PULMONARY COMPLICATIONS OF COVID-19 INFECTION POST-SIX MONTHS

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ABSTRACT

Background

COVID-19 has been linked to a wide range of long-term respiratory consequences after the initial illness, both clinically and radiologically..

Objectives

To find the prevalence of post covid respiratory complications and their relation with HRCT findings after six months from infection.

Material and Methods

This cohort study was conducted in different Sulaimani city's COVID-19 centers from September 1st to November 30, 2021; a total of 100 patients (65 male and 35 female), a mean age of 45.5 (18-91 years old) were randomly collected. All patients had High-Resolution CT during acute infection, followed by second HRCT 6 months after the initial infection.

Results

Among 100 cases in the study, 64% of the patients have one or more chest symptoms, particularly cough (40%) and dyspnea (31%). Regardless of the age and comorbid illnesses, cough and chest tightness are predominantly found among female patients; moderately infected patients are more prone to have post-COVID symptoms than others (p-value 0.003 except for hemoptysis was 0.013). Concerning HRCT findings most common initial HRCT findings were ground glass opacity at 100%, consolidation49%, and reticulation at 46%, while on the follow-up scan, reticulation was the predominant finding at 44%. In addition, a significant correlation was found between cough and dyspnea with consolidation, crazy paving, and reticulation (p-value <0.001).

Conclusion

Cough and dyspnea are predominant features after six months and significantly correlate with HRCT findings of consolidation, crazy paving, and reticulation during active disease; smoking is not a risk factor for pulmonary complications.

Keywords: *SARS-Nov-2, high-resolution CT scan, ground glass opacity, reticulation.*

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INTRODUCTION

The long-term pulmonary outcomes of COVID-19 survivors are unknown since this pandemic is a novel disease. Symptoms and clinical manifestations or abnormal clinical parameters that remain for two weeks or more after the onset of COVID-19 and do not recover to a healthy baseline can be termed long-term consequences of the disease [1]. Most respiratory symptoms were identical to those during COVID-19's acute phase; however, it is possible that other consequences have not been discovered yet [2]. Disease prolongation and morbidity are well-recognized, especially in elderly-aged groups [1]. Same as other acute respiratory infections, cough is one of the most commonly mentioned symptoms by COVID-19 infected patients [3-6], not only during the active phase but continued even after acute infection [7], up to 19 days in another study 4 weeks after the first presentation [5,7], regardless of the initial severity of the infection. [8,9] other common respiratory symptoms among post-COVID-19 survivors are dyspnea, chest pain, and tightness [10-13].

Interestingly, those patients admitted to the intensive care unit during active corona infection with female gender predominance, in contrast to those admitted to the ward, have less dyspnea after full recovery and have gender equality, mainly at 6-12 weeks after discharge from the hospital [14].

Persistent HRCT imaging abnormalities have been recorded up to Day 37 after the onset of symptoms of COVID-19 and in another study conducted in China 90 days after discharge [15,16]. According to a meta-analysis, even 60–100 days after the initial manifestation, abnormalities in CT lung scans persisted in 35% of patients [2]. In COVID-19, the best timing for follow-up imaging to assess radiological clearance is uncertain. [17] .Ground-glass opacities were the most common remaining lesions, preceded by linear opacifications. [18] .Spontaneous pneumothorax has been described as a COVID-19 consequence in approximately 1.7%of patients [19]. However, the frequency of post-COVID-19 fibrosis will take time; a preliminary study of COVID-19 patients discharged from the hospital indicated high fibrotic lung function abnormalities [20].

Lung fibrosis after COVID-19 is more common among the elderly, and multifocal initial lung involvement [21] at autopsy, pulmonary fibrosis is commonly found in COVID-19 fatal cases [22] .

