	120/80	89	13	37.5	-	+	+	-	-	1d prior
20)	48	M	T2DM	60%	75/50	130	18	36	-	-	+	-	-	2d prior

Table 2. Laboratory test results of patients on admission

Case	Laboratory Tests											Culture Tests			
	BS	ESR	CRP	LDH	D dimer	Ferritin	Pro BNP	Leuco.	Neutro.	Lympho.	COVID-19 RT PCR	Direct Smear	Serum Galactomannan	Sputum Culture	Blood Culture
1)	113	47	99	600	1491	>800	-	15.5	90%	10%	+	-	-	Acinetobacter Baumanni (MDR)	Enterococcus Faccium Staphylococcus saprophyticus Acinetobacter L woffi (MDR)
2)	129	36	59.9	1015	3827	>800	618	10.8	85%	11%	+	Gram negative bacilli	-	E coli	-
3)	50	39	12	305	1747	222	704	16.5	85%	15%	-	-	-	-	-
4)	156	22	45	1002	303	>800		12.1	90%	10%	+	-	-	-	-
5)	181	54	43.7	873	586	>800	422	7.2	89%	11%	+	Gram negative cocci and bacilli	+	Klebsiella pneumoniae (CRE)	-

Case	Laboratory Tests											Culture Tests			
	BS	ESR	CRP	LDH	D dimer	Ferritin	Pro BNP	Leuco.	Neutro.	Lympho.	COVID-19 RT PCR	Direct Smear	Serum Galactomannan	Sputum Culture	Blood Culture
6)	171	8	88	1256	4029	318.9	2770	14.3	92%	7%	-	Gram negative bacilli	-	Klebsiella pneumoniae	-
7)	113	78	42	621	723	351.7	-	2.8	70%	30%	+	-	-	Candida albicans	-
8)	390	14	5	377	1084	-	-	16.3	95%	5%	+	Candidiasis	+	Nocardia asteroides	Staphylococcus epidermidis
9)	139	15	10.4	-	-	-	-	12	90%	10%	+	-	-	-	-
10)	134	37	35	616	3655	432		26	90%	5%	+	Gram negative bacilli	+	Klebsiella pneumoniae (ESBL) Aspergillus	-
11)	312	5	6	865				17.4	90%	10%	-	-	-	-	-
12)	127	35	27	618	343	180	465	9.7	87%	9%	+	Gram-positive cocci Gram negative bacilli	+	Aspergillus S. aureus P. aeraginosa E. coli	-
13)	131	97	85	313	2389	650	-	14.7	87.7	8.2	-	-	-	-	-
14)		42	69	1002				19.7	95%	5%	-	-	-	-	-
15)	641	89	36	309	478	121	2480	8.3	89%	11%	+	-	-	-	-
16)	77	36	59.4	552	2940	793	-	3.7	72%	23%	+	-	-	-	-

Case	Laboratory Tests											Culture Tests			
	BS	ESR	CRP	LDH	D dimer	Ferritin	Pro BNP	Leuco.	Neutro.	Lympho.	COVID-19 RT PCR	Direct Smear	Serum Galactomannan	Sputum Culture	Blood Culture
17)	136	80	112	412	320	>800	-	4.4	90%	10%	+	Gram negative bacilli	-	Enterococcus CoNS E. coli	-
18)	127	30	6	486	1160	177	-	10	90%	10%	-	Gram negative bacilli	-	Klebsiella pneumoniae	-
19)	101	29	53	271	450	-	-	9.8	90%	10%	-	-	-	-	-
20)	297	110	15.2	544	2578	532	324	7.2	75%	20%	-	-	-	-	-

Table 3. Treatments, therapeutics, and outcomes of patients

Case	Prior COVID	CT Findings	Treatment					Outcomes				
			Rem-desivir	Toclizu-mab	Reci- Gen	Antibiotics	Antifungals	ICU Admit	Intubated	Pulmonary Emboli	LOHS	Final Condition
1)	-	Bilateral cavities	+	+	+	Azithromycin Ceftriaxone	Amphotericin B	-	+	-	8 d	Deceased
2)	+	RLL cavity 45mm	+	+	-	Ceftriaxone Levofloxacin	-	+	+	+	12d	Deceased
3)	+	RML mass 30x31x24 mm	+	-	-	Vancomycin Ciprofloxacin Ceftriaxone	Amphotericin B	-	-	-	1d	Survived
4)	+	LUL single cavity 30 mm	+	-	+	Levofloxacin	-	-	-		5d	Survived
5)	-	LUL cavity	+	+	-	Ciprofloxacin Colistin Linezolid Meropenem	Amphotericin B	+	+	-	25d	Deceased

