

COVID-19 lung alterations still evident at 60-day follow-up chest CT in asymptomatic patients despite negative rRT-PCR testing

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Abstract

Several patients who have recovered from COVID-19 pneumonia showed persistent infection at follow-up chest CT (31-63 days after disease onset) despite being asymptomatic and testing negative at rRT-PCR.

Introduction

Italy was the first European country to confront the COVID-19 pandemic outbreak. Despite a high death toll, it is now observing the aftermath of the disease.

The Centers for Disease Control have issued return-to-work criteria based on real-time reverse transcription-polymerase chain reaction (rRT-PCR) and symptoms improvement [1], which, however, do not include imaging findings.

The purpose of this report is to compare the findings of chest CT with the rRT-PCR results in the follow-up of patients discharged after hospitalization for COVID-19 pneumonia.

Materials And Methods

Patient Population

The Institutional Review Board of (*BLINDED*) approved this retrospective study; informed consent was acquired before every CT. Medical records of all consecutive patients admitted for COVID-19 pneumonia from January to April 2020 in (*BLINDED*) were reviewed. Inclusion criteria were: a) hospitalization for SARS-CoV-2 confirmed by positive rRT-PCR b) non-contrast chest CT at admission c) hospital discharge with full clinical recovery d) follow-up chest CT performed at least 30 days after initial symptoms onset.

Chest CT visual and quantitative analysis

Chest CTs were acquired without contrast administration on a 64-row scanner and reformatted with 2 mm slice thickness. A single reader (*BLINDED*) visually evaluated all the exams and assessed the presence of features attributable to residual COVID-19 pneumonia.

Quantitative lung analysis was performed on all CT scans using a dedicated suite [2] (3DSlicer); segmentations were performed by three readers (*BLINDED*). Lung parenchyma volumes were extracted (Figure 1), in line with previous research [3], into well-aerated (%WAL, -950 to -701 Hounsfield Units [HU]), ground-glass opacity (%GGO, -700 to -501 HU), poorly aerated (%PAL, -500,-101) and non-aerated (%NAL, -100, +100 HU).

Statistical analysis

Logistic regression tests were performed to find the best lung volume to monitor COVID-19 pneumonia at follow-up. The dependent variable was the visual evidence of residual disease. Statistical significance

was set at $p < .05$.

Results

From January 25th to April 21st, 2020, 401 patients hospitalized for COVID-19 underwent a CT scan at admission. Thirty-six patients who had a follow-up chest CT from April 11th to 24th were included in the study.

Of these, 21/36 (58%) presented visual evidence of COVID-19 disease at CT after a median of 47 days from symptoms onset (Interquartile Range [IQR], 43-56, max. 63). %GGO yielded the highest Likelihood Ratio (13.74, $p = .007$), and a median volume of 6% was present in all cases.

14/21 (66%) patients tested negative at RT-PCR after a median of 31 days from discharge (IQR 31-33). Detailed clinical and statistical data are shown in Table 1.

Table 1. Clinical data and demographics

	Overall	Follow-up CT: COVID-19	Follow-up CT: negative	
Male	27	15	12	
Age - IQR	59 [50-69]	64 [58-70]	51 [47-56]	
Smoke habit	3	3	0	
PaO2 at admission - median mmHg, IQR	70 [65-80]	68 [61-72]	77 [69-86]	
Hospitalization - median days, IQR	7 [7-7]	7 [7-7]	7 [7-7]	
Oxygenation support with low-flow O2	16	11	5	
ICU admission	2	2	0	
Interval between initial symptom and follow-up CT - median days, IQR	49 [43-58]	43 [43-43]	47 [45-49]	
Interval between discharge and follow-up CT - median days, IQR	32 [31-34]	31 [31-35]	32 [31-34]	
rRT-PCR - negative tests after discharge	25	14	11	
Interval between discharge and rRT-PCR - median days, IQR	17 [16-26]	19 [17-25]	17 [16-22]	
Quantitative CT analysis results - median percentage of lung volume, IQR				
	Overall	Follow-up CT: COVID-19	Follow-up CT: negative	Logistic regression
%WAL at admission	83% [73-86]	84% [77-86]	86% [83-88]	
%WAL at follow-up	89% [87-90]	88% [86-90]	91% [90-91]	LR=7.99 p=.047
%GGO at admission	9% [7-13]	9% [7-11]	6% [6-9]	
%GGO at follow-up	6% [5-7]	7% [5-7]	5% [4-5]	LR=13.74 p=.007
%PAL at admission	5% [4-7]	5% [4-6]	4% [4-5]	
%PAL at follow-up	3% [3-4]	4% [3-4]	3% [3-3]	LR=11.33 p=.011
%NAL at admission	1% [1-3]	1% [1-2]	1% [1-2]	

%NAL at follow-up	1% [1-1]	1% [1-1]	1% [1-1]	LR=6.64 p=.034
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%WAL (Well-aerated, -950 to -701 HU); %GGO (Ground-glass opacity, -700 to -501 HU); %PAL (Poorly aerated, -500,-101); %NAL (Non-aerated, -100, +100); LR (Likelihood ratio chi-square test).

Discussion

Our study suggests that several patients with COVID-19 discharged after hospitalization still present an active infection at follow-up CT, despite being asymptomatic and having tested negative at rRT-PCR in the majority of cases. These results are in keeping with a similar report for chest X-Ray [4] and highlight the lack of an evidence-based algorithm for declaring a patient as disease-free.