MATERIALS AND METHODS

Study design and participants: This cohort study was conducted in different Sulaimani city's COVID-19 centers from September 1 to November 30, 2021, with a total of 100 patients selected randomly; all of them had High-Resolution CT during acute infection. Then after six months, a second HRCT was done for all of them after taking informed consent from all study participants; we excluded the following patients those aged less than eighteen years, with symptoms duration less than six months from the initial infection, those who were not willing to participate, or had a history of chronic lung diseases, mechanically ventilated cases during the active disease process and pregnant ladies.

The Research Ethics Commission of the Kurdistan board for medical specialties approved the study on July 11, 2021.

Data collection and validation tools

Clinical data and demographic features like (age, sex, education, cigarette smoking, past medical history, course of the disease, and first HRCT that was taken in all of them during the acute course of the infection) were taken directly from the patients as in our city we have not electronic medical records. All of the included cases sought medical help as they complained of persisting one or more clinical symptoms during acute infection and were interviewed face-face in outpatient clinics, both governmental and private clinics, finishing six months after the first COVID-19 presentation. They were asked to report the newly occurring. Persistent symptoms, or any symptoms worse than before COVID-19 development, particularly chest symptoms such as cough, chest tightness, chest pain, dyspnea, and hemoptysis, then follow HRCT taken in Sulaimani Radiology Center, HRCT scans were achieved with a single inspiratory phase, Patients were taught to hold their breath to reduce motion artifacts. The tube voltage for CT acquisition was 120kVp with automated tube current modulation. (Thickness of 1.5mm and increment of 1.2mm) in transverse slice orientation using either hybrid iterative reconstruction (iDose level 5, siemens). The first HRCT images were cross-compared during the active disease state and the follow-up image. One experienced radiologist and one pulmonologist evaluated the HRCT features.

RESULTS

Among a total of enrolled 100 cases, 35 % of them were female, and 65% were male; the median age was 45.6±16.4, ranging from 18- 91 years, 44% were younger than 40 years, 34% were aged between 40-60 and only 22% elder than 60 years old. The majority of the infected patients (43%) were lifelong non-smokers. In comparison, current smokers and ex-smokers compromised 36% and 10 %, respectively; the three most common comorbidities among the participants were hypertension (32%), diabetes (25%), and ischemic heart disease (13%). Meanwhile, half of them had no chronic illness. Regarding the severity of the disease during the acute stage, 43% had mild covid, 39% were moderate, and the rest, 18%, had severe disease.

The most common HRCT finding during the active state of the disease was GGO found among all of them; close to half (49%) had consolidation; another common finding was reticulation in 46%, crazy paving found in 43%, bronchiolar and interlobular thickening in 41%, on the other hand, the rest of the HRCT changes were uncommon and included cavitation, pneumothorax and pleural effusion which were less than 10%.

The most common self-reported symptoms by our participants were cough in 40% of them, then dyspnea accounts for about 31%, followed by chest tightness mentioned by 30%. In contrast, only 20 patients reported chest pain, and hemoptysis, the least common symptom, accounts for less than 10%. On the other hand, 36% of the cases claimed that they had no symptoms and went back to pre-corona health status. The dynamic HRCT changes after six months from the first symptoms illustrated that almost half of them returned to normal appearance in 49%, approximately reticulation is the most common lung finding in 44%, while GGO takes 23%, which is close to bronchiolar and interlobular thickening the difference is only 3%, less common presentation is pulmonary cavitation in 13 cases out of total cases, and ultimately crazy paving 9%, consolidation 8%, pleural effusion 3% and pneumothorax 1%.

