The role of HRCT in understanding interstitial lung involvement: Systemic Sclerosis versus COVID-19

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Abstract:

Introduction: The coronavirus disease 2019 (COVID-19) pandemic is a global emergency causing frequent lung involvement sharing features with clinical and radiological scenario of interstitial lung disease (ILD) in systemic sclerosis (SSc). In clinical practice, the striking similarities observed at computed tomography (CT) between the diseases make it difficult to distinguish a COVID-19 superinfection from a progression of SSc-ILD.

Objectives: The aim of our study was to identify the main CT features that may help distinguishing SSc-ILD from COVID-19 pneumonia.

Methods: This multicentric study included 22 international readers divided in the radiologist group (RAD) and non-radiologist group (nRAD). A total of 99 patients, 52 with COVID-19 and 47 with SSc-ILD, were included in the study.

Results: the CT parameters most frequently associated with SSc-ILD were: fibrosis inside focal GGO in the upper lobes; fibrosis in the lower lobe GGO; Reticulations in lower lobes, especially if bilateral and symmetrical or associated with signs of fibrosis. The CT parameters most frequently associated with COVID- 19 pneumonia were: CONS in the lower lobes; CONS with peripheral, both central/peripheral or patchy distributions; both anterior and posterior CONS; rounded-shaped GGOs in the lower lobes. After multivariate analysis, the presence of CONS in the lower lobes ($p < 0.0001$) and signs of fibrosis in GGO in the lower lobes ($p < 0.0001$) remained independently associated with COVID-19 pneumonia or SSc-ILD, respectively. On these bases, a predictive score which resulted positively associated with the COVID-19 diagnosis and which showed a 96.1% sensitivity and 83.3% specificity, is proposed.

Conclusions: The CT differential diagnosis between COVID Pneumonia and SSc-ILD is possible but a specific expertise is necessary. If an overlap of both diseases is suspected, the presence of consolidation in the lower lobes may suggest a COVID-19 pneumonia while the presence of fibrosis inside GGO may indicate a SSc-ILD. A score, which may further suggest the diagnosis of COVID-19, is also proposed for use in clinical practice.

Keywords: COVID-19, COVID-19 pneumonia, interstitial lung disease, Systemic Sclerosis, lung CT scan.

Introduction

The COVID-19 pandemic is a world health emergency characterised by an interstitial pneumonia and vascular damage that may lead to a severe and sometimes fatal outcome.[1] In Systemic Sclerosis (SSc), interstitial lung disease (ILD) is one of the main features of the disease. [2-3] During this pandemic, it has clearly emerged that COVID-19 and SSc may share similar radiological features.[4] Recently we raised the issue whether, in SSc, the onset of bilateral and subpleural lung alterations in chest HRCT were due to the rapid onset or progression of SSc-ILD or the overlap of COVID19 pneumonia. [5] In both diseases, the presence of bilateral and subpleural ground glass opacities (GGO), with or without consolidations, are the most frequent radiological alterations.[6] In SSc-ILD, the most common radiological pattern is NSIP with peripheral, bibasilar distribution of GGO and a lower proportion of reticulation, while usual interstitial pneumonia (UIP) (may be seen in up to a third of patients. [7-12] In COVID-19 patients, ILD pneumonia is characterized by bilateral GGO, evolving into consolidations, with a peripheral distribution mostly involving lower lung areas.[13] Even if none of the CT features of COVID-19 seems to be specific, lung CT has a fundamental role in the diagnostic algorithm for COVID-19 pneumonia. Recently, the Radiological Society of North America proposed a radiologic classification of COVID19 pneumonia which focused the attention on the fact that also a typical COVID-19 CT pattern may be found in other ILDs, such as that found in connective tissue diseases.[14] Therefore, the differential diagnosis between the two diseases is a real challenge in practice.

Drawing parallels between SSc-ILD and COVID-19 offers potential insight into both diseases as well as being of practical clinical relevance. On this background, the primary goal of our study was to identify the main CT features that may help distinguishing SSc-ILD from COVID-19 pneumonia. The secondary endpoint was to evaluate the performance, on chest CT, of radiologists and non-radiologists/clinicians in differentiating SSc-ILD from COVID-19 pneumonia, based on their expertise, as well as their concordance.

