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Chest high-resolution computed tomography is associated to short-time progression to severe disease in patients with COVID-19 pneumonia

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ABSTRACT

Objective: In patients with mild COVID-19 pneumonia, chest high-resolution computed tomography (HRCT) is advised when risk factors for severe disease (i.e., age > 65 years and/or comorbidities) are present, and can influence management strategy. The objective was to assess whether HRCT is associated to short-time development of severe disease in patients with COVID-19 pneumonia.

Methods: Seventy-seven consecutive patients (mean age, 64 ± 15 years) with mild COVID-19 pneumonia (no or mild respiratory failure) that underwent HRCT were retrospectively identified. Fifty-two on 77 patients had reported risk factors for severe disease. A chest-imaging devoted radiologist recorded, on a per-examination basis, the following HRCT features: ground-glass opacity, crazy-paving pattern, consolidation, organizing pneumonia (OP) pattern, mosaic attenuation, and nodules. The extent of each feature (total feature score, TFS) was semi-quantitatively assessed. Total lung involvement (TLI) was defined as the sum of all TFSs. The study outcome was defined as the occurrence of severe disease (moderate-to-severe respiratory failure) within 15 days from HRCT. Logistic regression analysis was performed to assess if age, comorbidities, and HRCT features were associated to severe disease.

Results: On univariable analysis, severe disease was significantly associated with age > 59 years (29/47 patients, 61.7%) ($p = 0.013$), and not significantly associated with having comorbidities (22/44 patients, 50.0%). On multivariable analysis, TLI >15 and OP pattern >5 were independently associated to severe disease, with odds ratio of 8.380 ($p = 0.003$), and of 4.685 ($p = 0.035$), respectively.

Conclusion: Short-time onset of severe COVID-19 was associated to TLI >15 and OP pattern score > 5. Severe disease was not associated to comorbidities.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the agent causing the SARS-CoV-2 disease (COVID-19) ongoing pandemic, responsible of a constantly growing number of infections and deaths worldwide [1]. Clinical presentation of COVID-19 is variable. While some patients are asymptomatic, the disease can manifest with symptoms such as fever, dry cough, and dyspnea, possibly progressing to respiratory failure requiring admission to intensive care unit (ICU) and death [2].

To date, real-time reverse transcription-polymerase chain reaction (RT-PCR) of viral nucleic acid is regarded as the reference standard for COVID-19 diagnosis [3]. The peculiar COVID-19 pandemic contingency we are facing, along with possible constraints in having fast RT-PCR testing, has made high-resolution computed tomography (HRCT) a potentially valuable tool for helping referring physicians in the clinical decision making process. Radiologic societies worldwide released consensus statements and advice documents, in order to clarify the role of imaging in diagnosis and management of patients with suspected or diagnosed COVID-19 [4–7]. In particular, in patients who show mild respiratory disease and RT-PCR positivity or moderate-to-high pre-test probability of COVID-19 in the absence of RT-PCR test, imaging is advised for age > 65 years and comorbidities such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, arterial hypertension, and immunocompromise [6]. In this scenario, HRCT can provide a baseline examination for future comparison and assessment of comorbidity-related abnormalities, thus influencing the management and follow-up strategy.

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In the last months, many studies focused on the diagnosis of COVID-19 pneumonia, investigating main and ancillary HRCT features [8–10], as well as typical and atypical imaging patterns [11,12]. As far as we know, a few studies [13–16] evaluated whether HRCT can predict the clinical course of disease by means of individual findings (e.g., consolidation, air bronchogram, central lung involvement, pleural effusion, and percentage of well aerated lung parenchyma) or combined findings (e.g., computed tomography [CT] severity score). We therefore aimed to contribute to the evolving knowledge on disease by evaluating whether HRCT has a prognostic role in the early stage of disease.

The purpose of the study was to assess whether HRCT is associated to short-time development of severe respiratory failure in patients with COVID-19 pneumonia.