On follow-up visits most common symptoms were cough. It was more observed among women p-value of 0.003, older than 60 years, and never smokers with the same p-value <0.001, while dyspnea was more observed among male patients (p-value of 0.06), and those persons older than 60 years p-value of 0.01, and again in never smokers with significant p-value <0.001. Chest tightness is predominantly found among female patients compared to male patients, with a p-value of 0.001, more among older than 60 years p-value of 0.003. In never-smokers (p-value 0.061), the second most commonly mentioned symptom by male patients was chest pain p value 0.6, in contrast to other clinical symptoms among young and middle-aged populations p value 0.55, and in never-smoked groups, p-value <0.001. According to our results, we found a strong correlation between having diabetes and developing post-COVID cough in comparison to the rest of the symptoms p-value of 0.005, while in those who have hypertension, the most frequently mentioned symptoms were cough but not significantly correlated; on the other hand, chest tightness is predominant finding than other symptoms p value 0.008 among those patients who have ischemic heart disease. A strong positive correlation exists between a cough and having had a moderate initial COVID infection. Subsequently, dyspnea, chest tightness, chest pain, and hemoptysis were to a lesser extent but with significant correlation for all of them p value <0.001 apart from hemoptysis, which was 0.013.

We found a powerful correlation between the first HRCT findings of reticulation, consolidation, and crazy paving with the development of cough and dyspnea after six months of initial infection, with a p-value of <0.001. We did not find any correlation between other rare findings, such as pleural effusion and pneumothorax with later cough presentations, bronchiolar and interlobular thickening, and pneumothorax were significantly linked to post COVID dyspnea, ultimately pulmonary cavitation and pleural effusion do not show a strong correlation. Initial HRCT presentations of crazy paving, consolidation, and reticulation made post-COVID survivors more prone to developing chest tightness p value <0.001 in the case of crazy paving and reticulation and 0.006 in the case of consolidation. A Strong correlation was found between survivors who complained of chest pain and their HRCT showing bronchiolar and interlobular thickening (p-value 0.001), reticulation (p-value 0.005), and crazy paving (p-value 0.006). In contrast, only 14 cases of those with consolidation in their HRCT developed chest pain during the follow-up visit. A correlation was not obtained between chest pain with cavitation, pneumothorax, and pleural effusion. The least common post-COVID symptoms of hemoptysis were more observed in those patients who presented with radiological findings of crazy paving and cavitation with the same p-value of 0.001, while

its relation with consolidation was again significant p-value 0.029, and only six survivors among all of them who got hemoptysis had reticular lung changes at first presentation. No correlations were found between post-COVID hemoptysis with pneumothorax and pleural effusion at the beginning of the disease process.

The predominant HRCT finding was normalising previous lung parenchymal changes after six months; this is more obvious among young aged male patients and current smokers with significant p <0.001, regarding the second most common HRCT presentation, i.e., reticulation found among female patients who never smoke with very significant p-value <0.001, and age distribution between 40-60 years p value 0.001, GGO also more predominant in female gender p value 0.049, and unlike other findings its more obvious among old age groups p value 0.002, and never smokers as well p value 0.011, bronchiolar and inter lobular thickening more commonly seen among never smokers, p-value <0.001, also its more in male survivors p value 0.295. it has aged 40-60 years p-value of 0.007. Majority of the patients with hypertension, their HRCT goes back to complete normally after six months from acute infection p value 0.115, followed by those who have diabetes mellitus and ischemic heart disease (p-value 0.001 and 0.072 respectively), reticulation negatively correlated with diabetes p in value 0.001, hypertension p value 0.407 and ischemic heart disease 0.015, while having hypertension made GGO finding more obvious in comparison to other chronic illnesses p value 0.004.bronchiolar and interlobular thickening have a positive correlation with DM and IHD but are not related to HTN.

Table 1. The association between socio-demographic characteristics and smoking history with respiratory symptoms after six months from initial infection with COVID-19.

Socio-demography and smoking history		Chest symptoms after six months									
		ough	p-value	Chest pain	p-value	Chest tightness	p-value	dyspnea	p-value	hemoptysis	p-value
Gender	Female	21	0.003	8	0.6	18	0.001	15	0.060	3	1
	Male	19		12		12		16		5	
Age	<40	10		7		9		8		2	
	40-60	14	<0.001	7	0.550	8	0.003	11	0.011	5	0.251
	>60	16		6		13		12		1	
Residency	Urban	28	0.716	14	0.824	21	0.771	18	0.037	7	0.436
	Rural	12		6		9		13		1	
Occupation	Student	1		0		0		1		0	
	Employed	13		9		12		11		7	
	Unemployed	5	0.001	3	0.429	3	0.015	3	0.028	0	0.181
	Retired	12		5		9		8		1	
	Housewife	9		3		6		8		0	
Smoking	Current smoker	2		0		5		2		1	
	Ex-smoker	5		2		3		2		1	
	Passive smoker	4	<0.0001	1	<0.001	3	0.061	2	<0.001	0	0.305
	Social smoker	1		2		2		4		1	
	Never smoker	28		15		17		21		5	

