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CHEST

CT imaging findings in lung transplant recipients with COVID-19

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Abstract

Objectives Our goal was to compare the chest computed tomography (CT) imaging findings of COVID-19 in lung transplant recipients (LTR) and a group of non-transplanted controls (NTC).

Methods This retrospective study included 51 consecutive LTR hospitalized with COVID-19 from two centers. A total of 75 NTC were included for comparison. Images were classified regarding the standardized RSNA category, main pattern of lung attenuation, and longitudinal and axial distribution. Quantitative CT (QCT) analysis was performed to evaluate percentage of high attenuation areas (%HAA, threshold −250 to −700 HU). CT scoring was used to measure severity of parenchymal abnormalities.

Results The imaging findings of COVID-19 in LTR were significantly different from controls regarding the RSNA classification and pattern of lung attenuation. LTR had a significantly higher proportion of patients with an indeterminate pattern on CT (0.31 vs. 0.11, $p = 0.014$). The most frequent pattern of attenuation in LTR was predominantly consolidation (0.39 vs. 0.22, $p = 0.144$) followed by a mixed pattern of ground-glass opacities (GGO) and consolidation (0.37 vs. 0.20, adjusted $p = 0.102$). On the other hand, the most common pattern in NTC was GGO predominant (0.58 vs. 0.24 of LTR, $p = 0.001$). LTR had significantly more severe parenchymal disease measured by CT score and %HAA by QCT (0.372 ± 0.08 vs. 0.148 ± 0.06, $p < 0.001$).

Conclusion The most frequent finding of COVID-19 in LTR is a predominant pattern of consolidation. Compared to NTC, LTR more frequently demonstrated an indeterminate pattern according to the RSNA classification and more extensive lung abnormalities on QCT and semi-quantitative scoring.

Key Points

- *The most common CT finding of COVID-19 in LTR is a predominant pattern of consolidation followed by a mixed pattern of GGO and consolidation, while controls more often have a predominant pattern of GGO.*
- *LTR more often presents with an indeterminate pattern of COVID-19 by RSNA classification than controls; therefore, molecular testing for COVID-19 is essential for LTR presenting with lower airway infection independently of imaging findings.*
- *LTR had more extensive disease by semi-quantitative CT score and increased percentage areas of high attenuation on QCT.*

Keywords COVID-19 · Computed tomography · Quantitative CT · Lung transplant

Abbreviations

%HAA	Percentage of high attenuation areas
COVID-19	Coronavirus disease 2019
CT	Computed tomography
GGO	Ground-glass opacities
ICU	Intensive care unit
LTR	Lung transplant recipients
NTC	Non-transplanted controls

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RSNA Radiological Society of North America
RT-PCR Real-time protein chain reaction

Introduction

After 2 years of the current coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-nCoV-2, most published data about the prognosis of COVID-19 have been published about immunocompetent patients. For patients with solid organ transplantation, prior reports show mixed results on the COVID-19 prognosis, including outcomes worse than controls [1, 2] and mortality comparable to non-transplanted individuals [3, 4]. Since the main site of clinical manifestation of COVID-19 infection is the lung, lung transplant recipients (LTR) may be particularly vulnerable by virtue of the allograft itself being the target of the novel coronavirus infection [5]. In LTR patients, COVID-19 mortality ranged from 12 to 46% [6–12].

In COVID-19 pneumonia, the severity and extension of lower respiratory tract involvement are usually assessed by chest computed tomography (CT). Chest radiography is often inaccurate in the initial stages of pulmonary infection [13]. CT is extremely sensitive for diagnosing ground-glass opacities (GGO), a typical imaging feature of COVID-19 pneumonia [14, 15]. Although CT is not necessary for the diagnosis of COVID-19 pneumonia, typical imaging findings are helpful when combined with suggestive symptoms to allocate these patients to a holding room for contagious disease while waiting for the results of the real-time protein chain reaction (RT-PCR) test. Also, chest CT is valuable to detect both alternative diagnoses and complications (e.g., acute respiratory distress syndrome, pulmonary embolism, and heart failure) [16].