2. Material and methods

2.1. Study population

By performing a computerized search, we identified all the consecutive adult patients with suspected COVID-19 who underwent chest HRCT examination in our COVID-19-center between March 08, 2020, and April 16, 2020. The disease severity was classified according to the following criteria from the Italian Society of Emergency Medicine (SIMEU) [17]: (i) category I disease, including fever without respiratory failure and normal chest X-ray; (ii) category II disease, including fever with chest X-ray and arterial blood gas test indicating lung focus and/or mild respiratory failure (partial pressure of arterial blood oxygen [PaO2] $>$ 60 mmHg); (iii) category III disease, including fever with moderate-severe respiratory failure (PaO2 $<$ 60 mmHg in room air); (iv) category IV disease, including respiratory failure with suspected initial acute respiratory distress syndrome (ARDS) or complicated pneumonia; and (v) category V disease, consisting of ARDS. Treatments included oxygen therapy and/or continuous positive airway pressure (CPAP) ventilation in patients with category III-IV disease, and orotracheal intubation with invasive ventilation in patients with category IV-V disease, respectively [17].

Of 192 eligible subjects we excluded 104 patients with negative RT-PCR test for SARS-CoV-2, and 11 patients with SIMEU category III-V at the time of HRCT. Final study population included 77 patients (40 men and 37 women; mean age, 64 ± 15 years) showing confirmed positive result for SARS-CoV-2 from RT-PCR test and SIMEU category I-II disease at the time of HRCT. Flowchart of patient selection is presented in Fig. 1. In the case of multiple HRCTs, only the baseline examination was included in the analysis.

2.2. HRCT examinations

Examinations were performed on a 64-row scanner (LightSpeed, General Electric, Milwaukee, Wisconsin, USA), with the patient in the supine position. The whole thorax was scanned volumetrically at suspended full inspiration, with acquisition parameters as follows: tube potential, 120 kV; tube current modulation range, 100–350 mA; gantry revolution time, 0.6 s; detector configuration, 64 mm × 0.625 mm; reconstructed section thickness and reconstructed interval, 1.25 mm. Iodinated contrast administration (iomeprol 350 mgI/mL, [Iomeron, Bracco Imaging, Milan, Italy]) was performed in 4/77 patients (5.2%).

Two sets of images were reconstructed and displayed, namely a first set with high-spatial-frequency algorithm and pulmonary parenchyma windowing (level, −500 HU; width, 1700 HU), and a second set with soft tissue algorithm and windowing (level, 50 HU; width, 350 HU).

2.3. Image analysis

A radiologist with 10 years of experience in thoracic imaging reviewed all the chest HRCT examinations on a picture archiving and communication system workstation (Suitestensa Ebit srl, Esaote Group Company, Genoa, Italy), blinded to patients' clinical and laboratory data.

For each patient, the reader recorded the following six main HRCT pulmonary features: (i) ground-glass opacity (GGO); (ii) crazy-paving pattern; (iii) consolidation; (iv) parenchymal findings of organizing pneumonia (OP) (i.e., GGO or consolidation triangular or polygonal in shape, perilobular pattern, bronchial dilatation, reverse halo sign, linear and band-like opacities, and signs of fibrosis) (18); (v) mosaic attenuation; and (vi) nodules.

On a per-examination basis, each lung was divided into three zones, as follows: upper zone (above the carina), middle zone (from the carina to the inferior pulmonary veins), and lower zone (below the inferior pulmonary veins), resulting in a total of 6 zones (3 per lung). The reader assessed the zonal extent of each of the over-mentioned six HRCT pulmonary features, scoring it semi-quantitatively as follows: score 0 if there was no involvement; score 1 in the case of <25% involvement; score 2 for a ≥ 25% to <50% involvement; score 3 for a ≥ 50% to <75% involvement; score 4 for ≥75% involvement [15]. Therefore, the total score for each pulmonary feature (total feature score [TFS]) ranged 0–24. Total lung involvement (TLI) was defined as the sum of all TFSs.