Table 2. The association between socio-demographic characteristics and smoking history with post-six-month HRCT findings.

Sociodemography and smoking history		Post 6 months HRCT findings							
		normal	p-value	Ground glass appearance	p-value	Bornchiolar /&interlobular thickening	p-value	consolidation	p-value
Gender	Female	9	0.001	12	0.049	9	0.295	5	0.124
	Male	40		11		11		3	
Age	<40	30		5		3		2	
	40-60	15	0.001	7	0.002	9	0.007	2	0.170
	>60	4		11		8		4	
Residency	Urban	40	0.035	17	0.816	12	0.181	5	0.683
	Rural	9		6		8		3	
Occupation	Student	9		1		0		0	
	Employed	24		9		10		3	
	Unemployed	11	<0.001	0	0.002	1	0.090	0	0.205
	Retired	2		9		6		3	
	House wife	3		4		3		2	
Smoking	Current smoker	31		3		0		0	
	Ex-Smoker	5		1		3		1	
	Passive smoker	3	<0.001	2	0.011	2	<0.001	1	0.062
	Social smoker	2		3		2		1	
	Never smoker	8		14		13		5	

Table 3. The association between socio-demographic characteristics and smoking history with post-six-month HRCT findings .

Sociodemography and smoking history		Post 6 months HRCT findings							
		cavitation	p-value	Crazy paving	p-value	Reticulation	p-value	Pleural effusion	p-value
Gender	Female	6	0.366	4	0.716	26	<0.001	1	1
	Male	7		5		18		2	
Age	<40	3		3		11		2	
	40-60	7	0.198	4	0.826	17	0.001	1	0.796
	>60	3		2		16		0	
Residency	Urban	7	0.118	6	0.707	26	0.014	3	0.557
	Rural	6		3		18		0	
Occupation	Student	0		0		1		0	
	Employed	6		5		15		3	
	Unemployed	1	0.508	2	0.659	5	<0.001	0	0.738
	Retired	3		2		12		0	
	House wife	3		0		11		0	

Table 3. Continued..

Smoking	Current smoker	0		9		4	0	
	Ex-Smoker	1		1		5	0	
	Passive smoker	2	0.007	0	0.041	3	0	0.536
	Social smoker	1		0		2	0	
	Never smoker	9		8		30	3	

<0.001

DISCUSSION

Sixty-four percent of our patients with a proven COVID-19 infection continue to have ongoing morbidity that is similar to symptoms during the active disease process, for instance, dry cough, dyspnea, chest tightness, and chest pain, only 8% of the cases complained about hemoptysis; meanwhile, 36% of the cases had no any symptoms and returned to their usual state of health after six months from acute infection, these post COVID-19 symptoms differ significantly from country to country and population, the most prevalent symptoms, according to some research, were cough, low-grade fever, and exhaustion, all of which could reoccur and remit[23].