Although imaging features of COVID-19 pneumonia are well known in the general population, data in patients with transplantation is limited. In chest radiographs, parenchymal opacities can be seen in 48 to 72% of LT patients with SARS-nCoV-2 pneumonia, with a predominance of bilateral infiltrates [11, 17]. Reports describing the CT findings in LTR with COVID-19 pneumonia are also limited. In a French cohort including 35 LT inpatients with COVID-19, 90% of patients had GGO and 46.2% had consolidation on chest CT, but the predominant pattern of disease and the RSNA classification is unknown [7].

The purpose of the present study was to evaluate the CT imaging findings of pulmonary manifestations of COVID-19 infection in hospitalized LTR and compare it to the CT findings in hospitalized non-transplanted controls (NTC).

Methods

Patient population

We retrospectively identified 51 consecutive adult LTR from two institutions hospitalized for COVID-19 from July 01, 2021, to February 9, 2022. All patients had documented SARS-nCoV-2 infection diagnosed by RT-PCR and at least one chest CT performed within 48 h of hospitalization. For the comparative arm, a total of 75 hospitalized patients with no history of immunosuppression or lung transplant matched for age, vaccination status, and comorbidities were enrolled during the same timeline. Inclusion criteria for controls were the same as those for patients with lung transplantation. The retrospective study was approved by the Institutional Review Board of the participating institutions with waiver of consent.

Demographics (age, gender), comorbidities (hypertension, diabetes, and cardiovascular disease), clinical symptoms (fever and cough), vaccination status, and time of transplantation were recorded. Clinical outcomes including intensive care unit (ICU) admission and 30-day mortality were also assessed. In case more than one CT study was performed for the same patient, only the first CT was included in the study. Images were de-identified and transferred to a cloud-based Dicom viewer for analysis.

CT image evaluation

Images were reviewed by two chest radiologists with more than 10 years of experience. If the radiologists initially had discordant decisions, a final decision was reached by consensus with a third radiologist.

In each scan, a predominant CT pattern was determined (predominantly or purely GGO; predominantly or purely consolidation; mixed GGO and consolidation; absence of GGO or consolidation). Findings were also classified according to their location (unilateral vs. bilateral) and their distribution in the axial plan (peripheral, central, diffuse, or random) and in the longitudinal plan (upper, lower, or diffuse). For axial distribution, a 30-mm distance from the pleura was determined as the boundary between inner and outer zones. For longitudinal distribution, the tracheal carina divided the upper and lower lung zones. Diffuse distribution was defined as lesions that were distributed across boundaries, whether axial or longitudinal.

COVID-19 pneumonia CT patterns were categorized as typical, indeterminate, atypical, or negative based on the Radiological Society of North America (RSNA) Expert Consensus Statement [14]. Typical appearance consisted in one of the following: (a) peripheral, bilateral, GGO with or without consolidation or intralobular lines; or (b) multifocal GGO of rounded morphology with or without consolidation or intralobular lines; or (c) reverse halo sign or findings of organizing pneumonia. Indeterminate appearance comprised

cases of absence of typical features and presence of GGO with non-rounded and non-peripheral distribution. Atypical appearance was defined as absence of typical or indeterminate features with presence of common findings for pneumonia of different etiologies, such as lobar/segmental consolidation without GGO, discrete centrilobular nodules, lung cavitation, or smooth interlobular septal thickening with pleural effusion.

The lesions' appearances on axial CT images were classified following a 3-point scale: 0, normal attenuation; 1, GGO; and 2, consolidation. The affected lung parenchyma was assigned a score on a 6-point scale according to the extent of lobar involvement in each lobe: 0, none; 1, < 5%; 2, 5–25%; 3, 25–50%; 4, 50–75%; and 5, > 75%. The scores for each lobe were summed and a global severity CT score with possible values from 0 to 25 was obtained [18].