Materials and Methods

Patients and images selection

Patients enrolled in the study were divided into COVID-19 and SSc-ILD patients. The COVID-19 group included patients with both positive by RT-PCR for COVID-19 and available chest CT imaging, performed within two weeks since the PT-PCR diagnosis. COVID-19 patients were retrospectively recruited from Florence and Treviso hospital from March 1th to May 30th, 2020. For the SSc-ILD group, patients affected by SSc, fulfilling the 2013 ACR/EULAR criteria for SSc [15] and ILD, gender and age matched, were identified from 2015 to 2019. The identified CT

scans were directly downloaded from the hospital Picture Archiving and Communications Systems. Images were anonymized and randomized. Patients were identified with an alpha numeric code, in the respect of the privacy rules. The CT scans were saved as DICOM files and were shared with a Dropbox folder and then visualized with apposite DICOM viewer by reviewers. An access Dropbox code was provided only to the readers.

Methods and Study design

This retrospective, observational, multicentric, international study was approved by the Institutional Ethics Committee of Florence Careggi hospital (protocol number 17104_oss). In the first phase of the study, two chest radiologists with more than 5 years' experience in chest imaging evaluated all the CTs: disagreements were solved by a senior chest radiologist with more than 10 years of experience. These evaluations were considered as the gold standard for analysis of the correctness and definition of the predictive capacity of the various CT features elements. Then, two groups of readers were defined in order to evaluate all CTs, the radiologist group (RAD) and non-radiologist group (nRAD). The RAD included 7 radiologists of whom 4 chest radiologists, with at least more than 5 years of experience. The non-RAD group included 15 specialists, including 6 rheumatologists, 3 immunologists, 2 infectious disease specialists, 4 pulmonologists. Detailed information about reader's medical specialization, location of practice, SSc specific training, years of practice, COVID-19 specific training are shown in supplementary materials 1 (S1) were obtained for each physician participating in the study. Each reader reviewed the images of all patients using Picture Archiving and Communications Systems independently. All readers were blinded to diagnosis, laboratory assay results and demographic information including patient name, hospital of origin of the CTs and date of CT examination. Once obtained the results from the RAD analysis, we compared them with the reference results in order to evaluate which could be the parameters with significantly discriminating capability and subsequently we validated this with a regression model and with multivariate analysis.

After the analysis, our aim was also to obtain an incremental score positively associated with the COVID-19 diagnosis to identify the more likely cases with the highest probability of COVID-19 diagnosis.

Images analysis

Each reader was asked to fill an electronic database giving single (i.e. yes / no) or multiple (i.e. mostly anterior, mostly posterior / no prevalence) answers. No free-standing camp was present in order to make the evaluations homogeneous.

CT analysis was performed at three different levels of detail in order to reach the study's objectives: a first basic level of analysis, common for RAD and nRAD, a second advanced level, specific only for RAD and a third deeper analysis, made by the 4 chest radiologists only.

1° level) CT images were assessed by all readers for presence/absence of lung disease, as well as for side (monolateral/bilateral-asymmetric/bilateral-symmetric), prevalent distribution (anterior/posterior/no prevalence, central/peripheral/no prevalence/patchy). Parenchymal lesions assessment was also performed with the same variables, for upper and lower zones. Considered CT lesions were: consolidations (CONS), ground-glass opacities (GGO), crazy paving (CP), reticulations (RET) and honey combing (HC). As regards the whole disease, the prevalent localisation (upper/lower/no prevalence), involved lobes and the most extended lesion (CONS, GGO, CP, RET or HC) were also assessed. Air bronchogram inside CONS (always present/not always present/never present), were analysed, too. Lastly, pleural effusion, pericardial effusion, lymphadenopathy and oesophagus dilatation were assessed in terms of absence/presence. This level includes the analysis of 56 CT parameters.

2° level) Additionally, RAD were asked to define presence/absence of aspects resembling organizing pneumonia in CONS, as well as signs of fibrosis (defined by architectural distortions or bronchiectasis) in CONS, GGO and RET. They were asked also to identify pleural thickenings in the whole lung fields. The second level includes 14 more CT parameters.

3° level) Finally, the four chest radiologists, were asked to also assess the disease pattern (monofocal/multifocal/diffuse/focal and diffuse or white lung), GGO pattern (focal, diffuse or both) presence/absence of rounded GGO and presence /absence of fibrosis inside focal GGO. Third level includes the analysis of other 8 more CT parameters (Figure 1).

