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Clinical and Radiological Findings of COVID-19 Pneumonia in Immunodeficient Patients: A Single Center Retrospective Analysis

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Abstract

Objective: Various chest computed tomography (CT) manifestations of coronavirus disease-2019 (COVID-19) pneumonia have been reported in immunocompetent patients. In immunodeficient patients, the clinical manifestations and chest CT imaging findings may differ from usual patterns and may cause mistakes in the diagnosis and management. We evaluated the chest CT manifestations in patients with immunosuppression from various causes and to compare with those seen in immunocompetent patients.

Methods: Forty-four immunodeficient and 44 immunocompetent patients with positive real-time reverse transcriptase-polymerase chain reaction test for severe acute respiratory syndrome-coronavirus-2 having suspicious chest CT manifestations were included and the chest CT images were retrospectively evaluated. The making manifestations were divided as typical findings including ground-glass opacity (GGO)and/or consolidations, air bronchogram sign, crazy paving pattern, microvascular dilatation, halo sign&reverse halo signs and atypical findings including bronshiectasia, tree in bud appearance, pulmonary nodules, pleural effusion and cavitation.

Results: There were 28 males and 16 females in the immunodeficient group and 27 males and 17 females in the control group. A statistically significant difference was found in terms of the length of hospital stay and mortality. The most frequent symptom was fever in immunodeficient patients, while it was dyspnea in the control group. The most common underlying cause for immunosuppression was receiving chemo-radiotheraphy, and the lung&gastric cancers were the most common. In terms of CT features, GGO was the most common finding. A significant difference was found in crazy paving pattern and peripheral-subpleural distribution. Atypical findings were detected significantly higher in immunodeficient patients. When all patients considered together, there was a significant association between mortality and tree-in-bud appearance, pleural effusion, bronchiectasis.

Conclusion: In our study, there was an increased risk of more severe COVID-19 disease and a higher mortality rate in immunodeficient patients. Radiologists should consider COVID-19 pneumonia in cases of rare, atypical and vague CT findings in immunodeficient patients. Since the course of COVID-19 pneumonia may be more severe in immunodeficient patients, being aware of rare atypical findings will decrease morbidity and mortality rates.

Keywords: COVID-19, immunodeficiency, pneumonia

INTRODUCTION

The coronavirus disease-2019 (COVID-19) presents mild-to-moderate upper and lower respiratory tract manifestations in most of the cases. However, particularly older patients or patients with underlying chronic disease progress to severe pneumonia associated with massive alveolar damage and acute respiratory failure. Moreover, as the pandemic progressed, various other systems like musculoskeletal system, central nervous system have been shown to be involved (1,2). Definitive diagnosis requires a positive real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) test on respiratory specimens (3). Although, chest computed tomography (CT) is not recommended in the

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diagnosis and screening of the patients due to its lower specifity, it plays an important role with a low rate of missed diagnosis by revealing the abnormalities immediately. Various chest CT findings have been reported in COVID-19 patients, of which some are typical and frequently observed findings while others are atypical and rare. As shown in many studies and our previous studies, multifocal ground glass opacities (GGOs) with peripheral/subpleural distribution and accompanying areas of consolidation are the most frequently observed scenerio in immunocompetent patients. Additionally, perilesional/intralesional microvascular dilatation, halo and reversed halo signs have been reported as quite characteristic CT features of COVID-19 pneumonia, observed more commonly than non-COVID-19 viral pneumonia (4-6). However, in immunodeficient patients the clinical manifestations and chest CT imaging findings may differ from these usual patterns and may cause mistakes in the diagnosis and management. In this study, we evaluated the chest CT imaging findings seen in patients with immunodeficiency from various causes and to compare with those seen in immunocompetent patients.

