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Frequency of atypical pulmonary manifestations of COVID-19 patients on chest CT-scan: a cross-sectional study

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Abstract

Background Chest CT is a crucial diagnostic tool in COVID-19 due to its high sensitivity. Typical chest CT findings such as reversed halo sign, vascular enlargement, and air-bronchogram are commonly recognized in the pandemic, but finding atypical signs is essential to diagnose. We aimed to investigate the prevalence of the atypical manifestations during the two months of 2022 and compare the results to studies conducted before its outbreak.

Methods Those patients with positive, positive RT-PCR tests were reevaluated to see if they met the inclusion and exclusion. Demographic information of patients, including age and sex, was recorded. The computed tomography (CT) examination was carried out using a 100-slice scanner (Philips Brilliance 6 CT Scanner). Two radiology specialists evaluated SARS-CoV-2 RT-PCR-positive patients for atypical pulmonary CT findings separately. The obtained data were evaluated using R software version 4.1.1.

Results 606 confirmed COVID-19 cases were included in this study based on inclusion and exclusion criteria during January and February 2022. 55% of patients were female, and the median age was 56 (IQR: 42, 69). More than half of the patients (59%) had atypical findings on their pulmonary CT examination. These findings showed that pleural abnormalities were the most frequent atypical finding. Among pleural abnormalities, pleural thickening was the most common (17%). The double halo sign represented the least frequent atypical sign (0.2%).

Conclusions Atypical findings were more prevalent in this study than its predecessors, while we acknowledge that other factors, such as study design and patient population, could have impacted it. The presence of atypical signs generally was not correlated with specific demographic groups, while some of these signs were more frequent in particular groups.

Keywords COVID-19, SARS-CoV-2, Atypical signs, CT-scan

Background

In December 2019, the world encountered a new virus outbreak called coronavirus disease 2019 (COVID-19), leading to acute hypoxic respiratory failure and severe pneumonia [1–4]. According to the genomic sequencing analysis, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the Orthocoronavirinae subfamily of Coronaviridae. This subfamily includes the Middle East Respiratory Disease coronavirus (MERS-CoV), causing highly contagious diseases. SARS-CoV-2 mainly affects the upper respiratory tract [5–7].

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Since the pandemic's start, SARS-CoV-2 has evolved into new variants of concern. According to its genomic, Alpha (501Y.V1 or B.1.1.7), Beta (501Y.V2 or B.1.351), Gamma (501Y.V3 or P1), and Delta (G/478K.V1 or B.1.617.2) are different variants. These variations have been linked to a rise in COVID-19 cases or deaths [8, 9]. On 26 November 2021, WHO designated B.1.1.529 as a variant of concern and named it "Omicron". Following the original BA.1 variant, several subvariants of Omicron have emerged: BA.2, BA.3, BA.4, and BA.5. Omicron (BA.1) has more mutations than any previous SARS-CoV-2 variant with 50 mutations [10].

The most frequent symptoms of COVID-19 are fever, dry cough, dyspnea, sore throat, and fatigue. Other symptoms, such as abdominal pain, vomiting, and diarrhea, have been observed [7, 11]. Multiple studies have reported nonspecific or atypical symptoms in some COVID-19 patients [12].

Besides the clinical manifestation described above, the gold-standard method for diagnosing the SARS-CoV-2 infection is reverse transcription polymerase chain reaction (RT-PCR). However, the physicians use other paraclinical and diagnostic measures for early detection and to identify the extent of lung involvement [13–15]. Pulmonary computed tomography (CT) has been reported to have 97% sensitivity [16]. Thus, the obtained data in pulmonary CT examination plays an essential role in disease monitoring and the subsequent inquiry into the effectiveness and adequacy of our therapeutic approach [17]. The most commonly reported CT lesions include reversed halo sign, vascular enlargement, crazy paving patterns, reticular patterns, air-bronchogram, and airway or pleural changes. [13].

Additionally, radiologic information seen in COVID-19 individuals, such as vascular dilation, the air bubble sign, subpleural lines, the halo sign, the reverse halo sign, and bronchial dilatation, has been reported [18]. Unlike the typical signs of COVID-19 on chest CT scans, the atypical manifestations have not been paid attention so much. In a review article, researchers have summarized the atypical chest CT findings of COVID-19 patients are central involvement, isolated upper lobe involvement, solitary involvement, peribronchovascular involvement, lobar consolidation, tree-in-bud pattern, nodules, pleural effusion, pericardial effusion, subpleural sparing, and white lung [18]. COVID-19 pneumonia can make a CT scan look wrong and different; if it happens simultaneously as chronic lung diseases or disorders with the immune system over time. Knowing what these CT results show is essential to avoid incorrect diagnoses and delays in isolating these patients. Therefore, this study aimed to investigate the atypical pulmonary manifestations in COVID-19 patients and their frequency in the patient population during the first two months of 2022.

Methods

Study design and data collection

A cross-sectional study was performed on COVID-19 patients during January and February 2022 at Vali-e-Asr and Mousavi Hospitals in Zanjan, Iran. The RT-PCR-positive patients were reevaluated to meet the inclusion and exclusion criteria. The inclusion criteria include the following items: (1) patients older than 18, (2) positive RT-PCR test, and (3) taking a CT scan based on the physicians' order (according to the indication for diagnosing Covid-19). The following items are exclusion criteria: (1) had lung disease, (2) history of lobectomy, and (3) pregnant women; they were excluded from this study.

CT scan was ordered for patients based on their indication to diagnose Covid-19 from a specialist; we retrospectively reviewed the hospital's data. The Iran National Committee for Ethics in Biomedical Research approved this study with the ethics code of IR.ZUMS.REC.1401.175. Ethical considerations were explained to all patients, and consent was obtained from the patients.

CT imaging protocol

The CT examination was carried out using a 16-slice scanner (Philips Brilliance 6 CT Scanner, 32 detector) in a supine position with a single breath-hold. The CT imaging protocol parameters were as follows: scan direction (craniocaudally), tube voltage (120kV), tube current (100 mA), slice collimation (6×1.5 mm), pitch (1.5), rotation time (0.75 s), and scan time (18.02 s). Finally, slice thickness and an interval were set as 3 mm to reconstruct images.