Furthermore, positive scans were categorized by RAD readers with RSNA [14] and CO-RADS (1, 2, 3, 4, 5) classification.[16]

The definition of all CT lesions and anatomical references are available in (S2). The carina was adopted as anatomical landmark for upper and lower zones as well as for anterior and posterior location. We defined "peripheral lung" as two or three rows of secondary pulmonary lobules, forming a layer of three to four centimetres in thickness at the lung periphery, the central lung accounts for the remaining parts, adopting the definition reported by Nishino et al. [17] Patterns were defined as follows:

- Focal pattern: presence of nodule(s) or mass(es), following the definitions of the Fleischner society.[18] However, a lung mass needs to show well defined shape, namely rounded or oval, to be considered as focal lesion.
- Diffuse pattern: presence of alterations that do not meet the definition of neither nodule nor mass, following the definitions of the Fleischner society. However, masses with polygonal shapes were considered as manifestation of diffuse disease.
- (Multi)Focal and diffuse pattern: coexistence of both patterns (Figure 1)

For disease pattern, that consider the whole lungs field, we also adopt the term white lung, when the sum of all alterations covered almost the totality of lung parenchyma (>90%), making impossible to define if the global aspect was due to the coalescence of multifocal lesions, to an extended diffuse disease, or both

Statistical analysis

Each categorical variable was described as absolute and relative frequencies for each category stratified by diagnosis. In order to evaluate the interreader agreement Cohen's Kappa adjusted for multiple readers and its 95% confidence interval were used. A $K \geq 0.4$ was considered discrete, a $K \geq 0.6$ was considered good and a $K \geq 0.8$ was considered excellent. To assess the association between each CT parameter and the diagnosis a simple logistic regression model was used and OR and its 95% confidence interval were reported. According to the presence of association the predictive capability was described by AUROC and its 95% confidence interval. An AUROC ≥ 0.8 was considered good and an AUROC ≥ 0.9 was considered excellent. In order to reach the best predictive performance with the most economical model a multiple logistic regression model with backward selection method for CT parameters with excellent predictive capability and good interreader agreement was used. According to the multiple logistic model results a score weighted using log (OR) of each selected CT parameter was created. Using the AUROC a cut-off was selected, and its sensibility, specificity, positive predictive value and negative predictive value were reported. No external validation of the score cut-off was performed. The significant level was set to 5% for each analysis.

Results

This multicentric study included 22 international readers (NL, EC, MA, FM, SP, VV, FDC, GS, CB, SBR, JB, MH, CD, FL, BR, FDC, GDL, LZ, MS, ST, AC). A total of 99 patients were included in this study: mean age was 62.4 (ds) and 60.3 in COVID -19 and SSc-ILD, respectively; 19 patients were female in the SSc -ILD group and 23 in the COVID-19 group. The COVID-19 group included 52 patients and the SSc-ILD group included 47 patients, gender and age matched. Out of 70 CT parameters proposed to RAD readers for analysis, 39 showed a discrete and 33 a good intrareader agreement: only the latter were considered suitable for subsequent evaluations.

1.Interreader agreement

The full detailed results about interreader agreement are available in S3.

1.1 nRAD interreader agreement

In the nRAD group, the interreader agreement for the evaluation of all the different items is scarce (0.03-0.36). For this reason, it was not considered significant in the subsequent evaluations. (table 1).

1.2.RAD interreader agreement

In the RADs group, a discrete-good agreement for 47% of the items (33/70) was detected.
The RAD group obtained the following agreement (K Cohen): - right lobes lung involvement, 0.60 (0.58-0.63); - central vs peripheral RET in upper lobes, 0.60 (0.56-0.64); - CONS in lower lobes, 0.62 (0.58-0.66); - RET in lower lobes, 0.71 (0.67-0.75); - RET side, 0.66 (0.62-0.69);
- dilated oesophagus, 0.60 (0.56-0.64).

When readers were divided according to the skill concerning chest CT, chest RAD showed a better concordance for the items considered 68.4% (52/76), and the K Cohen between n-chest RAD and chest RAD was significantly different ($p < 0.05$) in 51.4% of items (36/70), and in 35.71% of variables (25/70) p-values was < 0.005 (Table 1). Considering Chest RAD, the agreement is good also for the evaluation of the following parameters: - CONS in upper lobes, 0.66 (0.6-0.72);
- fibrosis inside CONS upper lobes, 0.63 (0.58-0.68); - fibrosis inside focal GGO upper lobes, 0.63 (0.53-0.73); - fibrosis RET upper lobes, 0.65 (0.6-0.7); - distribution CONS lower lobes, 0.62 (0.57-0.67); - distribution (Ant/Post) CONS lower lobes, 0.62 (0.57-0.67); - rounded GGO lower lobes, 0.62 (0.53-0.72); - fibrosis GGO lower lobes, 0.64 (0.59-0.69); - fibrosis in RET lower lobes, 0.74 (0.69-0.8); - pleural effusion, 0.65 (0.6-0.7) (table 1).