Case	Prior COVID	CT Findings	Treatment					Outcomes				
			Rem-desivir	Tocilizu-mab	Reci- Gen	Antibiotics	Antifungals	ICU Admit	Intubated	Pulmonary Emboli	LOHS	Final Condition
6)	+	RLL cavity 45x50mm	+	-	-	Ciprofloxacin Imipenem Meropenem	Amphotericin B Voriconazole	-	-	-	16d	Survived
7)	-	RLL single cavity	+	-	-	Ceftriaxone Azithromycin	Amphotericin B Ketoconazole	-	-	-	6d	Survived
8)	+	Multiple cavitary nodules	-	-	-	Trimethoprim-sulfamethoxazole Ceftriaxone Imipenem Cefepime Vancomycin	Amphotericin B Posaconazole Isavuconazole	+	+	-	3d	Deceased
9)	-	RLL fibro-cavitary	-	-	-	Imipenem Meropenem Vancomycin Ciprofloxacin	-	-	-	-	23d	Survived
10)	+	left…emphysematous bullae 33mm Right emphysematous bullae 6mm	-	-	-	Vancomycin Clindamycin Meropenem Colistin Azithromycin Cefepime	Amphotericin B Voriconazole Fluconazole Nystatin	-	-	-	11d	Survived
11)	+	Right apex cavity 39x40mm LUL cavity 29x31 mm satellite cavities	-	-	-	Vancomycin Cefepime Metronidazole Ciprofloxacin Ceftazidime	Amphotericin B	-	-	-	6d	Deceased
12)	-	2 LLL cavities	-	-	-	Levofloxacin Colistin Cotrimoxazole Tobramycin Meropenem Vancomycin	Voriconazole	+	+	-	60d	Survived
13)	+	Cavitated nodules In RML and peripheral regions Largest Cavity 25x13mm	+	-	-	Vancomycin Meropenem	Amphotericin B		+	-	14d	Deceased

Case	Prior COVID	CT Findings	Treatment					Outcomes				
			Rem-desivir	Tocilizu-mab	Reci- Gen	Antibiotics	Antifungals	ICU Admit	Intubated	Pulmonary Emboli	LOHS	Final Condition
14)	+	LUL single cavity 55mm	+	-	+	Ceftazidime Meropenem Vancomycin	Amphotericin Voriconazole	-	+	-	7d	Deceased
15)	+	RLL cavity 25mm	+	+	-	Ceftazidime Vancomycin Colistin Clindamycin Azithromycin	Amphotericin B	+	+	-	3d	Deceased
16)	-	LUL single cavity	+	-	-	Vancomycin Tazocin Ceftriaxone	Amphotericin B Voriconazole		-	-	9d	Survived
17)	-	RLL cavity 40mm RUL cavity 16mm	+	-	-	Meropenem Vancomycin Ciprofloxacin	Amphotericin B	+	-	-	20d	Survived
18)	+	RLL cavity	-	-	-	Vancomycin Cefepime Clindamycin	-	-	-	-	17d	Survived
19)	-	Left lung base cavity 22mm	-	-	-	Ceftriaxone Azithromycin Vancomycin Clindamycin	-	-	-	-	11d	Survived
20)	+	Multiple cavities	+	-	-	Vancomycin Cefepime	Amphotericin B Voriconazole	-	-	-	12d	Survived

Discussion

To the best of our knowledge, this is the first-ever study to particularly investigate lung cavitary lesions in a tertiary referral center in Iran in such a large group of patients while also looking into the clinical characteristics, management, and possible sequelae of the condition in light of the literature. Cavitary pulmonary lesions appear to be rare findings among other COVID-19 evidence in scans, varying in leading cause and necessitating more investigations (3, 4) . The rates range from 1.7 to 11% among the late consequences of the COVID-19 infection (8). Several etiologies can lead to the development of lung cavities in COVID-19 patients. First and foremost, in most cases, we can attribute it to secondary or superinfections i.e., bacterial, fungal, and TB infections (5, 6, 9). Bacterial superinfection was the main probable cause in studies of Yin et al. and Yuan et al. in which eleven COVID-19 patients treated with high-dose antibiotics, antivirals, glucocorticoids, and mechanical ventilation for a long-term developed cavitary lesions during their one month of hospital stay (11, 12). The bacteria adhere to the necrotic tissue of the cavitary wall to create biofilm, thus making it harder for drugs to penetrate in and potentially rendering the drug ineffective. However, researchers have not proven yet that the virus coexists with bacteria in a biofilm (13, 14). Therefore, patients should undergo microbiologic testing as a diagnostic tool. Just as in our study, 8 (35%) patients had evidence of bacterial infection in sputum direct smear while 9 (5%) had positive sputum culture.