CT imaging interpretation

Obtained CT images were evaluated independently by a senior attending with experience of seven years in practice and a third-year radiology resident. CT images with both consensuses were included in the study. The third radiologist (with three years of experience) assessed the scans with disagreement. Initially, all patients were assessed for the presence or absence of atypical signs. In this study, atypical findings are (1) isolated upper lobe involvement, (2) solitary involvement, (3) peribronchovascular involvement, (4) lobar consolidation, (5) tree-in-bud pattern, (6) centrilobular nodules, (7) pleural effusion, (8) pleural thickening, (9) pericardial effusion, (10) subpleural sparing, (11) white lung, (12) halo sign, (13) reverse halo sign, (14) double halo sign, (16) target shaped opacity, (17) lymphadenopathy, (18) cavitation, (19) air bubble sign, and (20) airway changes.

Statistical analysis

The R software 4.1.1 was used to analyze the data. Clinical findings, patient age, and sex were all recorded in terms of relative frequency and percentage. The age is considered to be median (IQR). Pearson's Chi-squared test and Fisher's exact test were used to compare atypical results by sex. Patients' ages were also classified into three age groups: less than 40, 40 to 60, and more than 60. Additionally, they were compared using Fisher's exact test for unexpected outcomes.

Results

Demographics and atypical findings

After checking the patients based on inclusion criteria, we included 606 patients. The demographics and atypical findings of evaluated patients in our study are shown in Table 1. Some of the cases are shown in the figures (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16). According to obtained results, 55% of patients were female, and the median age was 56 (IQR: 42, 69) years. More than half of the patients (59%) of all investigated patients had atypical manifestations. Atypical findings on their pulmonary CT examination were more frequent in patients older than 60 (42%). The pleural thickening (Fig. 9) was the most frequent atypical finding (17%) in COVID-19 patients, while the double halo sign (Fig. 3) represented the least frequent atypical sign (0.2%). None of the patients presented cavitation on their lung CT scan.

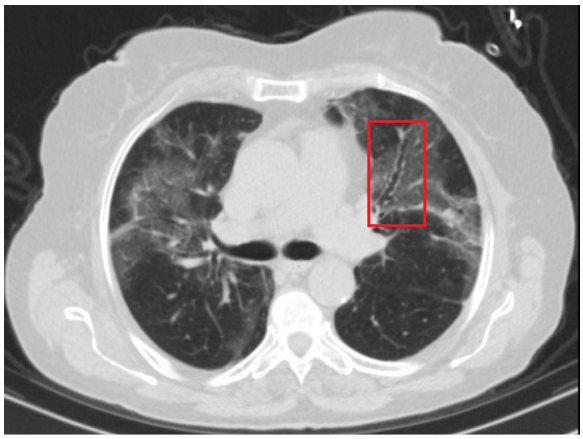

Fig. 1 Axial non-enhanced chest CT scan on the lung window of a 49-year-old woman patient with confirmed COVID-19 pneumonia shows bronchiectasis (red frame) in LUL and bilateral GGOs

Table 1 Demographics and the frequency of atypical findings

Variable	*N*[a] (total = 606)
Sex	
Female	332 (55%)
Male	274 (45%)
Age	56 (42, 69)[b]
Atypical findings	355 (59%)
Isolated upper lobe involvement	10 (1.7%)
Solitary involvement	17 (2.8%)
Peribronchovascular involvement	43 (7.1%)
Lobar consolidation	3 (0.5%)
Tree in bud pattern	3 (0.5%)
Centrilobular nodules	13 (2.1%)
Pleural effusion	39 (6.4%)
Pleural thickening	103 (17%)
Pericardial effusion	18 (3.0%)
Subpleural sparing	29 (4.8%)
White lung	15 (2.5%)
Halo sign	42 (6.9%)
Reverse halo sign	59 (9.7%)
Double halo sign	1 (0.2%)
Target shaped opacity	28 (4.6%)
Lymphadenopathy	29 (4.8%)
Cavitation	0 (0%)
Air bubble sign	14 (2.3%)
Airway changes	102 (17%)
Age group	
(0, 40 yrs]	145 (24%)
(40, 60 yrs]	208 (34%)
(more than 60 yrs)	253 (42%)

[a] *N*: number of patients (%)

[b] Median (IQR = Interquartile range)

Atypical findings according to sex and age

In this part, we investigated the prevalence of atypical findings according to sex and age. The presence of atypical findings on lung CT did not significantly differ in men compared to women (Table 2). Moreover, our analysis demonstrated that peribronchovascular involvement (Fig. 7, $p=0.003$), pericardial effusion (Fig. 8, $p=0.013$), and reverse halo sign (Fig. 10, $p=0.008$) were significantly more frequent in women than in men. However, pleural thickening (Fig. 9, $p=0.023$) and subpleural sparing (Fig. 12, $p=0.008$) were more common in men (Table 2).

Also, we studied the frequency of atypical manifestations based on age categories; we divided them into three groups. Patients younger than 40 (61%), 40–60 (55%), and older than 60 (60%) represented positive for atypical signs. However, the correlation between atypical findings in general and patients' age was insignificant ($p=0.5$). Our analysis indicated that solitary involvement ($p=0.018$), halo sign ($p=0.004$), reverse halo sign ($p<0.001$), target-shaped opacity ($p=0.011$), pleural