METHODS

Between 16 March-30 May 2020, 88 patients (44 immunodeficient and 44 immunocompetent) with positive rRT-PCR test for severe acute respiratory syndrome-coronavirus-2 having uspicious chest CT imaging findings of COVID-19 pneumonia (typical or atypical) were included in the study and the chest CT images were retrospectively evaluated. The exclusion criteria included a paucity of clinical or radiological data, a significant artifact on CT images and being under the age of 18. The radiological findings have been divided as typical findings including GGOs and/or consolidations (non-lobar/non-segmental), air bronchogram sign, crazy paving pattern, microvascular dilatation, halo sign and reverse halo sign and atypical findings including bronshiectasia, tree in bud appearance, pulmonary nodules, pleural effusion and cavitation. Additionally, the distribution of the pneumonic infiltration, presenting symptoms, underlying causes of the immunodeficiency and comorbidities of the patients were recorded. Mortality rates and the length of hospital stay were used as clinical markers. Chest CT images were evaluated in consensus by two experienced radiologists (NK and BE).

Statistical Analysis

Statistical significance level was set as $p<0.05$.

RESULTS

There were 28 male and 16 female patients in the immunodeficient group and 27 male 17 female patients in the control group. The mean age of the immunodeficient group was 58.6±12.17 versus 58.9±10.9 years in the control group. There was no significant difference between the two groups in terms of age and gender. Accompanying comorbidities in patients are shown in (Figure 1). Nineteen (43.1%) patients in the immunodeficient group and 3 (6.8%) patients in the immunocompetent group died during hospital stay and the rest of them were discharged. Additionally, the mean length of hospital stay was 16.13±14.15 days in immunodeficient patients and 10.18±5.87 in the control group. A statistically significant difference was found between the two groups in terms of the length of hospital stay and mortality ($p=0.012$ and $p<0.001$, respectively) The most frequent symptom was fever (54.5%) in immunodeficient patients, whereas it was dyspnea (84.1%) in the control group and there was a statistically significant difference in symptoms including fever, dyspnea, and confusion between the two groups ($p=0.005$, $p=0.005$, and $p=0.049$, respectively) (Table 1). The most common underlying cause for immunodeficiency was receiving chemo-radiotheraphy for cancer, and the lung &gastric cancers were the most common (13.6% and 9.1%, respectively) (Table 2). In terms of CT features, GGO was the most common finding and was detected in all chest CT scans (Figures 2-4). A significant difference was found in crazy paving pattern and peripheral-subpleural distribution of lesions between the two groups ($p=0.031$ and $p=0.006$, respectively) (Figure 3). Atypical findings, including bronchiectasis, pulmonary nodules, tree-in-bud appearance, and pleural effusion were detected statistically significantly higher in immunodeficient patients ($p=0.002$, $p=0.047$, $p<0.001$ and $p=0.001$, respectively) (Figures 2, 3, 5-7). When all patients were considered together, there was a significant association between mortality and tree-in-bud appearance, pleural effusion, bronchiectasis (each of $p<0.05$). In addition to these atypical findings, air bronchogram sign was associated with mortality ($p<0.05$) (Table 3).

