Short Communication

Comparison of pulmonary computed tomography scan findings and clinical symptoms of COVID-19 in three outbreak peaks in Isfahan, Iran

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Background: The aim of the present study was to investigate and compare the relationship between the anatomical distribution of pulmonary lesions in computed tomography scan of patients with COVID-19. **Materials and Methods:** This is a cross-sectional study that was performed in 2020–2021 in Isfahan on 300 patients infected with COVID-19 pneumonia. We collected data on the age, gender, and comorbidities of patients. In addition, we gathered data on the clinical manifestations of the patients from their medical records. **Results:** We noted a significant decline in symptoms such as fever and sputum production in the second and third peak in comparison to the first peak ($P < 0.05$). Moreover, cough and muscular pain were higher in the second and third peaks compared to the first peak ($P < 0.05$). Cough was the most common clinical manifestation related to the peripheral distribution of the involvements, bilateral lung disease, and right lower lobe (RLL) involvements in the first peak. In the second COVID-19 peak, fever and cough were the most common clinical findings, respectively, that were mostly associated with peripheral distribution and left lower lobe involvement. **Conclusion:** Cough was the most common clinical manifestation related to the peripheral distribution of the involvements, bilateral lung disease, and RLL involvements in the first peak. In the second COVID-19 peak, fever and cough were the most common clinical findings.

Key words: Clinical manifestation, COVID-19, computed tomography-scan, symptoms

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INTRODUCTION

In December 2019, reports emerged of new pneumonia of unknown etiology arising from Wuhan City, the capital of Hubei province in China. Countries across the world are facing serious problems due to the global outbreak of acute respiratory disease COVID-19 (novel coronavirus or severe acute respiratory syndrome-coronavirus-2) and the rapid spread of this disease.[1]

The most common clinical manifestations of COVID-19 pneumonia are fever, fatigue, dry cough, myalgia, shortness of breath, and gastrointestinal complications such as diarrhea and vomiting.[2,3] Based on current evidence, the manifestations of this disease vary in individuals, but the main manifestations include cough, upper airway inflammation, myalgia, headache, acute respiratory distress syndrome, decreased blood O_2 saturation, and pulmonary involvement on imaging studies.[4] It has also been declared that these pulmonary involvements are the most important prognostic factors in patients with COVID-19 infection.

Symptoms of COVID-19 infection at the onset of the disease include fever, cough, and fatigue, while there are other symptoms such as sputum production, headache, diarrhea, indigestion, and lymphopenia that

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appear approximately 5 days after incubation.[5] The time frame from the onset of COVID-19 symptoms leading to possible death varies from 6 to 41 days with an average of 14 days.[6] This period depends on the patient's age and the condition of the patient's immune system. Reverse transcription-polymerase chain reaction (RT-PCR) assays are currently used in clinics and are developed to confirm COVID-19. Although RT-PCR is the gold standard for definitive diagnosis of COVID-19 infection, due to the high level of false negatives and the unavailability of RT-PCR in the early stages of the disease for rapid diagnosis of patients, radiological examinations, especially computed tomography (CT) scan of the chest with thin incisions, has proved to be significantly effective in diagnosing the disease.[7]

A chest CT scan can not only be valuable in the early detection of pulmonary infection but also in follow-up of the patient. Chest CT findings are currently valuable in the process of clinical diagnosis.[8] In some cases, clinical features identified by chest CT scans of patients with a number of peripheral ground-glass opacities have been observed in the subpleural regions of both lungs.[9,10] This is possibly due to a systemic and localized immune response which leads to increased inflammation. However, COVID-19 has a number of unique clinical features, such as targeting the lower respiratory tract, which is associated with upper respiratory symptoms including runny nose, sneezing, and sore throat.[11,12]

Given the wide prevalence and importance of community health in this project, we decided to investigate and compare the relationship between the anatomical distribution of pulmonary lesions in CT scan of patients with COVID-19 with demographic changes, past medical history, and hospitalization rate. In this study, we investigated and compared the findings in three disease peaks in our country in contrast to most previous studies which reported data regarding a single or two outbreak peaks or during a COVID-19 peak.[13]

MATERIALS AND METHODS

This is a cross-sectional study which was performed in 2020–2021 in Sepahan Medical Imaging Center-Isfahan, Iran. The current study was conducted on patients infected with COVID-19 pneumonia with positive PCR and documented chest CT-scan based on the Iranian Society of Radiology Guideline.[14] The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and ethical approval was granted by the Ethics committee (Ethics code: IR.MUI.MED.REC.1399.1094).