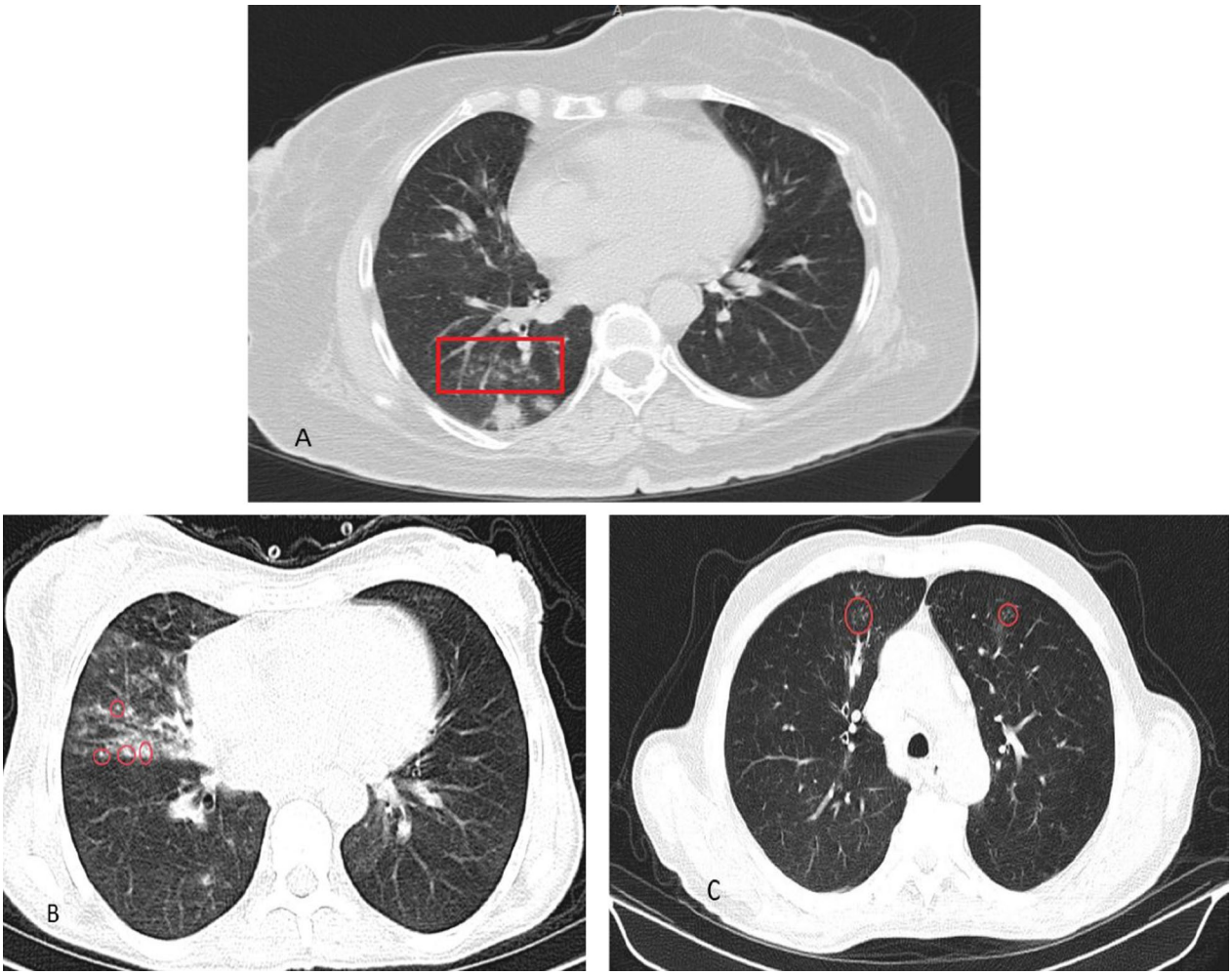

Fig. 2 Axial non-enhanced chest CT image on the lung window of patients with a positive RT-PCR test for COVID-19 shows Centrilobular nodules (red frames) **A** 63-year-old woman with two peripheral opacity in the RLL, **B** 42-year-old woman in RML, **C** 42-year-old woman in RUL and LUL

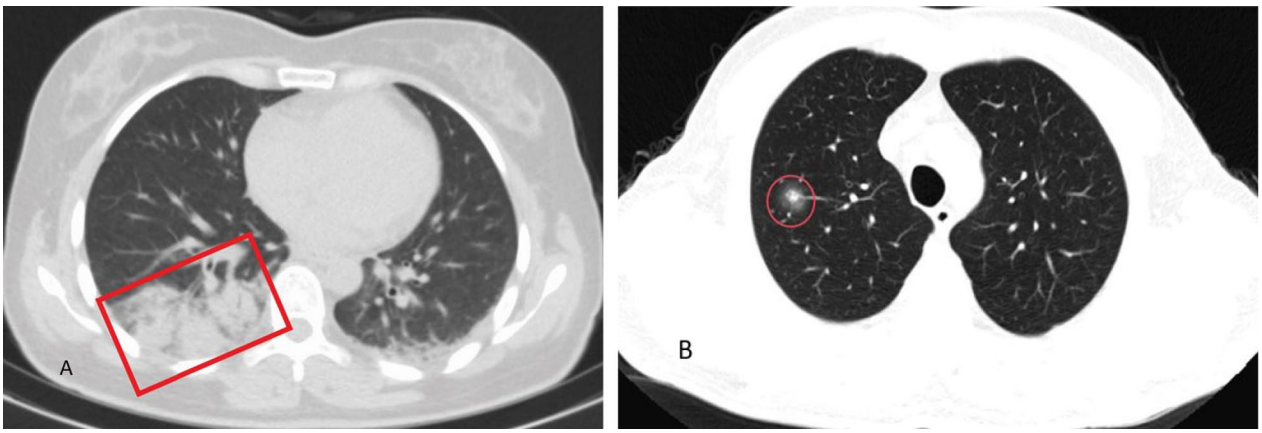

Fig. 3 Halo sign in **A** 38-year-old woman, **B** 44-year-old man with COVID-19. Axial non-enhanced chest CT image on the lung window shows consolidation surrounded by ground-glass opacity (red frame) in **A** RLL and **B** RUL