2. Diagnostic performance

2.1 nRAD diagnostic performance

The nRAD made a correct diagnosis (COVID-19 or SSc) in 77.5% (IC95%: 75.13-79.74). In particular, a correct diagnosis was achieved in 75.95% COVID-19 patients (499/657) and 78.95% SSc patients (510/646) (Table 2).

2.2 RAD diagnostic performance

The RAD made a correct diagnosis (COVID-19 pneumonia or SSc-ILD) in 83.92% of cases (80.95%-86.59% CI): a correct diagnosis was achieved in 86.61% COVID-19 pneumonia patients and 81.08% SSc subjects (Table 2). Diagnostic performance between nRAD and RAD were statistically different (p = 0.0008) (Table). Moreover, considering RAD subgroups, chest RAD made a correct diagnosis (COVID-19 pneumonia or SSc-ILD) in 86.53% patients (83.18% -89.43% CI) while the non-chest RAD in 72.04% (70.77-83.01 % CI). Correct diagnoses were achieved in 82.18% (82/101) and 88.40% (221/250) cases of COVID-19 pneumonia, respectively, and 72.04% (203/240) and 84.58% (67/93) cases of SSc, respectively.

A significant Difference between chest and non-chest RAD was found (p =0.0034) (Table 2).

3. predictive capability of CT parameters

The full detailed results about diagnostic performance are available in S4.

Good or excellent predictive capability were considered as relevant for differential diagnosis between COVID-19 pneumonia and SSc-ILD. The parameters predictive values were as follows.

Good: - number total of lesions, 0.82 (0.75 - 0.89); - fibrosis inside focal GGO upper lobes, 0.82 (0.75 - 0.90); - CONS lower lobes, 0.88 (0.82 - 0.94); - anterior / posterior lower lobes, 0.88 (0.82 - 0.95); - OP, 0.88 (0.82 - 0.95); - GGO distribution, 0.84 (0.76 - 0.91); - rounded GGO, 0.81 (0.73 - 0.89); - dilated oesophagus, 0.84 (0.76 - 0.91); - COVID RSNA, 0.88 (0.81 - 0.95).To note, the following parameters have a very good predictive capability: - CONS lower lobes distribution, 0.89 (0.82 - 0.95); - air bronchogram inside CONS lower lobes, 0.89 (0.82 - 0.95); - fibrosis, 0.90 (0.84 - 0.96).

Excellent: - side of CONS lower lobes, 0.90 (0.84 - 0.96); - fibrosis inside focal GGO lower lobes, 0.91 (0.85 - 0.97); - fibrosis GGO lower lobes, 0.91 (0.849 - 0.967); - RET lower lobes, 0.91 (0.85 - 0.96); - RET side lower lobes, 0.91 (0.85 - 0.96); - RET distribution lower lobes, 0.91 (0.85 - 0.96); - ant post RET, 0.92 (0.86 - 0.97); - sign of fibrosis RET, 0.92 (0.86 - 0.97).

All detailed predictive parameters are reported in S4.

4. Discriminating CT parameters

The chest RAD group obtained the best interreader concordance. Therefore, possible discriminating CT parameters between COVID-19 pneumonia and SSc-ILD were defined, considering only those that showed good concordance and good or excellent discriminating capability.

Therefore, CT parameters most likely associated with SSc-ILD were:
fibrosis inside focal GGO in the upper lobes; fibrosis in lower lobe GGO; RET in lower lobes, especially if bilateral and symmetrical or associated with signs of fibrosis.
The CT parameters most likely associated with COVID- 19 pneumonia were: CONS in the lower lobes; CONS with peripheral, both central/peripheral or patchy distributions; both anterior and posterior CONS; rounded-shaped GGOs in the lower lobes. (Table 3).

5. Multivariate analysis

A multivariate regression model was developed to select variables independently related to the diagnosis of COVID-19 pneumonia. Considering the 99 patients involved, the 9 parameters identified as good predictors were too many to perform a multivariate analysis. For this reason, only the 5 most significant, easier to verify, and showing good reproducibility and good/excellent predictive ability, were chosen:

1) CONS in lower zone, 2) rounded GGO in lower zone (both predictive for COVID-19 pneumonia); 3) fibrosis in GGO in lower zone, 4) inside focal GGO fibrosis in the upper zone and 5) lower lobes RET (all predictive for SSc-ILD).