Secondly, 3 (15%) patients in our study had evidence of fungal infection such as Candida Albicans and Aspergillus in their direct smears or sputum cultures. One of our patients

showed an established Mucormycosis which complicated his prognosis and led to his death. Although pulmonary Mucormycosis used to be rare in the first place, CAPM (COVID-19-associated pulmonary Mucormycosis) became relatively prevalent during the pandemic so much that many studies have focused on this area, one of which reported lung cavities in 69% of them (15). In a follow-up study on post-COVID-19 cavity characteristics (16), 9 patients were discovered to have lung cavities, 4 out of 7 patients had recovered from severe COVID-19, 5 patients had CAPA (COVID-19 associated pulmonary aspergillosis)- two of whom grew Klebsiella in their sputum cultures as well-, a patient was a case of Mucormycosis and another one a case of Mycobacterial infection; eventually representing fungal infection as the most common cause of the cavities. Therefore, another tool for further assessment would be serum galactomannan which turned out positive in 4 patients (20%) in our study. In another study, among the 10 recovered patients from severe COVID-19, 8 of them presented with a single cavitary lesion, 5 out of 9 were found to have positive serum galactomannan, while 2 out of 7 had a positive fungal culture for Aspergillus spp (17) .

It is worth mentioning that the patient's past medical history, immune and inflammatory responses, and even the probability of developing pulmonary emboli or infarcts after COVID-19, can play an important role (18). Diabetes mellitus is the most common comorbidity in COVID-19 cases with pulmonary cavitation (8, 9, 18). This is probably because of the high prevalence of diabetes in all COVID-19 patients, specifically the critically ill patients. Likewise, in our study, 9 (45%) patients were diabetic. Despite the possible roles of comorbidities, lung cavities in COVID-19 patients can develop regardless. For instance, in our study, 4 (20%) patients declared no noticeable past medical history. Another surprising case was an otherwise healthy severe post-COVID-19 patient who developed primary spontaneous tension pneumothorax and further hydropneumothorax as a result of the pulmonary cavity (19). Chronic cysts can rupture during forceful cough and cause pneumothorax. Cavitary lesions might as well raise the chance of pneumothorax by extending to the pleura. Similarly, another case report by Chen et al. presented a treated COVID-19 patient who was otherwise healthy and without a history of smoking, but two days later the patient felt a sudden chest stuffiness which then turned out to be a large cavity in the lung (18).

This study suggested that even though most viral infection lesions in the lungs are absorbed and cured well, we might still need to pay attention during the post-COVID period mainly by following up their chest CT scans. In addition, even iatrogenic factors such as high-dose corticosteroid therapy can help develop lung cavities (9). On the other hand, high-dose corticosteroids are quite necessary for the management of COVID-19 itself, especially during the acute phase; therefore, it brings up a dilemma and makes our decision harder. We administered high-dose corticosteroids for severe cases of COVID-19 in our center because of the inflammation and cytokine release. Furthermore, physicians use low-dose corticosteroids in the post-COVID-19 period to decrease inflammation ~~as well~~. For instance, the anti-inflammatory effects of corticosteroids can improve a patient's condition in ICU who suffers from severe COVID-19 pneumonia with dependency on oxygen both clinically and radiologically by returning the patient to his daily activities with great exercise tolerance (20).

In addition, corticosteroids play a potential role in CAPA (COVID-19-associated pulmonary aspergillosis) (21), as both corticosteroids and Tocilizumab can act as risk factors for CAPA (22). On top of that, we can also blame Tocilizumab for pulmonary aspergillosis and lung cavities ((23, 24, 25), being administered in 4 (20%) patients in our study (mostly severe cases). Nevertheless, lung cavities are discovered in non-COVID-19 individuals as well; most prevalently following a bacterial and fungal infection or mycobacterial and parasitic organisms with less likelihood. It can also be a result of pulmonary infarction or emboli and neoplastic illnesses, though with less frequency (14). Corticosteroids were described as a risk factor for aspergillosis in lung disease patients long before the COVID-19 pandemic. They act by decreasing the activity of macrophages against fungal infections and suppressing their migration, while macrophages and neutrophils act as the main immune defense against Aspergillus spp. Although patients rarely get involved with Aspergillus by using frequent doses of corticosteroids mainly used in our settings, we should pay attention to the duration and dose, particularly in pneumonia patients with cavitary lesions (26). Our investigations ruled out the possibility of pulmonary emboli except for one patient. On one hand, aseptic necrosis which happens when a bland infarct occurs can form cavities in the lung tissue (13).