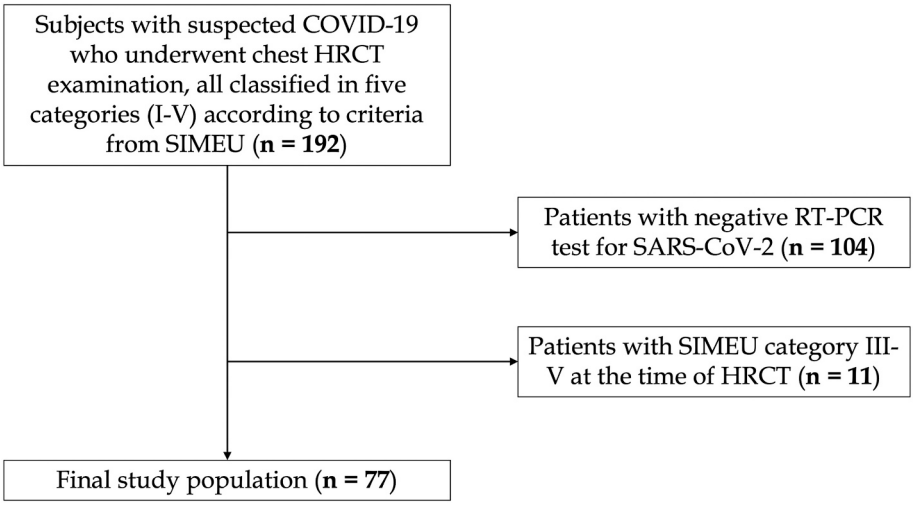

Fig. 1. Flowchart of patient selection.
HRCT: high-resolution computed tomography; SIMEU: Italian Society of Emergency Medicine; RT-PCR: real-time reverse transcription-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Presence of significant pleural effusion (>3 cm) was also evaluated.

2.4. Clinical data analysis

For all patients we recorded age, sex, presence of comorbidities (number and type), time from symptoms onset and HRCT examination, and SIMEU category as assigned by the referring physician (both at the time of HRCT, as well as the worst one observed in the 15 days following the examination). When not clearly reported by the referring physician, the SIMEU category was derived by the study coordinator, who was not involved in image analysis, and was unblinded to clinical data. This occurred in 26/77 patients at the time of HRCT, and 17/77 patients in the 15 days following HRCT.

For the purpose of analysis, we dichotomized SIMEU categories into two groups, namely: (i) mild disease group, including patients with no or mild respiratory failure (SIMEU category I or category II); (ii) severe disease group, including patients with moderate-to-severe respiratory failure or ARDS (SIMEU category III to V).

2.5. Statistical analysis

After checking for data normality with the Shapiro–Wilk test, we presented clinical data and HRCT features with mean ± standard deviation or median with the interquartile range (IQR). Proportions were coupled with 95% confidence intervals (95%CI) when relevant.

First, we performed a receiver-operating characteristic (ROC) analysis, using the Youden index to calculate the cut-off of TFS, TLI, and age better balancing sensitivity and specificity in assessing the study outcome. The latter was defined as the occurrence of severe disease in the 15 days following the examination, i.e. the shift from SIMEU category I-II at the time of HRCT to SIMEU category III-V. The area under the curve (AUC) was calculated as well.

Second, we run a logistic regression analysis with the stepwise approach to assess which of the clinical variables and HRCT features was associated as an independent predictor of the study outcome occurrence. The model included age, sex, number of comorbidities and the HRCT features showing the strongest association with the outcome at the preliminary univariable analysis, performed with the chi-square test. TFS, TLI and age values were dichotomized using the operative cut-offs obtained with ROC analysis before entering them in the model.

Statistical analysis was performed using a commercially available software (MedCalc Software bvba, version 18.11.6, Ostend, Belgium). The alpha level was set to 0.05.

Our referring Ethical Committee approved the study. The acquisition of informed consent was waived, due to the retrospective design.

3. Results

3.1. Study population

Clinical characteristics of the study population are detailed in Table 1. The median time between symptoms onset and HRCT examination was 5 days (IQR, 2–9 days). Forty-four over 77 patients (57%) had ≥1 comorbidities, while 20/77 (26%) patients had ≥2 comorbidities. Cardiovascular diseases were the most frequent ones (32/77, 42%). In the 15-day period following HRCT examination, 38/77 patients (49%) developed severe disease. The median time between HRCT and severe disease onset was 1 day (IQR, 1–2 days).