Post-COVID chest symptoms

Although COVID-19-related symptoms improved over time, we found that Cough is the first and most frequently reported complaint mentioned by 40% of our patients six months after initial presentation. This is similar to other studies (follow-up time ranging from 6 weeks to 4 months) [24-31]; the prevalence varies substantially between studies and is likely to be influenced by patient characteristics, therapy, follow-up time, and outcome criteria[7] the exact cause unknown still but may be related to hypersensitivity of the airway, as there is a concept that SARS-CoV-2 attacks the sensory nerves causing neuroinflammation and neuroimmune interactions that are common to all of these symptoms. Although it is unclear why some people get post-COVID-19 syndrome, female sex, as parallel to our study, 21% (p-value: 0.003) and the degree of severity of COVID-19 might be considered important prediction factors [8,26,32-34], strangely, 34% of young people below 40 years their cough resolved at follow-up visits. However, about 16% of those who were older than 60 years still complained of dry cough; according to our results, smoking was not a risk factor for post-COVID-19 cough as the majority of the cases who had cough were a non-smoker, and the majority of a current smoker had no coughing [7].Patients with a mild initial severity were also observed to have a persistent cough, unlike these studies [8,35], despite that most of our cases had mild baseline COVID-19 severity. In comparison to moderate and severe the prevalence of cough are more among moderate groups higher p-value <0.0001, Most reported initial HRCT finding among those post COVID-19 survivors that have cough are reticulation, followed by consolidation, crazy paving in contrast to another study which stated that there is no correlation between symptoms and HRCT finding after three months [36].

As in other studies, dyspnea is our participants' second most common persistent symptom, 31% after six months from acute infection. However, their duration differed, for example, after three months [2,37], and in other studies, six months after recovery [18,24,38,39]. The exact cause of persisting or worsening dyspnea after acute infection is unknown. However, some researchers have discussed the long-term effects of SARS-CoV-2 infection and demonstrated that dyspnea and chest pain are caused by cell injury because of a strong innate immune response with inflammatory up-regulation [40], infection of dorsal root ganglion neurons that contain nociceptors may have a role in persisting dyspnea even after acute infection[7]. According to our study, dyspnea is more common among male patients than female patients; this concept is opposite to other studies that found it predominantly among females than males [11,41] .Also, dyspnea was more mentioned among those population groups older than 60 years p-value: 0.011. Concerning the smoking state among our participants, dyspnea was found predominantly among never smokers. According to another study, the most common complaint described by smokers was dyspnea, which could indicate underlying pulmonary disease [42]. We excluded those past COVID-19 survivors with chronic lung disease.

Chest pain and tightness were also mentioned by 20% and 30% of our COVID survivors after six months, while in other studies at the 60-day follow-up studies, 20% of COVID-19 survivors experienced chest discomfort. [43-45] .Although male patients mention chest pain, there is no strong correlation between gender, age, and chronic

underlying disease. Meanwhile, chest tightness was mentioned more by female patients and never smoked persons; with a significant p-value of less than 0.001, similar to other symptoms again, chronic illness has no impact on its prevalence but is more prominent among moderately affected COVID-19 infection and positively correlated to each other.

Lastly, hemoptysis is less frequently mentioned by our patients after recovery, accounting for only 8%; even during the active state, it is a less predominant finding[3,46]; the presence of hemoptysis makes the possibility of other complications higher, for instance, superadded bacterial infection, mainly tuberculosis, or fungal infection like mucormycosis[47], although its more reported among male patients but there we did not find a correlation with age, gender, smoking state, and underlying comorbidities. Same as other symptoms, it is more prevalent among moderately infected persons p-value of 0.013; the most common initial HRCT finding concerning hemoptysis was crazy paving and cavitation, with an equal p-value of 0.001.

Radiological pulmonary manifestations of post-COVID -19 infections

Although the bulk of our patient's HRCT returns to normal after six months from the first presentation, accounting for 49%, same as another study at time intervals of 3 months, follow-up found that most patients' HRCT lung abnormalities were resolved the following discharge entirely [37], another study found that about half of COVID-19 survivors had lung radiological abnormalities linked with persisting symptoms six months following symptom onset [41]. COVID-19 may cause lung scarring, which may cause recurrent dyspnea and cough in long-term COVID-19 patients [48]. Another possible cause of persisting symptoms concerning radiological abnormality may be due to the immunopathological basis that coronaviruses interact with and change the intracellular host environment during infection to replicate efficiently [49]. Moreover, subsequently, Because of the continuing inflammatory process in patients who have been cured of COVID-19, they may acquire permanent fibrotic interstitial lung disease; according to records available, approximately 40% of COVID-19 patients develop ARDS, and 20% of ARDS cases are severe. [50] Pulmonary fibrosis is a well-known ARDS complication. Post-COVID-19 fibrosis diagnoses have also been recorded, although mostly without histopathologic evidence and with a range of non-standard radiologic descriptions such as "fibrotic strips." Nevertheless, most follow-up research has proven that persisting radiological abnormalities after ARDS are of little clinical significance and are even uncommon in the era of protected lung ventilation [51].