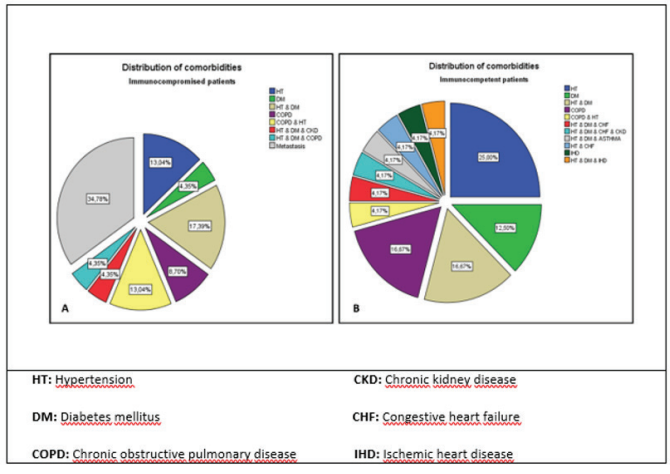

Figure 1. Distribution of comorbidities for both groups of the patients

Table 1. Demographics, prognosis and initial symptoms of the patients			
	Immunocompromised patients (n=44, %)	**Immunocompetent patients (n=44, %)**	**p values**
Demographic			
Gender			
-Male n (percentage)	28 (63.6%)	27 (61.3%)	p=0.826
-Female n (percentage)	16 (36.3%)	17 (38.6%)	
Age (years)			
-Range	30-77	33-86	p=0.898
-Mean (± SD)	58.6±12.17	58.9±10.9	
Prognosis			
Length of hospital stay			
-Mean (± SD)	16.13±14.15 (1-73)	10.18±5.87 (3-30)	**p=0.012***
Survey (mortality)			
- n (percentage)	19 (43.2%)	3 (6.8%)	**p<0.001***
Symptoms			
Fever: n (percentage)	24 (54.5%)*	11 (25%)	**p=0.005***
Dyspnea: n (percentage)	25 (56.8%)	37 (84.1%)*	**p=0.005***
Cough: n (percentage)	17 (38.6%)	16 (36.4%)	p=0.826
Fatigue: n (percentage)	11 (25%)	6 (13.6%)	p=0.177
Loss of taste or smell: n (percentage)	12 (27.3%)	6 (13.6%)	p=0.113
Nausea and vomiting: n (percentage)	5 (11.4%)	2 (4.5%)	p=0.237
Myalgia: n (percentage)	9 (20.5%)	7 (15.9%)	p=0.580
Headache: n (percentage)	1 (2.3%)	1 (2.3%)	p=1.000
Confusion: n (percentage)	6 (13.6%)*	1 (2.3%)	**p=0.049***

*There was statistically significant relationship between two groups (p value <0.05), SD: Standard deviation

Table 2. The cause of immunosuppression in the patients	
Underlying causes for immunosuppression	**Frequency n=44, (100%)**
Lung cancer: n (percentage)	6 (13.6%)
Gastric adenocarcinoma: n (percentage)	4 (9.1%)
Non-Hodgkin lymphoma: n (percentage) Multiple myeloma: n (percentage) Acute myeloid leukemia: n (percentage)	Each of 3 (6.8%)
Breast cancer: n (percentage) Esophageal cancer: n (percentage) Endometrial cancer: n (percentage) Pancreatic cancer: n (percentage) Unknown primary: n (percentage)	Each of 2 (4.5%)
Hepatocellular cancer: n (percentage) Renal cell carcinoma: n (percentage) Liver transplantation: n (percentage) Cholangiocellular cancer: n (percentage) Testicular tumor: n (percentage) Femur osteosarcoma: n (percentage) Glioblastoma multiforme: n (percentage) HIV: n (percentage) HIV+ lung cancer: n (percentage) Malignant melanoma: n (percentage) Bladder cancer: n (percentage) Myastenia gravis: n (percentage) Hairy cell leukemia: n (percentage) Tongue cancer: n (percentage) Thrombocytosis disease: n (percentage)	Each of 1 (2.3%)

DISCUSSION

Immunodeficiency is one of the important underlying conditions that may be associated with a more severe course of most viral infectious pneumonia, including influenza (7). It could also be pre prepared for COVID-19. However, there are currently limited data on the prognosis, clinical presentations and the CT imaging findings of the disease in immunodeficient patients, which may differ from those seen in immunocompetent adults. Reported studies also have conflicting results. Some studies have shown that the mortality and morbidity of COVID-19 is higher in immunodeficient patients due to the higher levels of viral load (8-10), while other studies reported no statistically significant risk of more severe COVID-19 in these patients (11). Previously, some viral respiratory infections were shown to be associated with more severe manifestations in patients on long-term immunosuppressive medications (12,13). A prospective cohort monitoring COVID-19 cases throughout China revealed poorer outcomes from COVID-19 in patients with cancer with a higher risk of severe events including admission to the intensive care unit, requiring invasive ventilation, and death compared with patients without cancer (14). However, any significant differences were not found in the study by Miyashita et al. (15) regarding COVID-19 mortality among 334 patients with cancer compared with those without cancer. Moreover, as the pandemic progresses corticosteroids decreases mortality in patients with severe COVID-19 pneumonia, implying a favorable effect of suppressed immune response during the disease (16). In COVID-19, a hyperinflammatory state with increased levels of cytokines, including IL-6, is generated and