The inclusion criteria were outlined as age more than 18 years, referring to our medical imaging center from April to December 2020, chest CT scan pathognomonic for COVID-19 infection in correlation with clinical manifestations, positive PCR test for COVID-19, complete medical records, and signed written consent to participate in this study. We should also note that the patients in the first peak entered the study solely based on clinical manifestations and CT scan findings due to restricted PCR tests. However, in later peaks, positive PCR test was an addition to the inclusion criteria. The exclusion criterion was patient's decision to exit the study.

We included all patients who met the inclusion criteria based on the census method. Data of patients were categorized based on the time of referral to three groups: Patients referred in April-June 2020 made up the first COVID-19 infection peak in Iran. Patients referred in July-September 2020 formed the second COVID-19 infection peak in Iran and patients referred in October-December 2020 made up the third COVID-19 infection peak in Iran.

The collected data included age, gender, and comorbidities of patients (including diabetes mellitus, cardiovascular diseases, renal diseases, hepatic diseases, and immunodeficiency). Additional data on the clinical manifestations of patients were also extracted from patient's medical records. We should note that patients who had the inclusion criteria were examined in our radiology center and the symptoms of the patients were asked and noted by expert clinical assessor before undergoing chest CT scan. Body temperature, cough, shortness of breath, sputum production, fatigue, headache, anorexia, chest pain, diarrhea, and vomiting were recorded in the radiology center. Data regarding further treatment plan (home quarantine, hospitalization, and intensive care unit [ICU] admission) or death of the patients were collected through patients follow-ups using the telephone.

We should note that all CT scans were conducted using a 16 detector CT scanner (brilliance CT, Philips medical systems, Cleveland, OH) in the supine position. Other CT parameters were kVp: 100; mAs: 50–100; pitch: 1.5; thickness: 4 mm. The window was set as mediastinal (window level, 50 HU; window width, 400 HU) and lung (window level, −400–−700 HU; window width, 1200 ± 1500 HU). The automatic tube current modulation (ACM) activated for the CT scan protocols. We used Y_Detail YD filters and 768 matrix to reconstruct images with 2 mm reconstruction. Chest CT scans were performed and reconstructed using 2 mm thick images from the upper thoracic entrance to the lower surface of the costophrenic angles of the chest. Comprehensive protective measures for technicians included wearing isolation gowns, caps, masks, protective goggles, gloves,

and shoe covers. Scanning rooms were regularly disinfected; all patients wore face masks for protection.

All CT scan clichés were viewed by two radiologists blinded to the study using a single console. In case of disagreement between the two radiologists, the third radiologist with over 10 years of experience examined the images. The images were examined for the following radiological signs: Ground-glass opacities, consolidation, number of affected lobes, bilateral lung disease, affected lobes (right upper lobe, right middle lobe, right lower lobe [RLL], left upper lobe, left lower lobe [LLL]), para-hilar involvements, peripheral distribution, crazy-paving pattern (ground-glass opacity with reticulation), air bronchogram, pleural effusion, lymphadenopathy, and pulmonary nodules and atelectasis.

The collected data were entered into the IBM® SPSS® Statistical Package for the Social Sciences (SPSS) version 24. $P < 0.05$ was considered as significance threshold.

RESULTS

In this study, we evaluated the data from 300 patients with COVID-19 infection that were categorized in three distinct peaks. Our data showed that 94 patients were included in the first peak of the COVID-19 crisis, 103 patients in the second peak and 103 patients in the third peak. Based on initial analysis, there were no significant differences between patients in three peaks regarding mean age, height, weight, body mass index (BMI), and gender distribution ($P > 0.05$).