After the selection process, the 2nd,3rd, and 5th parameters were excluded and only the 1st and 4rd parameters were considered as independent factors: presence of lower lobes CONS ($p < 0.0001$) and signs of fibrosis in GGO lower lobes ($p < 0.0001$) (Table 4). After the multivariate analysis, we proceeded with the construction of a score which might identify the CT associated with the COVID-19 diagnosis (OR: 2.67, IC95%: 1.76-4.07), as follows:

- CONS: 4 points if presents, 0 if absent
- GGO: 5 points if present without fibrosis, 0 if present with fibrosis, 3 if absent.

This score showed an excellent predictive capability because the area under the ROC curve was 0.97 (0.94-1.00 CI) (Table 4 and Figure 2). The score cut off was 4, a score ≥ 4 being associated with a diagnosis of COVID-19 pneumonia. The score diagnostic performance was 96.1% sensitivity (86.5% -99.5% CI) and 83.3% specificity (69.8% -92.5% CI). The negative predictive value was 95.2% (83.8% -99.4% CI), and the positive predictive value was 86.0% (74.2% -93.7% CI).

Discussion

This study is important because of the potential for systemic sclerosis patients to contract COVID-19 and because the well-recognised radiological features of SSc-ILD can provide valuable insight into diversity and potential classification of the features of COVID-19 on lung CT imaging. Our data show that a differential diagnosis between COVID-19 and SSc-ILD is possible in practice employing the CT images. Specifically, the results showed that the presence of consolidations in the lower lobes is an independent CT diagnostic feature for COVID-19 pneumonia, while fibrosis inside GGO in the lower lobes independently may indicate a SSc-ILD diagnosis (Figure 8A and 8F).

In the last year, COVID-19 pneumonia has represented a new challenge for the radiologist but also for the clinicians that must be able to perform a differential diagnosis. [19-20] Recently, the RSNA identified 3 CT patterns of COVID19 pneumonia: 1) peripheral and bilateral GGO, regardless the coexistence of consolidation; 2) crazy-paving or multifocal rounded GGO, regardless the coexistence of consolidation or crazy-paving; 3) findings of organizing pneumonia. The authors themselves admitted that the typical features of COVID-19 pneumonia could also be secondary to other lung diseases, such as those related to connective tissue diseases.[7,14] In fact, the most common radiological pattern in SSc-ILD is NSIP with peripheral, bibasilar distribution of GGO and a lower proportion of coarse reticulation.[4,8-12] On top of radiological similarities, we should not forget also the clinical similarities, because dyspnoea, fatigue and non-productive cough can be observed in both diseases. Otherwise, fever and rapid onset shortness of breath are peculiar for COVID-19 pneumonia. [21-24] However, the absence of fever should not lower the suspicion for a SARS-CoV-2 infection in symptomatic SSc patients, particularly in those on immunosuppressors, when fever response can be absent. In practice, when the COVID-19 spread out, it was hard for clinicians to provide an accurate diagnosis. In this context, lung CT has a pivotal role in the diagnostic algorithm for patients with suspected COVID-19 pneumonia. For this reason, a predictive score may be useful for radiologists. In our study, the main CT features related to COVID-19 pneumonia and SSc-ILD were evaluated to identify the specific lesions that could help in differential diagnosis. We decided for a multi-step evaluation of CT alterations considering the relative expertise of all the readers and the best interreader agreement found among chest RAD group, in the analyses shared with other readers, highlights the relevance of a specific expertise in chest CT for imaging evaluation. However, we were surprised to note a low agreement among chest RAD in distinguish between prevalent anterior/posterior (or no prevalence) distribution of lung disease and of lower zones GGO, regardless of the clear anatomic landmarks. This may suggest that the presence of more than one alteration may produce a confounding effect in interpreting the