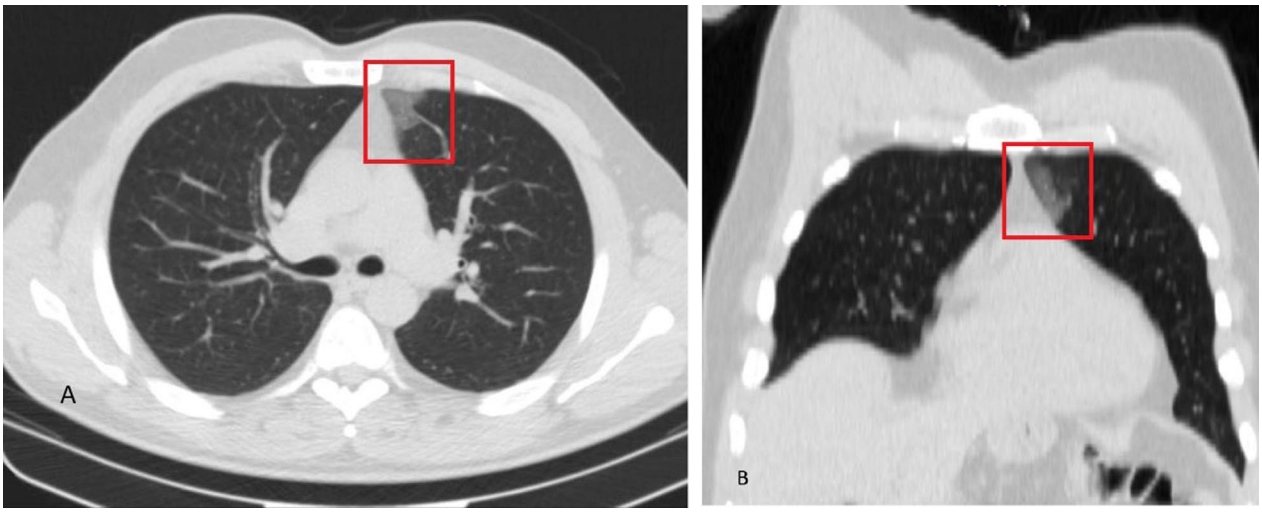

Fig. 4 Isolated upper lobe involvement in a 50-year-old man. Axial (**A**) and coronal (**B**) non-enhanced chest CT images on the lung window show GGO in the LUL (red frame). The LLL and right lung are entirely normal

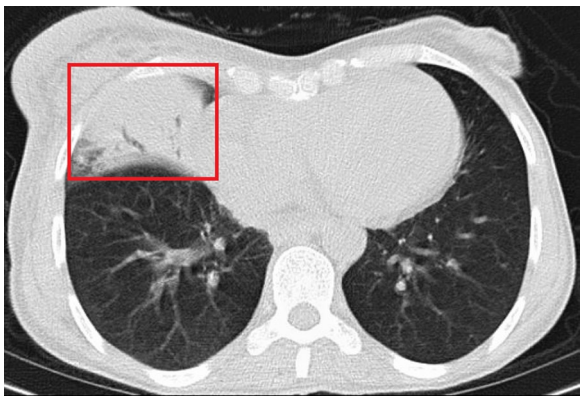

Fig. 5 COVID-19 pneumonia in a 42-year-old woman. Axial non-enhanced chest CT scan image on the lung window shows non-segmental parenchymal consolidation (red frame) with air bronchogram in RML

effusion ($p < 0.001$), pleural thickening ($p < 0.001$), white lung ($p < 0.001$), lymphadenopathy ($p < 0.001$), airway changes ($p < 0.001$) and pericardial effusion ($p = 0.040$) were significantly different between age categories. Besides, most were more frequent in patients older than 60 (Table 3).

Discussion

Due to the high sensitivity of pulmonary computed tomography examination in diagnosing SARS-CoV-2 infections, it is essential to investigate its disparate radiologic manifestations. Contrary to the typical findings which have been robustly canvassed since the start of the pandemic, atypical manifestations generate a significant problem in diagnosis, and their prevalence can

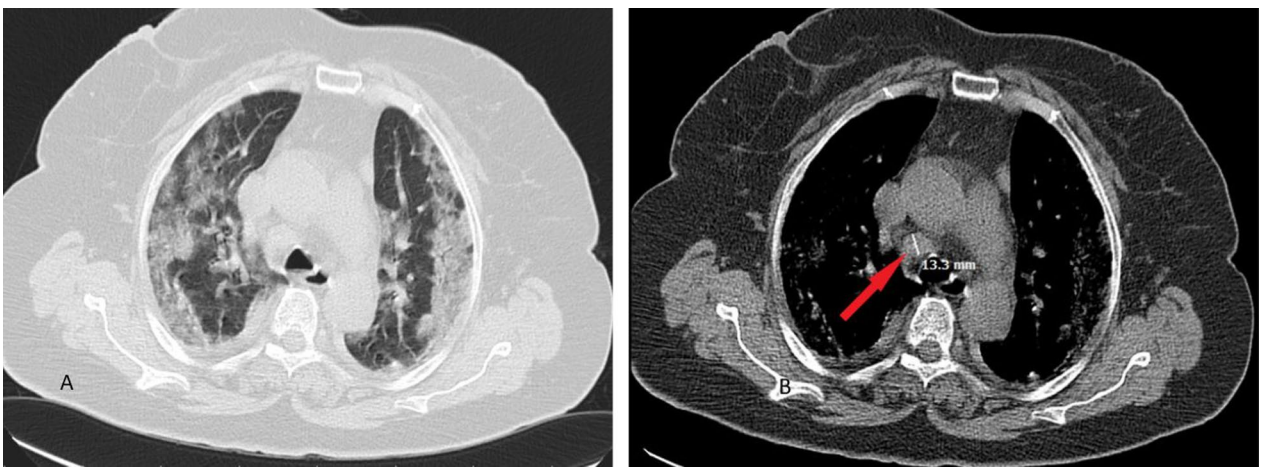

Fig. 6 A 55-year-old man was admitted to the emergency room presenting cough and dyspnea. Axial non-enhanced Chest CT scan images on the lung (**A**) and mediastinal (**B**) windows respectively show bilateral GGOs and lymphadenopathy (short axis > 10 mm) in the lower paratracheal station (red arrow)