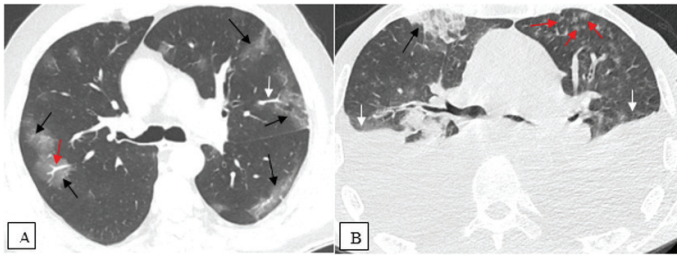

Figure 2. Axial CT images showing. A) Multifocal/multilobar GGOs with predominantly peripheral in distribution (A, black arrows) in a 61-year-old immunocompetent male patient presenting with cough, myalgia, and dyspnea, who had no comorbidities and who was discharged from the hospital 19 days later. Note also the perilesional (A, white arrow) and intralesional (A, red arrow) microvascular proliferation and B) A patchy peripheral GGO with superimposed areas of consolidations in the right middle lobe (B, black arrow) in a 69-year-old immunocompromised male patient presenting with cough, fatigue, and fever, who had a history of gastric cancer and died 24 days after being hospitalized for COVID-19 pneumonia. Note the presence of obvious bilateral pleural effusion (B, white arrows) in this immunocompromised patient in addition to multiple small centrilobular nodules with tree-in-bud appearances (B, red arrow) in the left lung, which was probably associated with bacterial superinfection

GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019, CT: Computed tomography

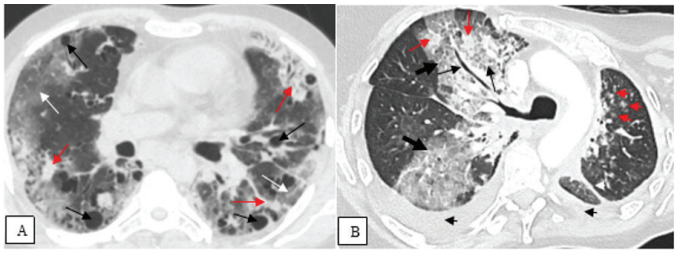

Figure 3. Axial CT images showing. A) Bilateral patchy and confluent GGOs predominantly peripheral in distribution (A, white arrows) mixed with areas of irregular consolidations (A, red arrows) in a 43-year-old immunocompromised male patient presenting with fever, cough, confusion, and dyspnea, who had testicular carcinoma with pulmonary metastases and died 9 days after being hospitalized for COVID-19 pneumonia. Note also the multiple pulmonary metastases seen as cystic lesions following chemotherapy (A, black arrows). B) Unilateral GGOs without peripheral predominance (B, thick black arrows) associated with areas of superimposed consolidations (B, red arrows) and reticulation resulting in crazy paving pattern (B, black arrow) and an air bronchogram sign (B thin black arrow) in the right lung in a 49-year-old immunocompromised female patient presenting with dyspnea, myalgia and fever, who had a history of lung cancer with liver metastases and died 7 days after being hospitalized for COVID-19 pneumonia. Note the presence of bilateral moderate pleural effusions (B, black arrowheads) and multiple small centrilobular nodules with tree-in- bud appearances (B, red arrowheads) in the left lung, which was probably associated with bacterial superinfection. The interlobar pleural thickening is also seen (B, white arrowhead)

GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019, CT: Computed tomography

suggested as an endogenous pathway in the pathophysiology of both pulmonary damage and multiorgan complications