Software-based evaluation of the well-aerated lung parenchyma was performed on a dedicated workstation using the extension Chest Imaging Platform (Applied Chest Imaging Laboratory) of the open-source 3D Slicer software (version 4.10.2, https://www.slicer.org) [19]. A fully automatic lung segmentation and analysis of lung parenchyma histogram was obtained using soft tissue kernel (Fig. 1). In case of unsatisfactory lung segmentation, the user amended the lung contours with a manual tool. The definition of percentage of high attenuation areas (%HAA) by software segmentation was set at the interval between −250 HU and −700 HU according to reports from the literature [20, 21].

Statistical analysis

SPSS software (version 24.0, IBM) was used to process the data. Continuous variables were expressed as means ± SD, and categorical variables were expressed as numbers. The chi-square test was used for categorical variables, and Welch's *t*-test was used for continuous variables. The level of significance was set at 0.05. Bonferroni correction was used when performing multiple tests and the *p* value was adjusted (raw *p* value multiplied by number of tests) accordingly when appropriate [22].

Results

Patients

A total of 126 patients were enrolled in this study. Of them, 51 patients had lung transplantation (58.8% male; mean age 47.2 ± 11.3 years) and mean time from lung transplantation was 22 ± 8 months. There were no significant differences in age, gender, vaccination status, comorbidities, and interval between symptom onset and time of imaging between the two groups (Table 1). All patients included had been at least double vaccinated. Although both groups had a similar rate of intensive care unit admission, the LTR group had a higher all-cause 30-day mortality than controls (15.7% vs. 6.7%, $p = 0.102$).