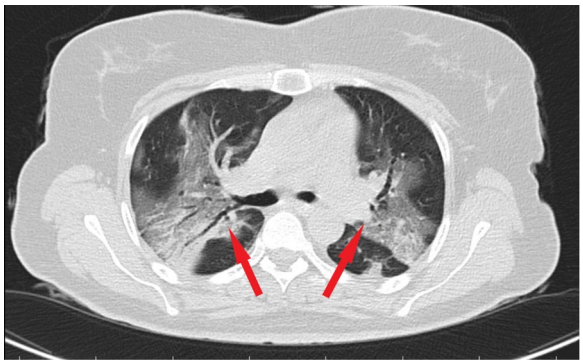

Fig. 7 50-year-old woman COVID-19 pneumonia patient with peribronchovascular involvement. Axial non-enhanced chest CT scan image on the lung window shows GGO along the peribronchovascular bundle from the central area to the periphery of both upper lobes (red arrows)

potentially vary with each variant of concern. In this study, we evaluated atypical findings in pulmonary CT examination in confirmed COVID-19 patients in the first two months of 2022. The results showed that 59% of patients had at least one atypical sign on their lung CT. On the other hand, atypical findings generally were not significantly different based on sex and age; However, the type of atypical radiologic signs could vary in patients regarding age and sex.

Compared to previous studies, our findings represented more incidence of atypical pulmonary signs in COVID-19 patients [19, 20]. Gurumurthy et al. [20] have investigated typical pulmonary manifestations of COVID-19 in India, reported the prevalence of atypical signs as 21.1% out of 298 cases, and reported that pulmonary cysts (9%) were the most frequent atypical

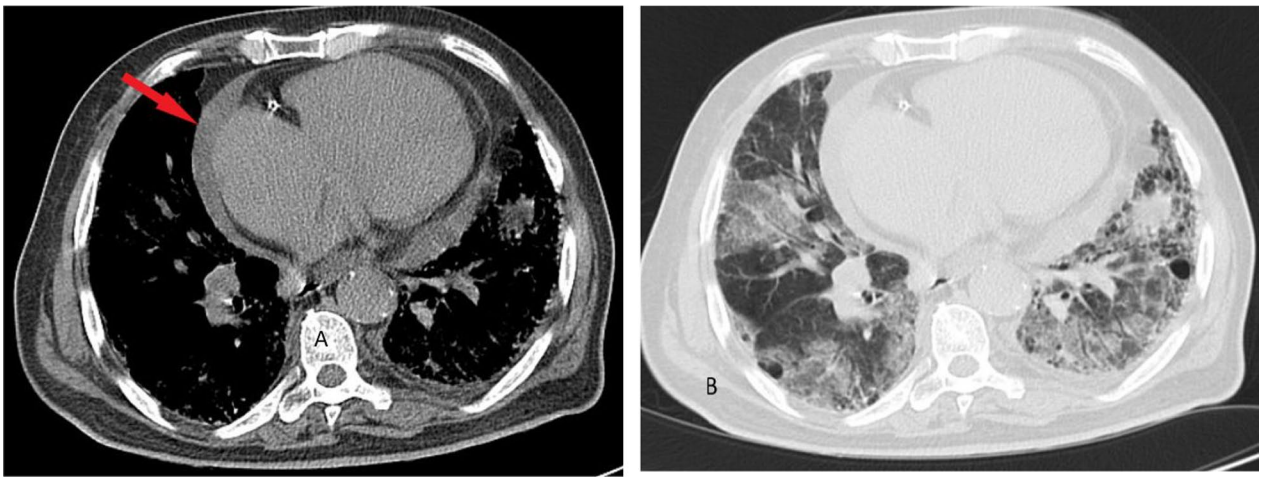

Fig. 8 CT images of a 77-year-old man with COVID-19 pneumonia. Axial non-enhanced chest CT scan image on the mediastinal window **A** shows pericardial effusion (red arrow). The axial image on the lung window **B** shows bilateral GGOs

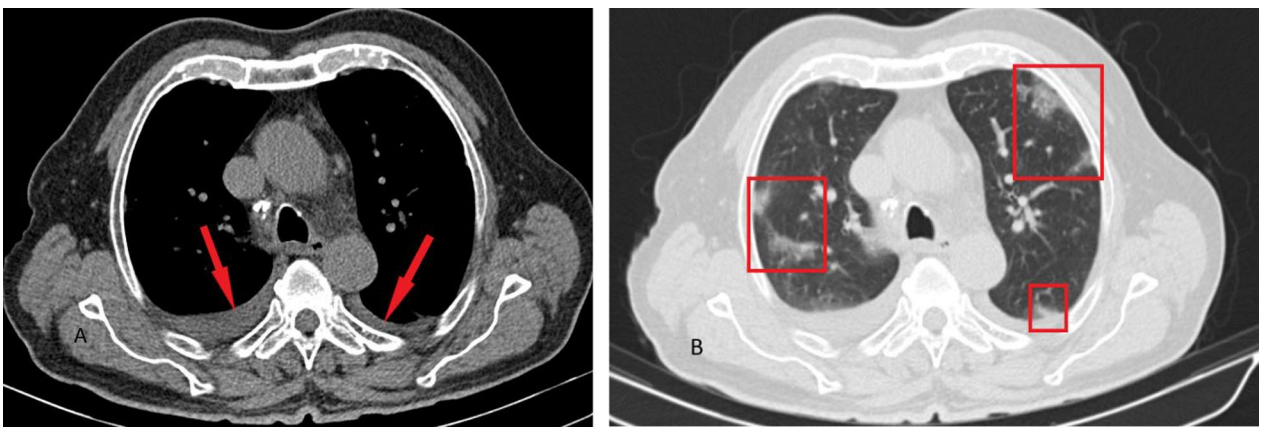

Fig. 9 CT images of a 78-year-old man with COVID-19 pneumonia. Axial non-enhanced chest CT scan image on the mediastinal window **A** shows mild bilateral pleural effusion (red arrow). The axial image on the lung window **B** shows bilateral GGOs (red frames)