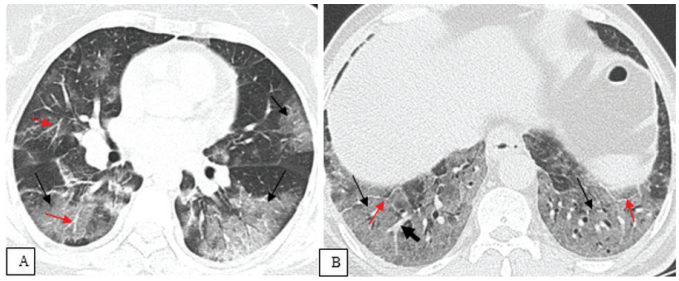

Figure 4. Axial CT images showing. A) bilateral patchy multifocal GGOs predominantly peripheral in distribution (A, black arrows) in a 56-year-old immunocompetent female patient presenting with cough and dyspnea, who had a history of hypertension, type 2 diabetes mellitus and asthma, who was discharged from the hospital 7 days after being hospitalized for COVID-19 pneumonia. Note also the intralesional microvascular dilatations (A, red arrows). B) Bilateral GGOs involving wide areas in the lower lobes (B, black arrows) associated with intralesional microvascular dilatation (B, thick black arrow) in a 61-year-old immunocompetent male patient presenting with dyspnea and cough, who died 30 days after being hospitalized for COVID-19 pneumonia. Note also the presence of fibrotic streaks associated with the GGOs (B, red arrows)

GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019, CT: Computed tomography

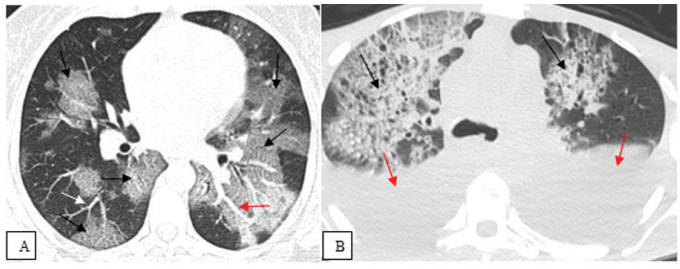

Figure 5. Axial CT images showing. A) multifocal peripheral and central/peribronchovascular GGOs superimposed with reticularion resulting in crazy paving pattern (A, black arrows) in a 33-year-old immunocompetent patient presenting with cough, dyspnea, and chest pain, who had a history of the atrial septal defect and who was discharged 15 days after being hospitalized for COVID-19 pneumonia in a 55-year-old immunocompromised patient presenting with fever, cough, dyspnea, and weakness. Note also the perilesional (A, white arrow) and intralesional (A, red arrow) microvascular dilatations B) Bilateral consolidative opacities at the circumferences of structural damaged emphysematous pulmonary parenchyma, which is more prominent in the right lung (B, black arrows). Note the presence of bilateral pleural effusion (B red arrows) in this immunocompromised patient presenting with fever, dyspnea, and cough who had a history of essential thrombocytosis and died 15 days after being hospitalized for COVID-19

CT: Computed tomography, GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019

of the disease, which is known as a cytokine storm. This could be expected to be less likely and milder in severity in immunodeficient patients (17-20). Similarly, the evaluation of 110 immunodeficient patients with COVID-19 obtained from a systematic review of 16 articles revealed that immunodeficient

patients seemed to have a favorable course (21). Additionally, a statistically significant risk of severe COVID-19 was not found among immunodeficient patients in a meta-analysis from China (22). However, the lack of a normal immune response can also be associated with the lack of protective antiinflammatory effects and higher possibility of developing co-infections in this