Based on the overall results, the average age of patients in a total of 3 peaks was 51.2 ± 14.3 years. Furthermore, on average, approximately 40% of patients were women and 60% of patients were men. The average BMI of patients over the period of 3 peaks in Isfahan was 27.44 ± 2.35 kg/m^2. These findings are outlined in Table 1.

Table 2 examines the frequency distribution of underlying diseases in the studied patients across the three peaks. Based on the results of the table, a significant difference was observed between the frequency distribution of underlying diseases of diabetes, chronic lung diseases, and cancer in the peaks ($P = 0.001$ for all).

Table 1: Evaluation of demographic characteristics of patients with coronavirus disease 2019 infection during 3 peaks in Isfahan

Variable	First peak	Second peak	Third peak	*P**
Age	51.05±13.82	50.49±14.70	52.46±16.06	0.25
BMI	26.95±2.23	27.85±2.46	28.01±2.74	0.51
Gender, *n* (%)				
Female	41 (44)	43 (42)	40 (40)	0.07
Male	53 (56)	59 (58)	60 (60)	
Total	94	103	103	

*Using one-way ANOVA test. BMI=Body mass index

In the first peak of COVID-19 infection (April to June 2020), the most commonly seen underlying diseases were cardiovascular disease, chronic lung disease, and cancer, respectively. While in the second and third peaks, the most frequently observed underlying diseases in patients were diabetes and cardiovascular diseases.

Table 3 examines the frequency distribution of common symptoms in the studied patients by peak in Isfahan. Based on the results of Table 3, a significant difference was observed in the frequency distribution of symptoms such as fever, sputum production, cough, muscle pain, anorexia, and diarrhea in the first, second, and third peaks ($P < 0.05$). However, no significant difference was observed in the frequency distribution of symptoms such as fatigue, shortness of breath, chest pain, nausea, headache, and sputum production in the first, second, and third peaks ($P > 0.05$). Symptoms of fever and sputum production decreased significantly in peaks two and three compared to the first peak in our research ($P < 0.05$). Furthermore, cough symptoms and muscle pain in the second and third peaks increased significantly in comparison to the first peak ($P < 0.05$).

Table 4 examines and outlines the frequency distribution of various outcomes in patients with COVID-19 over the three peaks. As the results of the table show, There were no significant differences between three peaks ($P = 0.091$).

Table 5 examines the frequency distribution and compares anatomical dispersions by peaks. Based on the results of the table, no significant difference was observed between anatomical dispersion in the three peaks in Isfahan ($P > 0.05$). Figures 1-4 indicate the various findings in chest multi-detector CT in different peaks.

Table 6 shows the frequency distribution and compares the pattern of lung lesions by outcome. There were significant differences between outcomes of cases and the following patterns: consolidation ($P = 0.031$), Peribronchovascular ($P = 0.002$), Crazy-paving pattern ($P = 0.029$) and Pleural effusion ($P = 0.007$). Based on these results, consolidation was observed mostly in cases with ICU admission (88.9%) and less in outpatients (52.7%). Peribronchovascular distribution was found mostly in patients with mortality (100%) and fewer in outpatients (71%). Crazy-paving pattern was also observed more in ICU admitted cases (33.3%) and none in cases with mortality (0%). Pleural effusion was only observed in ward-hospitalized cases (6.6%). Also . The rate of hospitalization was significantly higher among patients with para hilar involvements ($P = 0.019$)

Table 2: Investigation of the frequency distribution of underlying diseases in the studied patients by peak

Underlying diseases	First peak, *n* (%)	Second peak, *n* (%)	Third peak, *n* (%)	*P**
Diabetes	9 (14.5)	25 (40)	26 (37)	0.001
Cardiovascular	19 (30.5)	20 (32)	27 (38)	0.09
Chronic lung disease	15 (24)	6 (10)	3 (5)	0.001
Hepatic diseases	0	2 (3)	2 (3)	0.08
Renal diseases	8 (11)	6 (10)	7 (10)	0.50
Cancer	12 (20)	3 (5)	5 (7)	0.001
Total	62	62	70	-