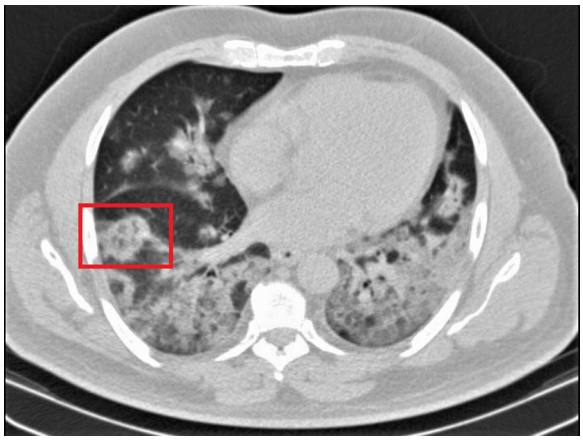

Fig. 10 Reverse halo sign in a 57-year-old man with COVID-19. Axial non-enhanced chest CT scan in the lung window shows an area of ground glass opacity surrounded by a ring-shaped consolidation (red frame) in RLL associated with bilateral air space opacities

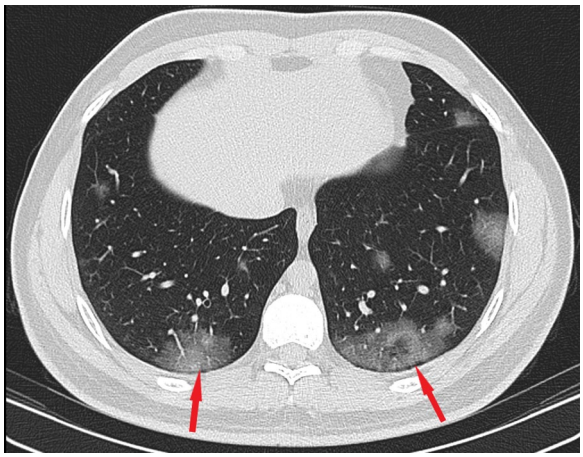

Fig. 12 Axial non-enhanced chest CT scan image of a 22-year-old man with confirmed COVID-19 pneumonia on the lung window. Bilateral peripheral patchy ground-glass opacities are shown, with areas of subpleural sparing (red arrows)

manifestations. Here, we demonstrated that pleural thickening was the most frequent atypical finding (17%), with 59% of SARS-CoV2 RT-PCR positive patients having at least one atypical radiologic sign on their lung CT imaging. Moreover, Haghighi-Morad et al. [19] have investigated the Atypical presentation of COVID-19 and have stated that 3% of patients had atypical findings on their lung CT. In another study, Korkmaz et al. [21] showed that nodular lesions were the most common atypical finding in COVID-19 patients. However, they have revealed that the atypical results can vary due to the pandemic period as they showed that central distribution, as an atypical manifestation, was significantly different between those infected during the first six months of the pandemic (March to August 2020) and in the second (September 2020 to February 2021). In these mentioned studies, contrary to our findings, the frequency of atypical pulmonary CT manifestations in males was higher than in females. Also, the frequency of atypical findings was higher in this study than in previous ones. These discrepant findings may be caused by variations in sample size, patient characteristics, epidemiologic variables in specific populations, disease severity, the number and variety of atypical parameters evaluated across studies, and most importantly, the variant identified as the primary concern during the survey. The frequency of atypical radiologic signs in COVID-19 patients relies on some variables, but it is not limited to the variation of concern.

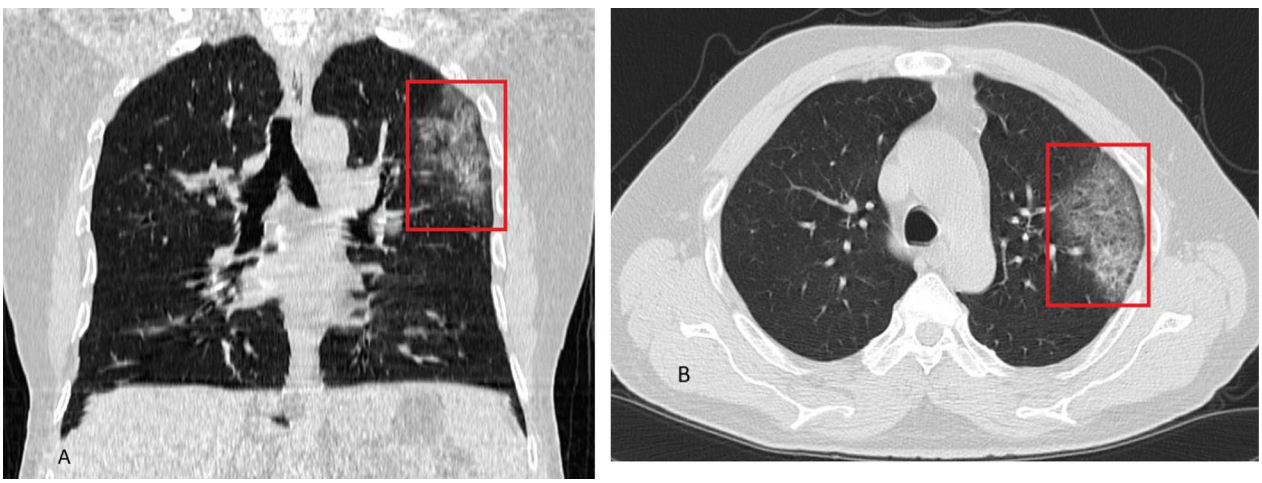

Fig. 11 Solitary involvement in a 61-year-old man with confirmed COVID-19 pneumonia. A solitary ground-glass opacity (GGO) (red frame) is seen in coronal (**A**) and axial (**B**) non-enhanced chest CT scan images on the lung window

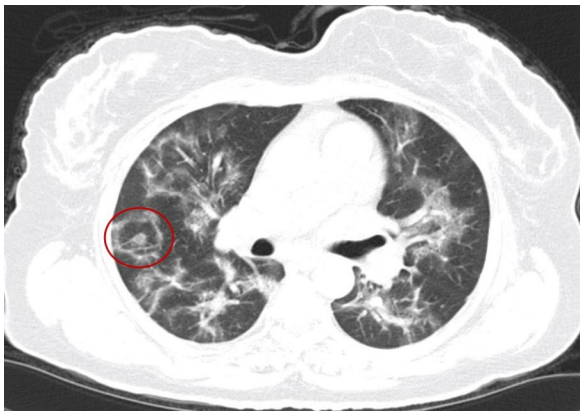

Fig. 13 Pulmonary target sign in a 51-year-old woman with COVID-19 pneumonia. axial non-enhanced chest CT scan image shows bilateral ground-glass opacities on the lungs field with a complete circle with a central dot in the RUL (red circle)