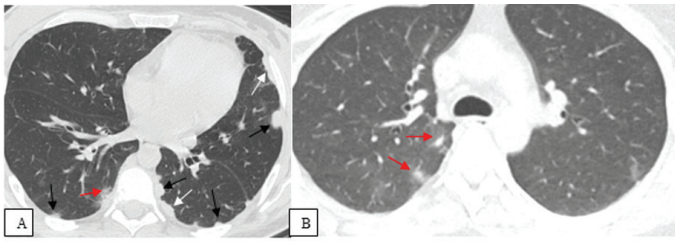

Figure 6. Axial CT images showing. A) Bilateral nodular pulmonary infiltration predominantly peripheral in distribution (A, black arrows) in a 30-year-old immunocompromised female patient presenting with cough, fatigue, and nausea who had a history of esophageal cancer and was discharged from the hospital 8 days after being hospitalized for COVID-19 pneumonia. Note also the subpleural GGOs (A, red arrow) and consolidations (A, white arrows). B) GGOs surrounding the nodular consolidations in the right lower lobe resulting in halo sign (B, red arrow) in a 51-year-old immunocompromised female patient presenting with fever and dyspnea, who had a history of diffuse large B-cell non-Hodgkin lymphoma was discharged from the hospital 10 days after being hospitalized for COVID-19 pneumonia

CT: Computed tomography, GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019

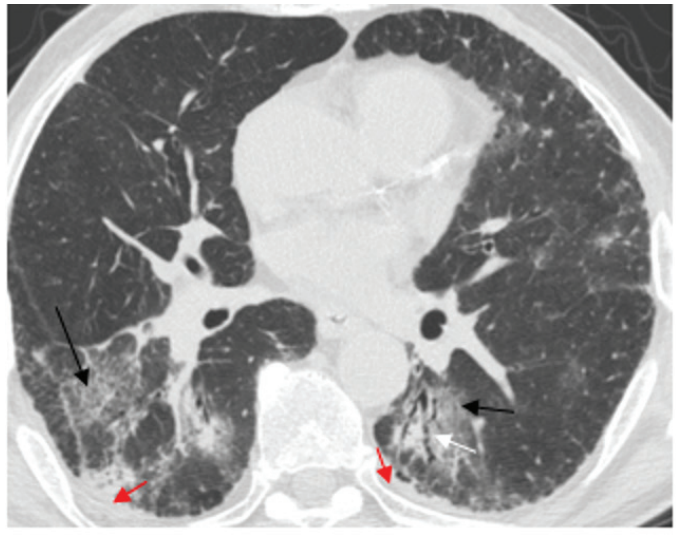

Figure 7. Axial CT image showing irregular consolidative infiltration in association with patch bilateral GGOs (black arrows) in a 71-year-old immunocompromised male patient presenting with dyspnea and fatigue who had a history of lung cancer, hypertension, type 2 diabetes mellitus and who was discharged from the hospital 14 days after being hospitalized for COVID-19 pneumonia. Note also bilateral small amounts of pleural effusion (red arrows) and the irregularly dilated bronchioles (bronchiectasis) (white arrow) in association with the pneumonic infiltration in the left lower lobe

CT: Computed tomography, GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019

Table 3. Chest CT findings of the patients

Chest CT findings	Immunocompromised patients (n=44, %)	Immunocompetent patients (n=44, %)	p values
Typical findings			
GGO: n (percentage)	44 (100%)	44 (100%)	*
GGO + consolidation: n (percentage)	30 (68.2%)	23 (52.3%)	0.127
Crazy paving pattern: n (percentage)	20 (45.5%)	30 (68.2%)	**0.031****
Air bronchogram: n (percentage)	22 (50%)	16 (36.4%)	0.197
Halo sign: n (percentage)	13 (29.5%)	10 (22.7%)	0.467
Microvascular dilatation: n (percentage)	13 (29.5%)	16 (36.4%)	0.496
Reversed halo sign: n (percentage)	0 (0%)	0 (0%)	*
All lobes involvement: n (percentage)	37 (84.1%)	40 (90.9%)	0.334
Peripheral-subpleural involvement: n (percentage)	37 (84.1%)	44 (100%)*	**0.006****
Peribronchovascular involvement: n (percentage)	35 (79.5%)	31 (70.5%)	0.325
Atypical findings			
Bronchiectasis: n (percentage)	13 (29.5%)	2 (4.5%)	**0.002****
Pulmonary nodules: n (percentage)	11 (25%)	4 (9.1%)	**0.047****
Tree-in-bud appearance: n (percentage)	18 (40.9%)	1 (2.3%)	**<0.001****
Pleural effusion: n (percentage)	18 (40.9%)	4 (9.1%)	**0.001****
One lobe involvement: n (percentage)	7 (15.9%)	4 (9.1%)	0.334
Cavitation: n (percentage)	0 (0%)	0 (0%)	*
Distribution of lesions			
One lobe involvement: n (percentage)	7 (15.9%)	4 (9.1%)	0.334
All lobes involvement: n (percentage)	37 (84.1%)	40 (90.9%)	0.334
Peripheral-subpleural distribution: n (percentage)	37 (84.1%)	44 (100%)*	**0.006****
Peribronchovasculary distribution: n (percentage)	35 (79.5%)	31 (70.5%)	0.325