On the other hand, the superinfection of bacteria on the infarct tissue can transform it into a cavity (10). Cases have been identified with pulmonary cavities that got involved with pulmonary emboli with the main alarming symptom of hemoptysis which was roughly observed in our patients. Chest pain, however, as another suspicious complaint was seen in 3 of our cases (15%) necessitating more assessments. Our patient with confirmed pulmonary emboli

presented with fever and dyspnea. (27, 28). One study explains the higher rate of pulmonary emboli in COVID-19 patients with cavities compared to the ones without. This was attributed to their higher BMI and older age; however, our patient was a 56-year-old male. These factors can also weaken the lung structure and predispose it to cavity formation (10). Another pathophysiology would be the long-term mucous which accumulates in the small bronchioles, leads to inflammation, and consolidates within the parenchymal lung tissue resulting in fibrosis, scarring, traction bronchiectasis, and ultimately cavities (29). Primarily, even though we intended to investigate all the cases thoroughly, we missed little data in some cases, inevitably leaving us with fragmentary clinical comparisons on some characteristics. Secondly, it should be noted that we opted to analyze our cases in the setting of a case-series study because there were no control cases. If there were matched control cases, we could conduct a much more in-depth analysis of the determinants of cavitation in COVID-19 patients. Another limitation was that we could not perform bronchoscopy and BAL (bronchoalveolar lavage) since nearly all the patients were severely hypoxic. Moreover, only articles in English were reviewed in this study. Researchers will need to carry out future studies to shed light on the matter.

COVID-19 has led to consequences becoming worrisome worldwide. Although pulmonary cavitation did not appear so common at first in COVID-19 patients, we detected 20 patients with lung cavities either concomitantly with COVID-19 or during their post-COVID-19 period. Lung cavities are among rare radiologic findings in acute-phase COVID-19 patients who are otherwise healthy and without risk factors. Yet, we concluded that we cannot attribute it directly to the virus, and other factors help form cavities in the lung tissue. In general, lung cavities are multi-etiological in pathogenesis, most prevalently following a bacterial or fungal superinfection in patients with comorbidities, particularly diabetes. As well as this, our management such as high-dose corticosteroids and Tocilizumab might have played an iatrogenic role in the development of cavitary lesions just like the post-treatment phase of Aspergillosis or Mucormycosis. Similar to our study, it commonly happens in the post-recovery phase of COVID-19 infection, thus necessitating follow-up scans and assessments.

Acknowledgments

The authors would like to thank the medical records section of the Shohada e Tajrish Hospital for providing the patients' medical reports for scientific purposes.

Funding: None declared.

Conflict of interest: None declared.

Consent for publication: All authors have reviewed the results and approved the final version of the manuscript.

Authors' contribution: The authors confirm their contribution to the paper as follows: RB came up with the study conception and design, SS and FE collected the data, and SS and FE prepared the draft manuscript.

References

1. Bidari Zerehpoosh F, Sabeti S, Bahrami-Motlagh H, et al. Post-mortem histopathologic findings of vital organs in critically Ill patients with COVID-19. Arch Iran Med 2021; 24: 144-51.
2. Rahimi FS, Afaghi S, Tarki FE, et al. Viral outbreaks of SARS-CoV1, SARS-CoV2, MERS-CoV, influenza H1N1, and ebola in 21st Century; a comparative review of the pathogenesis and clinical characteristics. Sch Med St J 2020; 2: 1-8.
3. Sun Z, Zhang N, Li Y, Xu X. A systematic review of chest imaging findings in COVID-19. Quant Imaging Med Surg 2020; 10: 1058-79.
4. Zheng Y, Wang L, Ben S. Meta-analysis of chest CT features of patients with COVID-19 pneumonia. J Med Virol 2021; 93: 241-9.
5. Amaral LTW, Beraldo GL, Brito VM, et al. Lung cavitation in COVID-19: co-infection complication or rare evolution? Einstein (Sao Paulo) 2020; 18: eAI5822. [in Portuguese, English]
6. Selvaraj V, Dapaah-Afriyie K. Lung cavitation due to COVID-19 pneumonia. BMJ Case Rep. 2020; 13: e237245.
7. Xu Z, Pan A, Zhou H. Rare CT feature in a COVID-19 patient: cavitation. Diagn Interv Radiol 2020; 26: 380-1.
8. Zoumot Z, Bonilla MF, Wahla AS, et al. Pulmonary cavitation: an under-recognized late complication of severe COVID-19 lung disease. BMC Pulm Med 2021; 21: 24.
9. Singh P, Tiwari S, Yadav A, et al. Pulmonary cavitation in follow-up COVID 2019 cases: An etiological perspective. Med J Armed Forces India 2022; 1-9.
10. Kruse JM, Zickler D, Lüdemann WM, et al. Evidence for a thromboembolic pathogenesis of lung cavitations in severely ill COVID-19 patients. Sci Rep 2021; 11: 16039.
11. Yin J LK, Liu S, et al. Radiology of thoracic complications in SARS. J Capital Med Uni 2003; 24: 401-4.