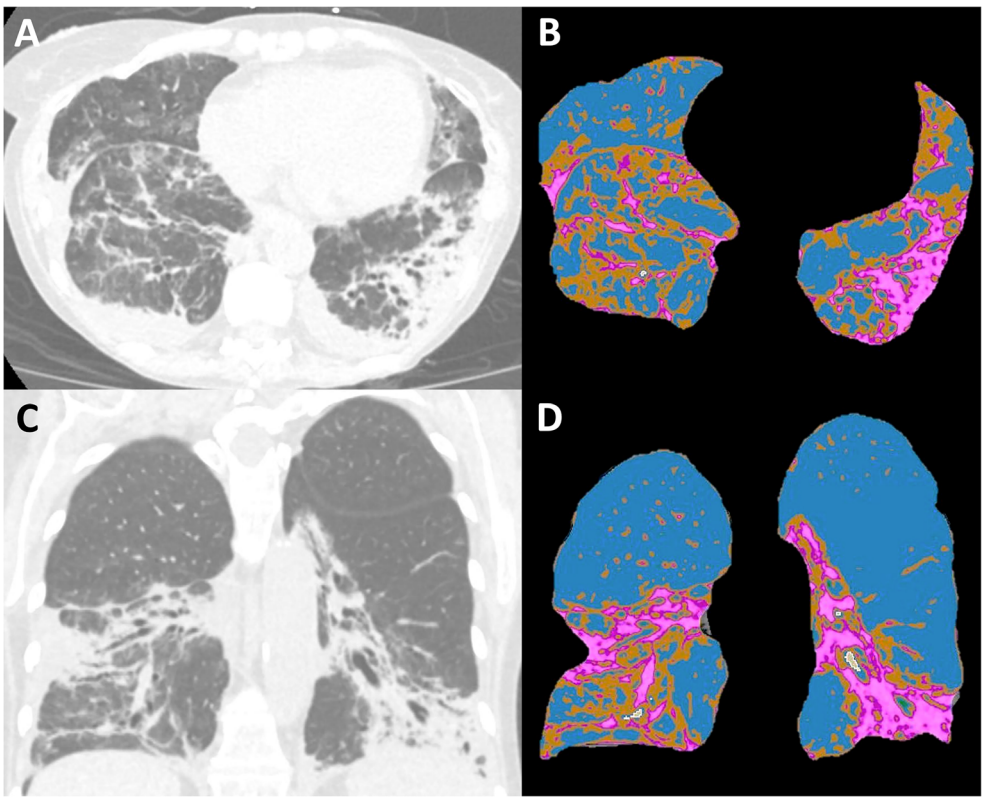

Fig. 1 A 55-year-old woman presenting with history of fever and cough. **A**, **B** Axial CT and threshold-based reconstruction demonstrates a consolidation pattern (pink) with adjacent ground-glass opacities (orange) in a random axial distribution. **C**, **D** Coronal CT and quantitative CT reconstruction depicts the lower lobe predominance of the opacities in this patient

Table 1 Patient characteristics

Characteristic	LTR (n = 51)	NTC (n = 75)	p value
Age, mean ± SD (years)	47.2 ± 11.3	45.6 ± 11.1	0.433
Male (n)	30 (58.8)	45 (60.0)	0.895
Diabetes	15 (29.4)	26 (34.7)	0.536
Hypertension	12 (23.5)	18 (24.0)	0.951
Vaccination (2 doses)	51	75	1.00
SpO_2 at presentation	89 ± 5.3	88 ± 4.9	0.286
Interval between symptom onset and imaging (days)	5.7 ± 1.1	6.1 ± 2.5	0.224
Intensive care unit admission	31 (60.8)	45 (60.0)	0.929
30-day mortality	8 (15.7)	5 (6.7)	0.102

Note. Unless otherwise indicated, data are presented as absolute prevalence and prevalence rates in parenthesis. *LTR*, lung transplant recipients; *NTC*, non-transplanted controls; *SD*, standard deviation; *SpO_2* peripheral oxygen saturation

CT imaging findings

The imaging findings of COVID-19 in LTR were significantly different from controls regarding the RSNA category (p = 0.007) and the main pattern of lung attenuation (p = 0.001) (Table 2). Although both LTR and NTC more often presented with a typical pattern according to RSNA classification, the prevalence in NTC was significantly higher compared to LTR (74.6% vs. 47.0%, p = 0.006). On the other hand, LTR had a higher prevalence of indeterminate imaging pattern compared to controls (31.3% vs. 10.6%, p = 0.14). The rate of atypical cases (17.6% vs. 10.6%, p = 1.00) and negative initial CT scan (11.7% vs. 4%, p = 1.00) were similar between LTR and NTC, respectively.

Table 2 Comparison of CT findings of COVID-19 pneumonia in lung transplant recipients and controls

Characteristic	LT (n = 51)	NLT (n = 75)	p value
RSNA category			
Typical	24 (47.0)	56 (74.6)	.006*
Indeterminate	16 (31.3)	8 (10.6)	.014*
Atypical	9 (17.6)	8 (10.6)	1.00*
Negative	2 (11.7)	3 (4)	1.00*
CT score, mean (SD)	13.8 (± 4.2)	7.1 (± 3.4)	.001
Main attenuation pattern			
GGO**	12 (23.5)	42 (56.0)	.001*
Consolidation**	19 (37.2)	16 (21.3)	.144*
Mixed GGO and consolidation	18 (35.3)	14 (18.7)	.102*
Axial distribution			.72
Peripheral	27 (52.9)	45 (60.0)	
Central	5 (9.8)	6 (8.0)	
Diffuse or random	17 (33.3)	21 (28.0)	
Longitudinal distribution			.99
Upper	0	1 (1.3)	
Lower	21 (41.2)	31 (41.3)	
Diffuse	28 (54.9)	40 (53.3)	
%HAA, mean (SD)	37.2 (± 8.1)	14.8 (± 6.3)	< .001

Note. Data are presented as absolute prevalence and prevalence rates in parenthesis. *%HAA*, percentage of high attenuation areas; *CT*, computed tomography; *GGO*, ground-glass opacities; *LT*, lung transplant; *NLT*, non-lung transplant; *SD*, standard deviation