The results of ROC analysis defining the operative cut-off values for the analysis are reported in Table 2.

3.2. HRCT features

HRCT findings are listed in Table 3. The most frequent HRCT features were GGO and OP pattern, reported in 66/77 (86%) and in 71/77 (92%) patients, respectively. The other features occurred with the following frequency: consolidation in 50/77 cases (65%), crazy-paving pattern in 43/77 cases (56%), mosaic attenuation in 32/77 cases (42%), and nodules in 20/77 cases (26%). Three patients (4%) had no visible lung involvement. Pleural effusion >3 cm in thickness was found in 1 patient.

Lung involvement was bilateral in 70/77 patients (91%), and unilateral in 4/77 (5%). Upper, middle, and lower lung zones were affected in 64 (83%), 72 (94%), and 73 (95%) of 77 patients, respectively. TFS values are reported in Table 3. Median TLI was 16 (IQR 8.75–22).

3.3. Association with severe disease

Results from logistic regression analysis are shown in Table 4. On univariable analysis, severe disease occurred at a significantly higher extent (p = 0.013) in patients older than >59 years (29/47 [61.7%; 95% CI 41.3–88.6]) than in ≤59 year-old patients (9/30 [30.0%; 95%CI

Table 1
Patient-related clinical variables.

Clinical variables	All patients (n = 77)
Age (mean ± standard deviation)	64 ± 15 years
Sex, n (%, 95%CI)	
Female	37 (48, 34–66)
Male	40 (52, 37–71)
Comorbidities, n (%, 95%CI)	
≥1 comorbidity (all types)	44 (57, 42–77)
≥2 comorbidities (all types)	20 (26, 16–40)
Cardiovascular	32 (42, 28–59)
Respiratory	9 (12, 5–22)
Chronic renal failure	3 (4, 1–11)
Tumors	10 (13, 6–24)
Obesity	4 (5, 1–13)
Diabetes mellitus	6 (8, 3–17)
Immunocompromise	3 (4, 1–11)

Table 2
Results of the receiver operating characteristic (ROC) analysis defining operative cut-off values.

Variables	Cut-off	AUC
Clinical features		
Age (years)	>59	0.663
HRCT features (score)		
GGO	>4	0.809
OP pattern	>5	0.851
Consolidations	>1	0.732
Crazy-paving pattern	>1	0.532
Mosaic attenuation	>0	0.660
Nodules	>1	0.565
TLI	>15	0.886

AUC: area under the curve; HRCT: high-resolution computed tomography; GGO: ground-glass opacities; OP: organizing pneumonia; TLI: total lung involvement (see the text for details).

Table 3
HRCT findings in the study population. Proportions are calculated over 77 patients.

HRCT findings	Number of patients with findings	TFS median (IQR)
HRCT features, n (%, 95%CI)		
GGO	66 (86, 66–100)	6 (2–8)
OP pattern	71 (92, 72–100)	5 (2–8)
Consolidations	50 (65, 48–86)	1 (0–3)
Crazy-paving pattern	43 (56, 40–75)	1 (0–2)
Mosaic attenuation	32 (42, 28–59)	0 (0–2)
Nodules	20 (26, 16–40)	0 (0–1)
Pleural effusion >3 cm	1 (1, 0–7)	–

HRCT: high-resolution computed tomography; GGO: ground-glass opacities; OP: organizing pneumonia; TFS: total feature score (see the text for details).