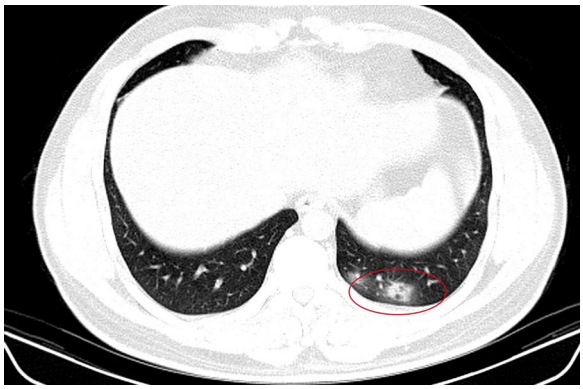

Fig. 15 Air bubble sign in a 37-year-old man with COVID-19 pneumonia. Axial non-enhanced chest CT scan image on the lung window shows a small air-containing space in the context of air space opacity in LLL (red frame)

In a systematic review and meta-analysis conducted by Zarifian et al. [22], pleural thickening (33.35%) and bronchial wall thickening (15.48%), were significant atypical lung CT findings, with other signs such as pleural effusion (6.96%), lymphadenopathy (5.19%), cavitation (1.1%), and pneumothorax (0.89%) being other atypical radiologic manifestations investigated. This study's findings were in the same line with our results. But the discrepancy was the halo sign which was not considered an atypical finding, and its prevalence was much higher (25.63%).

As Saha et al. [23] discussed, various types of pleural involvement and their frequencies vary depending on disease severity and stage, such as pleural thickening and pleural retraction, which are more common in early disease. In contrast, the prevalence of pleural effusion is much lower, and pneumothorax is uncommon. Our results are similar to previous studies regarding the frequency of pleural involvement. Bai et al. [24] have investigated the frequency of pleural lesions in 219 patients with COVID-19 and reported that common pleural abnormality among COVID-19 patients was pleural thickening (15%) followed by pleural effusion (4%), which is congruent with our findings. Recent studies have indicated the importance of pleural abnormalities in the disease outcome. Hence, it has been shown that patients with pleural effusion have more pulmonary inflammatory responses due to refractory disease [25]. More interestingly, Hussein et al. [26] have suggested that effusion development may have been solely related to the virus.

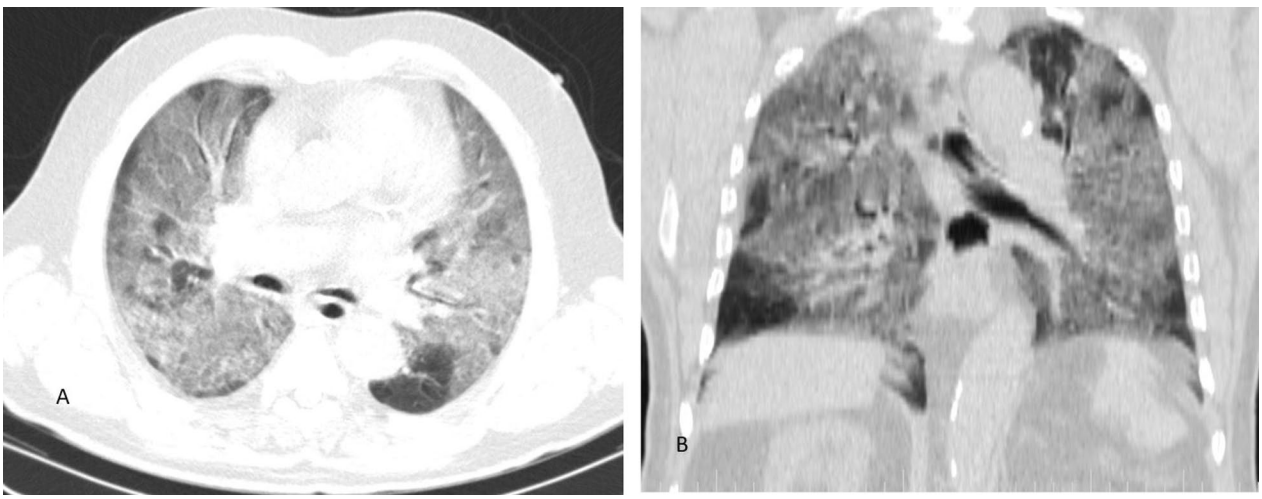

Fig. 14 Chest CT from an 80-year-old man with COVID-19 pneumonia. Axial (**A**) and coronal (**B**) Non-enhanced chest CT scan images show extensive ground-glass opacities in both lungs, giving a white lung appearance

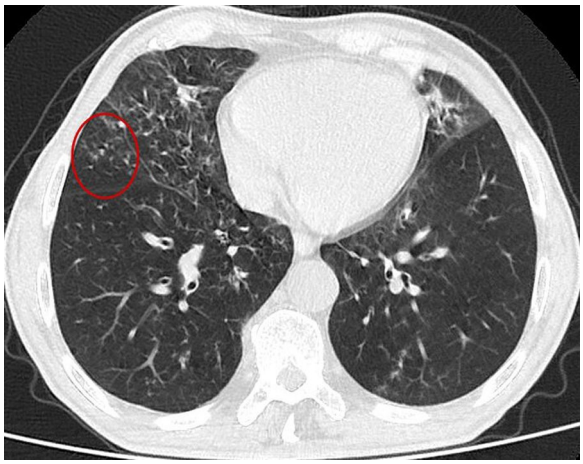

Fig. 16 Axial non-enhanced chest CT scan image on the lung window of a 59-year-old man with confirmed COVID-19 pneumonia shows Small nodules with a "tree-in-bud" pattern in the RML

Although RT-PCR is still the standard for diagnosing COVID-19, CT may at least partially bypass its limitations [27]. The high sensitivity of CT (97%) was confirmed using RT-PCR as the standard, but a poor specificity was noted (25%), with an accuracy of 68% for the diagnosis of COVID-19 [16]. As a result, typical CT findings may rule out false negative RT-PCR tests, but there is a significant overlap between COVID-19 and other viral pneumonia CT features [24]. Cycle threshold (Ct) levels and other important variables may be critical in evaluating viral load and illness severity [28]. Finding Ct association with atypical CT scan findings is important, but the lack of lab data made it impossible to assess it, limiting our study.