*Adjusted p value for Bonferroni correction

**Purely or predominantly GGO/consolidation

The main patterns of lung attenuation in LTR were a predominant pattern of consolidation (37.2% vs. 21.3% of NTC, p = 0.144) followed by a mixed pattern of GGO and consolidation (35.3% vs. 18.7%, p = 0.102). Figures 1 and 2 demonstrate two LTR with a predominant pattern of consolidation and a mixed pattern of GGO and consolidation, respectively. LTR more rarely presented with a predominant pattern of GGO only (Fig. 3), which was the most common presentation of NTC (23.5% vs. 56.0%, p = 0.001). There were no significant differences between the predominant axial and longitudinal distribution between both groups. More often patients had a predominantly peripheral distribution with a lower zone predominance of abnormalities.

The degree of pulmonary involvement measured by the CT score was significantly higher and almost double in the population of LTR (mean score 13.8 vs. 7.1, p = 0.001). Similar findings were found when measuring severity of involvement with QCT, with the LTR population presenting with significantly higher %HAA than controls (mean %HAA 37.2% vs. 14.8%, p < 0.001).

Discussion

A predominant pattern of GGO was seen in only 23.5% of patients with lung transplant, which could be explained by the immunocompromised state and the higher susceptibility to develop more severe forms of the disease with more

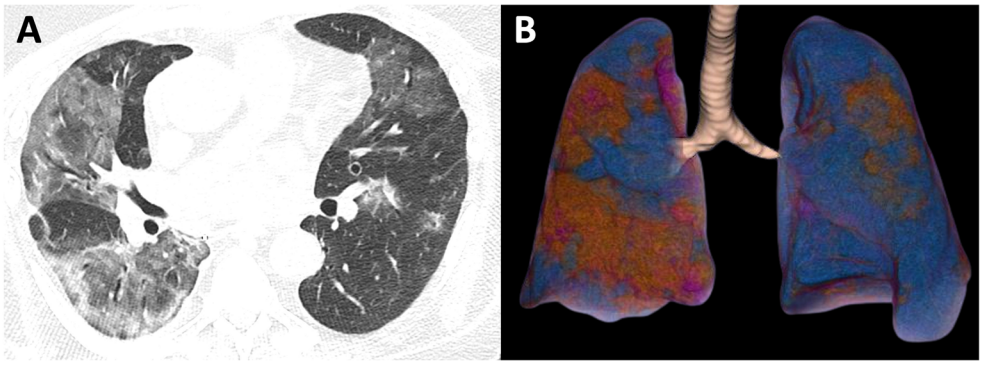

Fig. 2 A 44-year-old male with history of lung transplantation presenting with hypoxia. **A** Axial CT scan demonstrates a mixed pattern of ground-glass opacities and consolidation with diffuse axial distribution. **B** Threshold-based volumetric reconstruction shows the diffuse longitudinal distribution, right greater than left, as well as the areas of ground-glass opacities (orange), consolidation (pink), and normal lung (blue)

consolidation. On the other hand, NTC most often presented with a pure or predominant pattern of GGO (56.0%), which is consistent with prior reports in the literature of immunocompetent patients [15]. In addition to the higher incidence of consolidation, LTR had more extensive parenchymal disease compared to controls measured by both CT score and the %HAA on QCT. Also, the group of LTR more frequently showed an indeterminate pattern for COVID-19 according to RSNA classification, which highlights the importance of molecular testing for COVID-19 in immunosuppressed patients presenting with lower airway infection.

Data on the imaging findings in patients with solid organ transplant and LTR particularly are scarce in the literature. Abrishami et al reported that the prevalence of GGO and consolidation in hospitalized patients with kidney transplantation was 100% and 75%, respectively [23]. Messika et al reported a prevalence of 100% of GGO and 60% of consolidation in LTR admitted to the ICU with COVID-19 [7]. Predominantly, bilateral involvement was also reported in both series. The latter concluded that the imaging findings of COVID-19 in LTR are similar to non-immunocompromised individuals. However, our study demonstrates that there are important differences in the main pattern of CT findings of LTR and NTC, particularly regarding the higher prevalence of a predominant consolidation in LTR. Also, none of the studies has investigated the most common presenting imaging category according to RSNA classification for those patients.