*Using one-way ANOVA test

Table 3: Distribution of the frequency of common symptoms in the studied patients by peaks

Common symptoms	First peak, *n* (%)	Second peak, *n* (%)	Third peak, *n* (%)	*P**
Fever	92 (22)	63 (15)	58 (14.5)	0.02
Cough	53 (13)	66 (15.5)	84 (21)	0.01
muscle pain	43 (10.5)	47 (11)	62 (15.5)	0.04
Fatigue	39 (9.5)	17 (4)	22 (5.5)	0.08
Sputum	15 (4)	1 (0.25)	6 (1.5)	0.001
Hemoptysis	2 (0.4)	4 (1)	1 (0.2)	0.12
Headache	32 (8)	36 (8.5)	28 (7)	0.65
Diarrhea	22 (5)	41 (10)	16 (4)	0.01
Nausea	17 (4)	26 (6)	11 (3)	0.07
Shortness of breath	42 (10)	53 (12.5)	58 (14)	0.061
Anorexia	30 (7)	53 (12.5)	44 (11)	0.02
Chest pain	22 (5)	17 (4)	9 (2)	0.062

*Using one-way ANOVA test

Table 4: The frequency of various outcomes over the three peaks

Outcome	First peak, *n* (%)	Second peak, *n* (%)	Third peak, *n* (%)	*P**
Hospitalization	17 (18.1)	20 (19.4)	24 (23.1)	0.091
ICU admission	7 (7.4)	1 (1.0)	1 (0.9)	0.091
Death	0 (0)	2 (1.9)	1 (0.9)	0.091

*Using one-way ANOVA test. ICU=Intensive care unit

Table 5: The frequency and anatomical distribution based on chest computed tomography scan of coronavirus disease 2019 infection by peak

Anatomical distribution	First peak, *n* (%)	Second peak, *n* (%)	Third peak, *n* (%)	*P**
Bilateral	75 (15)	77 (13.5)	88 (14)	0.22
Right upper lobe	48 (10)	66 (11.5)	78 (12)	0.18
Right middle lobe	48 (10)	67 (12)	67 (10)	0.30
Right lower lobe	73 (15)	79 (14)	87 (13)	0.51
Left upper lobe	60 (12)	72 (13)	85 (13)	0.50
Left lower lobe	75 (15)	83 (14.5)	87 (13)	0.37
Peripheral distribution	88 (19)	83 (14.5)	99 (15)	0.11
Para hilar involvement	27 (5)	41 (7)	51 (8)	0.08

*Using one-way ANOVA test

We also evaluated and compared the anatomical distribution of pulmonary involvements and clinical manifestations of COVID-19 in the three peaks. Cough was the most common clinical manifestation related to the peripheral distribution of the involvements, bilateral lung disease, and RLL involvements in the first peak. The other common clinical manifestations were fever, fatigue and generalized body pain mostly observed in the peripheral distribution of the involvements.

In the second COVID-19 peak, fever and cough were the most common clinical findings respectively that were mostly associated with peripheral distribution and LLL involvement. The other common clinical manifestation was shortness of breath that was mostly observed with peripheral distribution and RLL involvement. We can also observe that cough was the most common clinical manifestation in the third peak that was mostly associated with peripheral distribution and RLL involvement respectively.

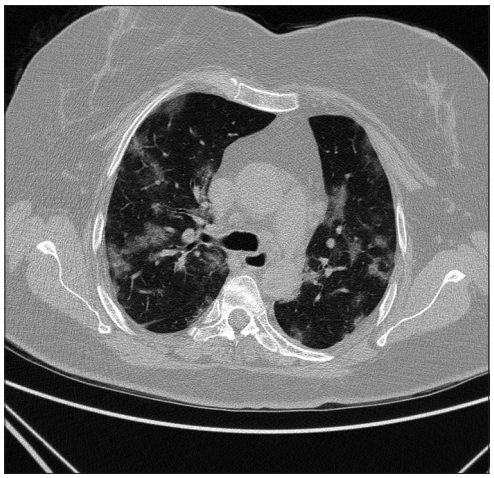

Figure 1: Chest multi-detector computed tomography scan, lung window, axial plane: Bilateral multifocal multilobar patchy ground glass opacities in a 60-year-old female without hospital admission in first peak