* It was not statistically calculated, ** There is statistically significant difference between two groups. CT: Computed tomography, GGO: Ground glass opacity

patient group, which may be associated with higher mortality. A large retrospective national cohort study from Spain showed that immunodeficient patients hospitalized with COVID-19 have higher odds of in-hospital death and complications than immunocompetent patients. These groups were reported as the vulnerable population for complicated COVID-19 and suggested to be closely monitored (23). Similarly, our study revealed a significantly higher mortality rate in immunodeficient patients than in the immunocompetent patients, regardless of the age. When we looked at the underlying causes for immunodeficiency in our patients, the most common were being under treatment for cancer, which may be the reason for this higher mortality. Some recent reports revealed a similarly high mortality rate in cancer patients with COVID-19 (24). Reports regarding the chest CT imaging findings in immunodeficient patients with COVID-19 pneumonia are scarce in the current literature. Severe pulmonary sequelae has been reported in a 12-year-old child with primary immunodeficiency during the follow-up of COVID-19 pneumonia (25). Bilateral GGOs with multiple nodules complicated with pneumothorax, pneumomediastinum and pneumopericardium has been reported in a 28-year-old woman with a medical history of combined variable immunodeficiency under treatment with intravenous immune globulin (26). In the study by Abrishami et al. (27) most chest CT findings in kidney transplant recipients on immunosuppression were found to be similar to those from other adult studies for the general population. They only reported unilateral involvement and consolidation as slightly more frequent in their patients (27). In our study, the most common chest CT finding was also GGO with or without accompanying consolidations, which is the most frequent imaging finding of COVID-19 in general population reported in the literature. However, in our study, the crazy paving pattern, which is consistent with the progressive phase of the disease was observed statistically significantly higher in the immunocompetent group. Peripheral/subpleural distribution of the infiltration was also observed significantly higher in immunocompetent patients. A significant correlation was found between the immunodeficient patient group and atypical radiological findings, including bronshiectasia, tree in bud appearance, pulmonary nodules, and pleural effusion. Our study also revealed a significant association between mortality and atypical findings, which were statistically significantly more frequent in immunodeficient patients.

Study Limitations

The limitations of our study included, the limited number of patients, the retrospective nature of the study, not being able to evaluation in terms of superinfection, which may be a confounder of the chest CT findings observed, particularly immunodeficient patients who may be more susceptible to secondary bacterial infections.

CONCLUSION

In our study, it was determined that there was an increased risk of more severe COVID-19 disease and a higher mortality rate in immunodeficient patients. Radiologists should consider COVID-19 pneumonia in cases of rare, atypical and vague CT findings in immunodeficient patients. Since the course of COVID-19 pneumonia may be more severe in immunodeficient patients, the detection of chest CT findings of the diagnosed patients and knowing the typical and atypical findings will decrease morbidity and mortality rates with a more accurate interpretation.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (no: 48670771-514.10).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.K., H.K.Y., F.Ş., H.Ö., Design: N.K., B.E., H.K.Y., F.Ş., H.Ö., Data Collection or Processing: N.K., B.E., M.K.T., Analysis or Interpretation: N.K., B.E., H.Ö., Literature Search: N.K., B.E., Writing: N.K., B.E., M.K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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