Almost every post-COVID-19 survivor had GGO in their baseline HRCT screen; meanwhile, during repeating HRCT, Finally, in a manner that attracts interest, this percentage dropped to around 23%, compared to another study in which its prevalence decreased from 80.4% to 62%[52].in contrast to this study, a conducted study revealed that GGO had remained the most common HRCT pattern after six months, suggesting the progressive regression of the inflammation and re-expansion of the alveoli[53]. In line with our study, consolidation was found in around 49% during the active state of the disease, notably during follow-up, with only 8% of them persisting in these changes [54]. This indicated that radiologically lungs normalise with time, although histopathological normalisation of lung tissue is needed for more accuracy.

Subsequent abnormality was bronchiolar and inter-lobular thickening, same as others; it reduced to almost half, while in another study, it reduced to a quarter compared to initial HRCT[52]. Reticulation is the predominant finding after acute infection in follow-up HRCT. It accounts for 44 %, meanwhile significantly correlating and commonly seen among female gender, ages between [40-60] years, and those who are non-smokers compared to other participants.

Cavitation, pneumothorax, and pleural effusion were the least common HRCT findings (8.4%, 8.4%, and 2%), respectively. Similar to other viral pneumonia (including SARS-CoV and MERS-CoV), even in severe illness seldom, pulmonary cavitation will appear [55]. Nevertheless, in COVID-19 illness, cavitary lesions have been reported over a long period (4–12 weeks). In a cohort of 689 COVID-19 pneumonia patients, Zoumot Z et al. reported 12 cases (1.7%)[56]. However, except for pleural effusion (1% only), the other two abnormalities became more common after six months. Pulmonary cavitation has recently been recorded in several single-patient case reports [57-59]. We speculate that the reasons for cavitation in these patients were multifactorial, with important contributors such as bacterial and fungal co-infection; SARS-CoV-2 specific inflammatory processes; COVID-19-related propensity to venous thromboembolism and possibilities to cause infarct and micro-infarcts contributing to cavitation;

and the severe morbidity[56]prevalence of cavitation among male patients are more than female, though not significantly correlated, also its more in middle-aged group population in comparison to young and elderly, a negative correlation was found between this rare HRCT finding and smoking as cavitation more prevalent among never smoked enrolled patients than active and passive smokers. Past medical history of chronic diseases is again not correlated with cavitation.

Pneumothorax has been documented in COVID-19 patients; however, it is uncommon and accounts for only 1% during recovery from 45 on initial presentation [60]. Pneumothorax incidence is increased by cavitary lesions expanding to the pleural surface, breaking of the thin cavity walls as a consequence of fibrosis and scarring of the lung, and subsequent remodeling and tethering, especially when pleural adhesions occur [60].

In conclusion sixty-four per cent (64% of 100) enrolled cases developed post-COVID pulmonary complications after six months. Particularly Cough 40% and dyspnea 31%, HRCT reticulation finding 44% more among those aged >60 years and never smokers; a strong correlation was found between clinical symptoms of cough and dyspnea, and initial radiological appearance of consolidation, crazy paving, and reticulation. P-value equal in all and <0.001. Crazy paving appearance is the only HRCT finding commonly observed among active smokers p-value of 0.041.

Limitations

Small sample study, Single-centre involvement, Lack of resources and medical documentation, and the short duration of follow-up.

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