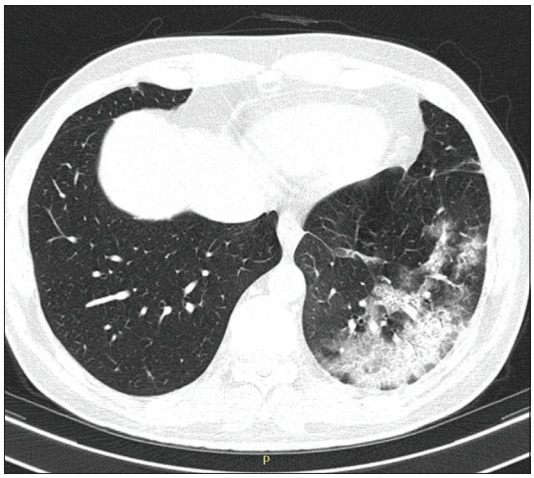

Figure 2: Chest multi-detector computed tomography scan, lung window, axial plane: Ground glass opacities with crazy paving appearance in left lung base in a 46-year-old man with hospital admission in second peak

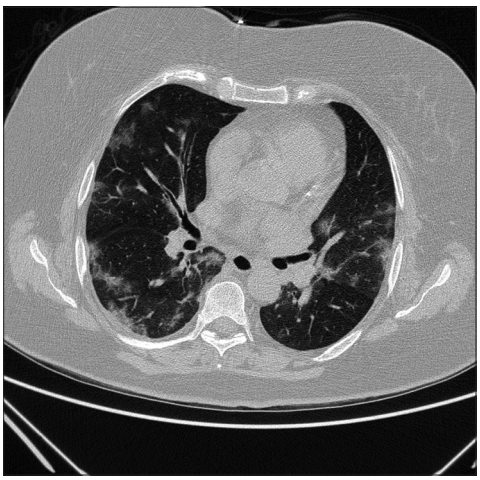

Figure 3: Chest multi-detector computed tomography scan, lung window, axial plane: Bilateral multifocal multilobar patchy ground glass opacities in a 62-year-old man who treated without hospital admission in third peak

Figure 4: Chest multi-detector computed tomography scan, lung window, axial plane: Ground glass opacities with reverse halo appearance in left lung base in a 34-year-old man without hospital admission in third peak

We also evaluated the relationship between clinical manifestations of COVID-19 and involvement patterns in pulmonary CT scan by peaks. We can see that the ground-glass pattern was mostly associated with fever and cough. Furthermore, consolidation and peribronchovascular patterns were associated with fever, cough, and generalized body pain in the first COVID-19 peak. In the second and third peaks, ground-glass and peribronchovascular patterns were mostly observed with fever and cough.

DISCUSSION

In this study, we evaluated the data from 300 patients with COVID-19 infection that were categorized in three distinct peaks. Based on our findings, fever and sputum production were often observed in the first peak among patients while these clinical manifestations decreased significantly in the second and third peaks. On the other hand, cough and muscle pain increased significantly in the second and third peaks. Evaluation of COVID-19 clinical symptoms and radiologic patterns of pulmonary involvements have high diagnostic values. Furthermore, we emphasize that these characteristics could alter during COVID-19 peaks. The rapidly increasing incidence of COVID-19 poses an unprecedented threat to public health. Subsequently, the early detection, diagnosis, isolation, and treatment of patients remain the most effective strategy against COVID-19.[15]

Analysis of anatomical dispersion showed no significant differences between peaks but the frequency of lymphadenopathy and air bronchogram in the second and third peaks decreased significantly. Considering the relationships between clinical manifestations and pulmonary CT scan patterns, we noticed that cough was the most common clinical manifestation related to the peripheral

Table 6: The Frequency distribution and comparison of lung lesion patterns based on chest CT scan by outcomes