Table 4
Results from the logistic regression model (endpoint: development of severe disease)

	Prevalence of outcome	Univariable analysis	Multivariable analysis
Variables	n (%, 95%CI)	p (Chi-square test)	OR (95%CI), p
Age > 59 years	29/47 (61.7, 41.3–88.6)	0.013	–
Sex (M)	23/40 (57.5, 36.5–86.3)	0.208	–
Comorbidities ≥1	22/44 (50, 31.3–75.7)	0.921	–
GGO >4	33/47 (70.2, 48.3–98.6)	<0.0001	–
OP pattern >5	27/32 (84.4, 55.6–100)	<0.0001	4.685 (1.111–19.755), 0.035
Consolidation >1	26/37 (70.3, 45.9–100)	0.001	–
TLI >15	32/40 (80, 54.7–100)	<0.0001	8.380 (2.087–33.647), 0.003

M: male; GGO: ground-glass opacities; OP: organizing pneumonia; OR: odds ratio; TLI: total lung involvement (see the text for details).

13.7–57.0]. On the contrary, the occurrence of severe disease was not significantly associated with having ≥1 comorbidities (22/44 [50.0%; 95%CI 31.3–75.7]) rather than <1 comorbidities (16/33 [48.5%; 95%CI 27.7–78.7]) (p = 0.921).

On multivariable analysis, TLI > 15 and OP pattern >5 were independently associated with the development of severe disease. Overall, the latter occurred in 33 over 42 patients with TLI > 15 and/or OP pattern >5 (78.6%; 95%CI 54.1–100), and in 26 over 30 patients with TLI > 15 and OP pattern >5 (86.7%; 95%CI 56.6–100). We excluded from the multivariable model the variables with the lowest association with the outcome at univariable analysis, i.e. crazy-paving pattern >1 (prevalence in patients with severe disease 14/38 [37%; p = 0.572]), mosaic attenuation >0 (22/38 [58%; p = 0.008]), and nodules >1 (7/38 [18%; p = 0.144]).

Example cases are illustrated in Figs. 2 and 3.

4. Discussion

There is intense debate on the use of HRCT in COVID-19 pneumonia, given the variability in locally available resources, and need for avoiding secondary exposure of patients and healthcare professional in the Radiology Department [19,20]. We found that short-term clinical evolution, i.e. a shift from mild disease (SIMEU category I-II) to severe disease (SIMEU category III-V) within 15 days from baseline HRCT, was significantly associated with the presence of an OP pattern score > 5, and a TLI score > 15. This association was also found in univariable analysis for patients aged >59 years.

In our series, about two third of patients mirrored the "clinical scenario 1" recently prompted by a Fleischner Society consensus document [6], which recommends chest imaging when mild features consistent with COVID-19 pneumonia coexist with risk factors for severe disease (age > 65 years or at least one comorbidity). Our results reasonably validate that indication to HRCT in order to provide a baseline examination for future comparison, and intensify the monitoring of patients with imaging findings predictive for clinical worsening.

However, in accordance with Wei et al. [21], we found no relationship between comorbidities and severe disease at multivariable analysis. This result is in contrast with previous Authors, who found comorbidities to predict several adverse outcomes [16,22], including admission to ICU and death [14]. The discrepancy might be related to confounding factors such as smoking status, and under-reporting of pre-existing pathologies impacting on COVID-19 outcomes [23]. This might also explain why about 50% of patients (16/33) with no comorbidities