Data on mortality associated with COVID-19 in LTR is limited to mostly retrospective studies with numbers ranging from 12 to 46% [6–12]. Our population had reported mortality in the lower end of this spectrum, particularly because all patients were vaccinated at least twice for COVID-19. Also, some of the other studies had mixed data from outpatient and inpatient, while others were done in more severe cases, which contributes to the wide range of the spectrum. Saez-Gimenez et al presented data on short-term outcomes of 44 LTR with confirmed COVID-19 and hospitalization to one of six Spanish referral centers with a mortality rate of 39% [17]. Kates et al found a mortality rate of 33% in 30 LTR recipients from the USA [24]. Coll et al reported a mortality rate of 46% in 50 LTR with COVID-19 from Spain [12]. Aversa et al reported on 32 LTR with COVID-19 from New York City with a mortality rate of 34% [25]. Further small case series on the outcomes of lung transplant recipients after COVID-19 revealed mortality rates between 10 and 25% [26, 27].

Our study has some limitations. First, there are limitations inherent to the retrospective nature of this study. Our sample size is small and is subject to selection bias especially in the

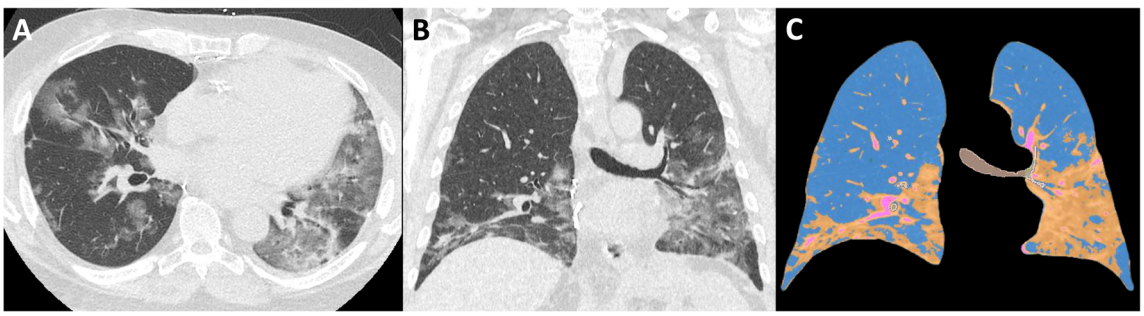

Fig. 3 A 61-year-old man with bilateral lung transplant presenting with shortness of breath for 6 days. **A** Axial CT demonstrates a predominant pattern of ground-glass opacities in a diffuse axial distribution, left greater than right. **B**, **C** Coronal CT and threshold-based reconstruction depicts the preferential involvement of the lower lobes, as well as the higher proportion of ground-glass opacities (orange) compared to consolidation (pink)

population of controls and would ideally benefit from propensity score matching. Although there was no significant difference in the time between symptoms and imaging between the two groups, this could also have influenced some of the imaging findings herein seen. The timeframe of the study was long, and we have not investigated how different variants of COVID could have influenced some of the findings. The primary goal of this study was to investigate the chest CT findings of COVID-19 in LTR and it was not designed or powered to investigate mortality in these patients; therefore, mortality outcomes should be interpreted with caution due to high risk of bias.

In conclusion, the most frequent pattern of lung attenuation in LTR are a predominant pattern of consolidation followed by a mixed pattern of consolidation and GGO, while NTC most often presented with a predominant GGO pattern. LTR more often present with an indeterminate pattern according to RSNA classification and are more likely to have more extensive lung abnormalities measured either by CT score or %HAA on QCT.

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Declarations

Guarantor The scientific guarantor of this publication is Bruno Hochhegger, MD, PhD.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- cohort
- multicenter study

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