12. Yuan C, Zhao D, Wang W, et al. Imaging manifestations of the cavitation in pulmonary parenchyma of SARS. Chin J Radiol 2004; 38: 466-9.
13. Marchiori E, Nobre LF, Hochhegger B, Zanetti G. Pulmonary cavitation in patients with COVID-19. Clin Imaging 2022; 88: 78-9.
14. Özgül HA, Alpaydın AÖ, Yiğit S, Gezer NS. Pulmonary cavitations as an atypical CT finding in COVID-19 patients. Clin Imaging 2021; 79: 1-2.
15. Garg M, Prabhakar N, Muthu V, et al. CT findings of COVID-19–associated pulmonary mucormycosis: a case series and literature review. Radiology 2022; 302: 214-7.
16. Rai DK, Priyadarshi RK, Karmaker S. Study to assess aetiology, clinical and imaging characteristics of post COVID-19 pulmonary cavitation. J Family Med Prim Care 2022; 11: 739-43.
17. Swain S, Ray A, Sarda R, et al. COVID-19-associated subacute invasive pulmonary aspergillosis. Mycoses 2022; 65: 57-64.
18. Chen Y, Chen W, Zhou J, Sun C, Lei Y. Large pulmonary cavity in COVID-19 cured patient case report. Ann Palliat Med 2021; 10: 5786-91.
19. Vardhan B, Biswas P, Chatterjee S, et al. Post-COVID-19 pulmonary cavitation and tension pneumothorax in a non-ventilated patient. J Family Med Prim Care 2022; 11: 1564-67.
20. Aissaoui H, Eskenazi A, Suteau V, Adenis A, Drak Alsibai K. Case report: Potential role of corticosteroids in the management of post-COVID-19 pneumonia. Front Med (Lausanne) 2021; 8: 686806.
21. Kakamad FH, Mahmood SO, Rahim HM, et al. Post covid-19 invasive pulmonary Aspergillosis: A case report. Int J Surg Case Rep 2021; 82: 105865.
22. Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among intubated patients with COVID-19: a prospective study. Clin Infect Dis 2021; 73: e3606-e14.
23. Adetiloye AO, Ghosh K, Villavicencio C, et al. Chronic pulmonary aspergillosis occurring post treatment of COVID-19 pneumonia with tocilizumab. Am J Respir Crit Care Med 2022; 205: A4518.
24. Gidwani V, Chauhan S. Pulmonary aspergillosis post-tocilizumab treatment in a patient with COVID-19 pneumonia. Chest 2022; 162: A384.
25. Witting C, Quaggin-Smith J, Mylvaganam R, et al. Invasive pulmonary aspergillosis after treatment with tocilizumab in a patient with COVID-19 ARDS: a case report. Diagn Microbiol Infect Dis 2021; 99: 115272.
26. Palmer LB, Greenberg HE, Schiff MJ. Corticosteroid treatment as a risk factor for invasive aspergillosis in patients with lung disease. Thorax 1991; 46: 15-20.
27. Selvaraj V, Dapaah-Afriyie K. Lung cavitation due to COVID-19 pneumonia. BMJ Case Rep 2020; 13: e237245.
28. Vangara A, Rahmlow TH, Gullapalli D, et al. COVID-19 and cavitary lesion in lung. Cureus 2023; 15: e34098.
29. Huffnagle GB, Dickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. Mucosal Immunol 2017; 10: 299-306.