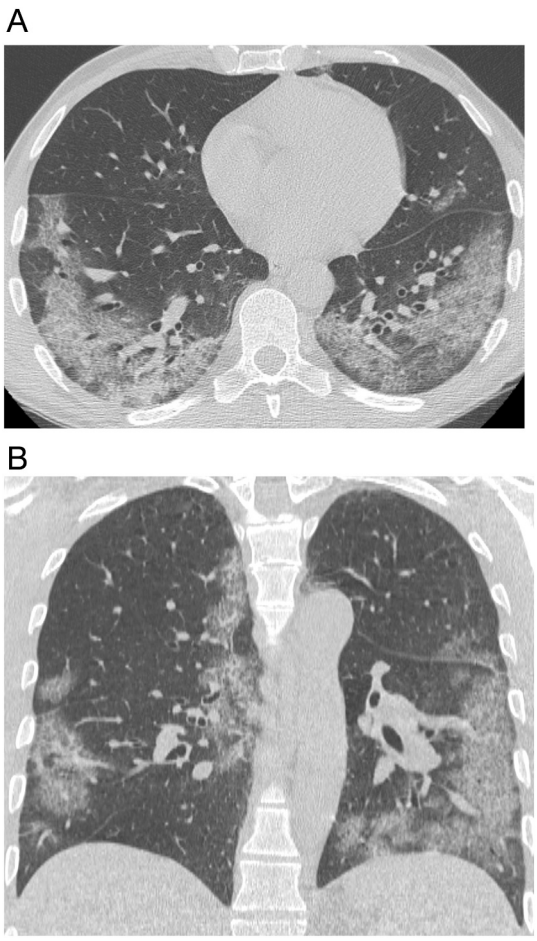

Fig. 2. 56-year-old man with confirmed severe acute respiratory syndrome coronavirus 2 disease (COVID-19) pneumonia and no comorbidities. High-resolution computed tomography (HRCT) was performed on day of hospital admission.
A–B, HRCT images on the axial plane (A) and on coronal reformation (B) depicted bilateral, peripheral ground-glass opacities (GGO) with crazy-paving pattern. Total lung involvement (TLI) score was 16, above the cut-off value of 15. After 5 days the patient developed respiratory failure (Italian Society of Emergency Medicine [SIMEU] category IV disease).

progressed to severe disease in our series. Our results suggest that, in the current scenario in which it is difficult to assess the presence or type of comorbidities representing risk factors [23], HRCT findings might help in identifying patients at risk of clinical progression by imaging features alone. Whether this can lead refining current indications to CT should be the matter for further research. Of note, our model included comorbidities as a whole rather than individually. This choice was related to the low prevalence of each comorbidity in our series, except for cardiovascular ones (42%). We believe that further studies on larger populations should address whether different comorbidities can affect prognosis at a different degree.

Our results on TLI are in line with previous studies showing that the extent of lung involvement, defined as CT score [15], CT severity score [16], or, conversely, well aerated lung parenchyma [14], is predictive of mortality, progression to severe disease, and ICU admission or death, respectively. This is reasonably related to the extensive diffuse alveolar damage (DAD) as the distinctive pathophysiological characteristic of the disease [24,25]. As expected from still limited knowledge on COVID-19 pneumonia, our results are difficult to compare with previous ones, e.g. in terms of definition of severe disease, method for assessing lung involvement, and amount of involved lung parenchyma that predicts clinical progression. While software-based methods such as the one