Pattern of pulmonary lesions	First peak, *n* (%)	Second peak, *n* (%)	Third peak, *n* (%)	*P**
Ground-glass opacities	87 (24)	92 (31)	97 (28.8)	0.06
Consolidation	73 (20)	39 (13)	56 (16.6)	0.055
Peribronchovascular	66 (18)	73 (25)	87 (25.9)	0.04
Atelectasis	55 (15)	50 (17.3)	54 (16)	0.07
Crazy-paving pattern	14 (4)	8 (3)	20 (6)	0.06
Rounded morphology	1 (0.3)	1 (0.3)	0	0.12
Air bronchogram	24 (7)	1 (0.3)	1 (0.4)	0.001
Reverse halo	14 (4)	14 (5)	17 (5)	0.23
Centrilobular lung nodules	1 (0.3)	4 (1)	0	0.51
Tree-in-bud pattern	1 (0.2)	1 (0.3)	0	0.13
Pleural effusion	1 (0.2)	1 (0.3)	3 (0.9)	0.89
Lymphadenopathy	12 (3)	7 (2)	1 (0.4)	0.001
Pulmonary nodules	7 (2)	4 (1)	0	0.04
Pulmonary emphysema	1 (0.2)	1 (0.3)	0	0.12

*Using one-way ANOVA test

distribution of the involvements, bilateral lung disease and RLL involvements in the first peak. In the second COVID-19 peak, fever and cough were the most common clinical findings, respectively, and were mostly associated with peripheral distribution and LLL involvement while cough, as the most common clinical manifestation in the third peak, was mostly associated with peripheral distribution and RLL involvement, respectively. The ground-glass pattern was mostly associated with fever and cough. Furthermore, consolidation and peribronchovascular patterns were associated with fever, cough, and generalized body pain in the first COVID-19 peak. In the second and third peaks, ground-glass and peribronchovascular patterns were mostly observed with fever and cough.

The main aim of this study was the evaluation of clinical manifestations and radiologic findings of COVID-19 infected patients within 3 distinct peaks in Isfahan, Iran. Similarly, Bernheim *et al*. evaluated pulmonary CT scan of 121 infected patients and showed that bilateral and peripheral ground-glass and consolidative pulmonary opacities were the most common findings that were mostly associated with cough and fever. Additionally, it was reported that cough was the most common clinical manifestation related to peripheral distribution.[16] Another study by Chen *et al*. showed that fever and cough were the most common findings of COVID-19 infection that were associated with ground-glass opacity and consolidation findings. It was also mentioned that peripheral distribution and LLL involvements were common findings of this infection.[17]

Wu *et al*. also evaluated chest CT findings in patients with COVID-19 and its relationship with clinical features. They mentioned that the frequency of fever and sputum production decreased over time among admitted patients while most patients had cough and generalized body pain. It was also concluded that the ground-glass pattern, consolidation, and peribronchovascular patterns were associated with cough and fever in patients and the most common anatomical involved site was the dorsal segment of the RLL.[18] Our findings of the first COVID-19 peak were also in line with these results. We emphasize that the frequency of fever and sputum production, lymphadenopathy and air bronchogram, patterns decreased significantly after the first COVID-19 peak.

Another vital point of this study was the reported increase in the ground-glass and peribronchovascular patterns in the second and third peaks. Raoufi *et al*. also showed that the decrease in the mortality rate of COVID-19 could be associated with CT findings including lower pulmonary artery CT diameter and round shape opacity.[19] Our study emphasizes the ability of radiologic features to provide prognostic imaging markers in patients with COVID-19 pneumonia.

The limitation of this study included conducting the survey in a single city while the COVID-19 pandemic had significantly spread in Isfahan. These results have little generalizability because they are collected from few centers. On the other hand, we compared the data from 3 distinct peaks and based on recent reports, the fifth peak has begun in Isfahan from April 2021 but the other countries are facing the third peak of COVID-19.

CONCLUSION

The frequency of clinical symptoms such as fever and sputum production had significantly decreased in later peaks compared to the first peak of COVID-19 in Isfahan. We also saw a significant increase in the ground-glass and peribronchovascular patterns in the second and third peaks that were mostly associated with fever and cough.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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