Awareness of CT findings, including atypical manifestations, can be considered an effective implementation to prevent misdiagnoses of COVID-19 patients. We showed that more than half of investigated patients were positive for atypical findings. The pleural abnormalities were shown to be the most frequent atypical manifestation in RT-PCR-positive patients in our study. It's essential to be aware of COVID-19's unusual pulmonary signs and their frequency to prevent misdiagnosis. This study's high sample size, which included 606 RT-PCR-positive patients, is one of its main advantages. Also, investigating atypic signs based on different age ranges and different genders is another one. However, our study contains some limitations. First, it is retrospective. Second, it didn't have variant-specific RT-PCR. Third, lab data's cycle threshold (Ct) levels weren't available; cases can be classified based on Ct.

Table 2 Atypical findings according to sex

CT findings	Female, $N=332$[a]	Male, $N=274$[a]	p-value[b]
Atypical findings	192 (58%)	163 (59%)	0.7
Isolated upper lobe involvement	5 (1.5%)	5 (1.8%)	0.8
Solitary involvement	9 (2.7%)	8 (2.9%)	0.9
Peribronchovascular involvement	33 (9.9%)	10 (3.6%)	0.003
Lobar consolidation	2 (0.6%)	1 (0.4%)	> 0.9
Tree in bud pattern	0 (0%)	3 (1.1%)	0.092
Centrilobular nodules	5 (1.5%)	8 (2.9%)	0.2
Pleural effusion	19 (5.7%)	20 (7.3%)	0.4
Pleural thickening	46 (14%)	57 (21%)	0.023
Pericardial effusion	15 (4.5%)	3 (1.1%)	0.013
Subpleural sparing	9 (2.7%)	20 (7.3%)	0.008
White lung	7 (2.1%)	8 (2.9%)	0.5
Halo sign	20 (6.0%)	22 (8.0%)	0.3
Reverse halo sign	42 (13%)	17 (6.2%)	0.008
Double halo sign	1 (0.3%)	0 (0%)	> 0.9
Target shaped opacity	11 (3.3%)	17 (6.2%)	0.092
Lymphadenopathy	16 (4.8%)	13 (4.7%)	> 0.9
Cavitation	0 (0%)	0 (0%)	
Air bubble sign	7 (2.1%)	7 (2.6%)	0.7
Airway changes	52 (16%)	50 (18%)	0.4

[a] *N*: number of patients (%)

[b] Pearson's Chi-squared test; Fisher's exact test

Table 3 Atypical findings in regards to patients' age

CT findings	(0, 40 yrs], $N=145$[a]	(40, 60 yrs], $N=208$[a]	>60 yrs, $N=253$[a]	*p*-value[b]
Atypical findings	89 (61%)	115 (55%)	151 (60%)	0.5
Isolated upper lobe involvement	3 (2.1%)	4 (1.9%)	3 (1.2%)	0.8
Solitary Involvement	9 (6.2%)	5 (2.4%)	3 (1.2%)	0.018
Peribronchovascular involvement	11 (7.6%)	10 (4.8%)	22 (8.7%)	0.3
Lobar consolidation	1 (0.7%)	2 (1.0%)	0 (0%)	0.3
Tree in bud pattern	1 (0.7%)	1 (0.5%)	1 (0.4%)	>0.9
Centrilobular nodules	3 (2.1%)	3 (1.4%)	7 (2.8%)	0.6
Pleural effusion	6 (4.1%)	4 (1.9%)	29 (11%)	<0.001
Pleural thickening	12 (8.3%)	26 (12%)	65 (26%)	<0.001
Pericardial effusion	2 (1.4%)	3 (1.4%)	13 (5.1%)	0.040
Subpleural sparing	8 (5.5%)	14 (6.7%)	7 (2.8%)	0.12
White lung	2 (1.4%)	0 (0%)	13 (5.1%)	<0.001
Halo sign	17 (12%)	17 (8.2%)	8 (3.2%)	0.004
Reverse halo sign	19 (13%)	29 (14%)	11 (4.3%)	<0.001
Double halo sign	0 (0%)	1 (0.5%)	0 (0%)	0.6
Target shaped opacity	10 (6.9%)	14 (6.7%)	4 (1.6%)	0.011
Lymphadenopathy	3 (2.1%)	4 (1.9%)	22 (8.7%)	<0.001
Cavitation	0 (0%)	0 (0%)	0 (0%)	–
Air bubble sign	5 (3.4%)	6 (2.9%)	3 (1.2%)	0.2
Airway changes	10 (6.9%)	26 (12%)	66 (26%)	<0.001

[a] *N*: number of patients (%)

[b] Pearson's Chi-squared test; Fisher's exact test

Conclusions

Our results showed that the prevalence of atypical pulmonary manifestations in COVID-19 patients was more than half of patients (59%). In individuals older than 60, abnormal findings on their lung CT examination were more common. The pleural abnormalities were the most frequent atypical findings in the studied patients. Among them, pleural thickening had the highest frequency than the others. Finally, it should be noted noticing atypical pulmonary manifestations of COVID-19 and its frequency is crucial to avoid misdiagnosis.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-1	Severe acute respiratory syndrome coronavirus-1
RT-PCR	Reverse transcription polymerase chain reaction
CT-scan	Computed tomography scan

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Author contributions

PI, EGh, SB, MA have made contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The current study had been approved by Vali-e-Asr and Mousavi Hospitals Hospital, Research and Ethical committee. Informed written consent was obtained from all individual participants included in the study.

Consent for publication

Written informed consent for the publication of this data was taken from the patients.

Competing interests

The authors declare that they have no competing interests.

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