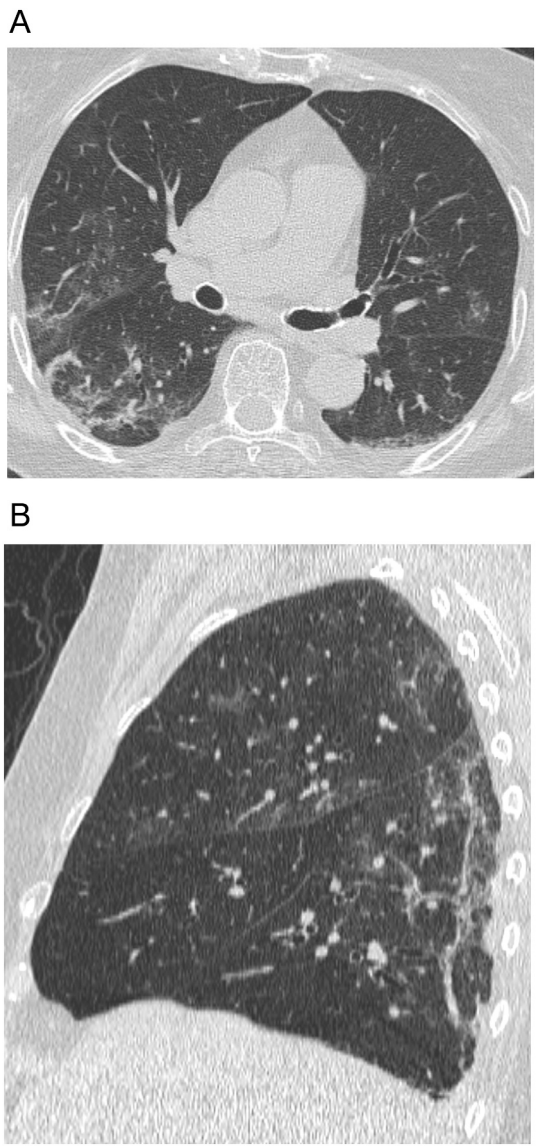

Fig. 3. 82-year-old man with confirmed severe acute respiratory syndrome coronavirus 2 disease (COVID-19) pneumonia and no comorbidities. High-resolution computed tomography (HRCT) was performed on day of hospital admission.
A–B, HRCT images on the axial plane (A) and on sagittal reformation (B) showed ground-glass opacities (GGO) and band-like opacities with a perilobular distribution, resembling an organizing pneumonia (OP) pattern. OP pattern score was 8 (above the cut-off value of 5). After 3 days the patient developed respiratory failure (Italian Society of Emergency Medicine [SIMEU] category III disease).

proposed by Colombi et al. [14] can expectedly provide reliable and repeatable quantitative assessment, TLI can reasonably be of help when software-based evaluation is unavailable, or provide more reproducible results than those of different software-based methods. Of note, differently from Feng et al. [16], who assessed lung involvement using opacification and consolidation, we calculated TLI as the sum of different TFSs, i.e. as one single index combining the amount of affected lung and the type of HRCT features (e.g., GGO, consolidation, crazy-paving pattern, and OP pattern). We believe this can better account for the spectrum of DAD-related findings with which COVID-19 pneumonia can present.

To the best of our knowledge, no previous studies assessed the role for OP pattern in assessing COVID-19 pneumonia. This feature has been recognized as a typical imaging marker in the later course of the disease [11], as well as in severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) [26,27]. OP pattern consists of bilateral, peripheral or peribronchial GGO or consolidation that are triangular or polygonal in shape, along with perilobular pattern, bronchial dilatation, linear and band-like opacities, and signs of fibrosis [18]. Characteristic histopathological presentation includes intra-alveolar organizing fibrous plugs, loose interstitial fibrosis, and chronic inflammatory infiltrates [24,25,28,29]. We found that an OP pattern score > 5, corresponding to about 20% of lung involvement, was predictive of short-time progression to severe disease. In accordance with the pathogenic pathway proposed by Siddiqi et al. [30], we hypothesize that the occurrence of an OP pattern in a patient with mild COVID-19 pneumonia can be an imaging marker of the ongoing host inflammatory response causing progression to severe disease. If confirmed by further studies, our result might be of help in identifying patients at risk of clinical evolution, or that can benefit from therapies targeted to the systemic hyperinflammation phase of the disease [30].

Several study limitations warrant mention. First, the study results have been observed in a small sample size, on a retrospective, single-center basis. Since the ongoing pandemic makes difficult designing and organizing prospective multicenter trials, we believe that our results can be of interest, as testified by the fact they are in line with previous ones in suggesting a potential prognostic role for HRCT [13–16]. Second, having involved one single reader made impossible evaluating the inter-reader agreement. Though results can be reasonably considered robust by having been obtained by a chest-imaging devoted radiologist, we acknowledge that further studies should be performed to assess the reliability of assessing TLI and OP pattern. Finally, we investigated progression to severe disease only, excluding long-term prognosis outcomes. However, the reported median time from clinical onset to ARDS development or ICU admission is 12 days according to Zhou et al. [31]. Thus, it is reasonably unlikely that progression from mild to severe disease occurs later than the 15-day period we selected. Studies on longer periods of time should assess clinical and imaging sequelae from COVID-19 pneumonia.

In conclusion, we observed that short-time onset of severe COVID-19 disease in patients who underwent HRCT was independently associated with the extent of lung involvement (TLI > 15) and OP pattern (score > 5). Severe disease was not associated to comorbidities in our series. Indeed, we observed clinical progression in about 50% of cases with no reported comorbidities, suggesting that HRCT has the potential to identify patients at risk of progression even beyond currently accepted and/or known risk factors. Further studies with prospective design should validate our results on a larger scale.

Declaration of competing interest

None.

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