Asymptomatic transmission is considered the Achilles' Heel of the current global strategy to control COVID-19 [5], and there is no available evidence that patients with positive CT findings are not capable of transmitting the infection. The premature reinstatement in the community of an individual with active disease may prevent the pandemic curve from decreasing.

Although preliminary and from a single center, our results may warn the medical community that 1) COVID-19 disease span is wide and may exceed 60 days 2) rRT-PCR alone seems inadequate to declare a patient as disease-free 3) chest CT may be the ideal tool not only for early diagnosis but also for disease monitoring and infection-control strategies, especially with the added value of quantitative analysis.

Declarations

Our study has been approved by the Institutional Review Board of Humanitas Clinical and Research Hospital (Rozzano, Milan).

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Figures

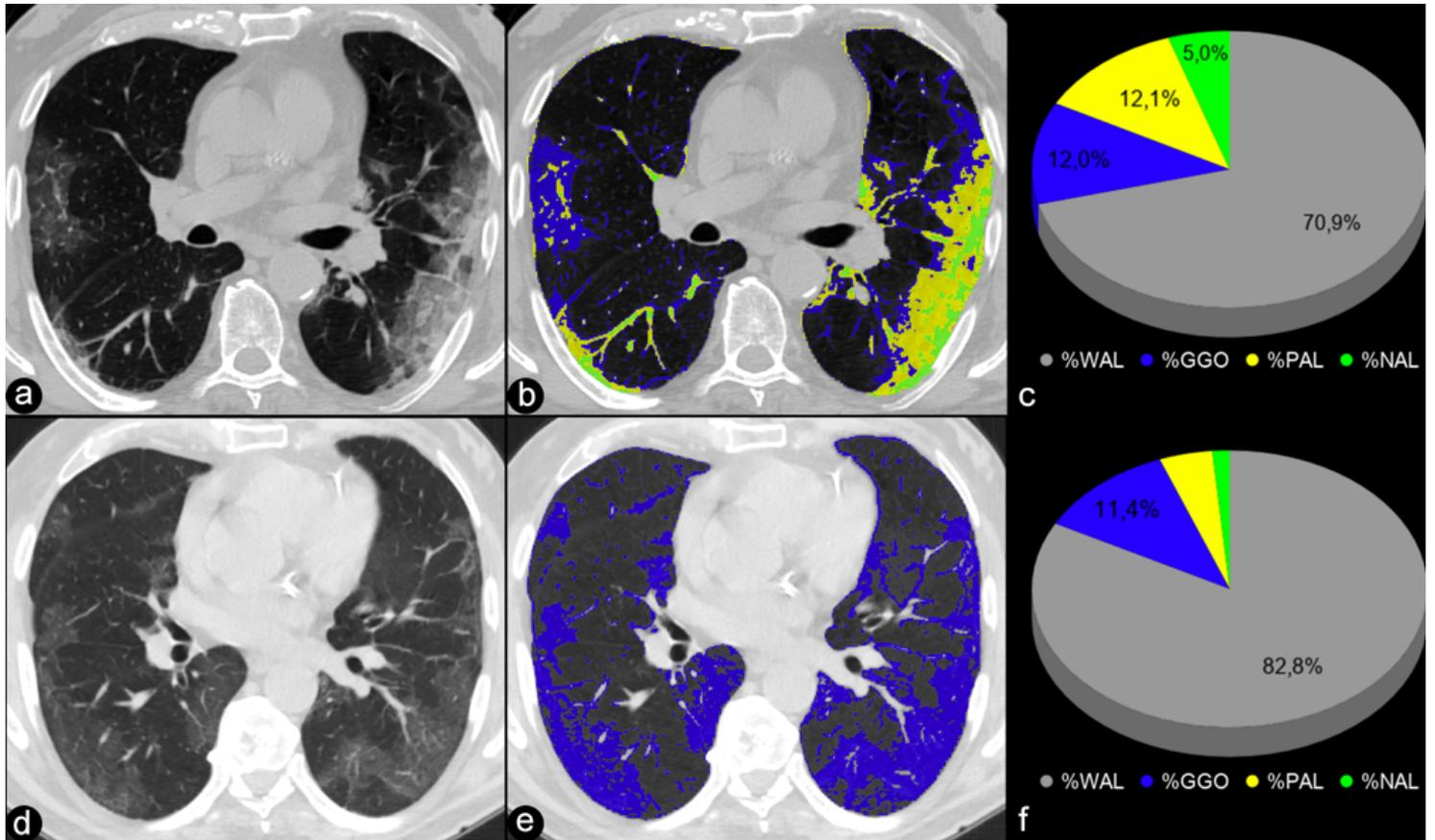


Figure 1

Chest CT of a 75-year-old man admitted for COVID-19 pneumonia. a) Bilateral peripheral ground-glass opacities and consolidation, predominantly in the left lung b) Quantitative analysis highlights in blue the ground-glass volume (%GGO), in yellow the poorly aerated (%PAL) and in green the non-aerated (%NAL) c) Pie chart representing the different volumes. Well-aerated lung (%WAL) is reduced to 71%. The patient recovered after 11 days of hospitalization and is tested negative at rRT-PCR 18 days after discharge. Fourteen days after, (58 days from disease onset, 43 from the first scan) the patient receives a follow-up CT (d), showing residual bilateral ground-glass opacities. Quantitative analysis (e) shows a marked decrease of %PAL (4%) and %NAL (1%), highlighting a residual 11 %GGO (f).