general disease distribution. In fact, all the CT features, considered alone, obtained higher agreement on both lung zones for anterior-posterior distribution, except for lower zones GGO. In SSc-ILD, GGO can be considered either inflammatory or fibrotic, while RET is usually interpreted as a fibrotic alteration.[25] Thus, we believe that GGO could have been occasionally interpreted as fine RET, and *vice versa*: a chest radiologist may be prone to interpret alterations resembling GGO, with signs of fibrosis, as fine RET. This can justify also the low agreement of RET presence in upper zones, where fibrotic fine RET may be less represented and considered as GGO. Following the same *rationale*, CP, defined as GGO superimposed on RET, may suffer for different evaluation in lower zones, where fibrotic alterations can be more pronounced and all considered as RET, instead of CP. On the other hand, our new definition of multifocal and diffuse pattern (Figure 1), as well as the relatively recent delineation of vessel thickening sign as a COVID-19 pneumonia feature, may have partially caused the low agreement for upper zones GGO pattern and vessel thickening: chest radiologist may be less used to evaluating both aspects. On the upper zones, where lung alterations may have more frequently a patchy-irregular distribution, the interpretation between focal and diffuse disease may represent an additional challenge. In fact, GGO may have blurred margins, making hard to define shape and dimensions. This can justify the lower agreement in GGO pattern assessment in upper zones. Moreover, HC showed a low agreement on upper fields. This was expected, since HC and paraseptal emphysema are in differential diagnosis and may be misinterpreted (Figure 3B).[26] In the modern digital age, we should also consider the opportunity of teleconsulting to offer the best expertise to all patients affected by rare diseases such as SSc. It should be noted that the only 2 cases of SSc ILD and COVID-19 pneumonia were misdiagnosed by most of nRAD, RAD and chest RAD readers (Figure 4). Moreover, in some subjects the coexistence of both diseases was wrongly suggested by chest RAD. Hence, regarding the RSNA statement,[14] we can state that the radiologic differential diagnosis is reliable on “pure” lung disease. Nevertheless, the identification of an overlap of both diseases is the most relevant issue from a clinical point of view. In fact, if there are no clinical doubts between the presence of COVID-19 Pneumonia or SSc-ILD, the relevance of CT evaluation in differential diagnosis is less significant. On the contrary, the real radiologic challenge is in identifying the lung disease in COVID infected SSc patients. This is confirmed by our results: the only aspects that may help in identifying COVID-19 pneumonia is consolidation (Figure 5), while fibrosis inside GGO is a sign of SSc-ILD (Figure 6A). However, consolidations can be absent, especially during the early phase of disease, when a clinical decision may be relevant and GGO is the only main feature and a prompt therapy is mandatory. In fact, consolidations were absent in the only subject with coexistence of both disease and few readers made the right diagnosis. Despite the few available data in literature,

this is in line with some case reports. Cheng et al [27] observed a COVID-19 pneumonia superimposed on SSc-ILD, with GGO as main manifestations. The authors stated that GGO could have been due to COVID-19 pneumonia on ILD, as well an increase in ILD. This suggest that a specific care should be used when only GGO is present. In fact, though associated signs of fibrosis may be suggestive for SSc-ILD alone, GGO without fibrosis may potentially represent both disease. On the other hand, Mariano et al [28] made a diagnosis of COVID-19 pneumonia on SSc-ILD thanks to the appearance of a consolidation superimposed on a UIP pattern in a SSc patient, in the right lower lobe. Evaluation of upper zones fibrosis in focal GGO¸lower zones RET did not result as independent predictor of SSc-ILD, as well as rounded lower zones GGO for COVID-19 pneumonia (Figure 7). In both diseases, the absence of fibrosis in focal alteration as well as lower rounded GGO may be encountered. Likely, fibrosis inside focal GGO in the upper lobes could be considered in case of suspected superimposition of COVID-19 pneumonia on SSc-ILD (Figure 8), because fibrotic alterations are not present during the acute phase of COVID-19 pneumonia and could be referred only to SSc-ILD (Figure 6B), though we cannot exclude that an acute focal manifestation of COVID-19 pneumonia may appear over focal signs of fibrosis. Furthermore, RET are less frequent in COVID-19 pneumonia (Figure 8). On the other hand, on an ILD background, the appearance of rounded GGO may raise the doubt of a COVID-19 overlapping on SSc-ILD (Figure 7).

The two principal items (presence of CONS and presence of GGO without fibrosis in the lower lobes) were included in the construction of a predictive score positively associated with the COVID-19 diagnosis (Figure 8). We may identify 3 different risk class for COVID-19 pneumonia: - *high risk* for COVID-19 pneumonia (5-9 points); - *probable overlap* COVID-19 pneumonia in SSc-ILD (4 points); and - *low risk* for COVID-19 pneumonia (0-3 points). The score showed an excellent diagnostic performance with high sensibility and specificity (Figure 2) and could be useful for the radiologist in practice. However, we recommend considering that GGO without fibrosis may be expression of non-fibrotic NSIP. We strongly suggest to consider the presence of both consolidations and non-fibrotic GGO as signs of COVID-19 pneumonia alone only in presence of other suggestive signs (i.e. rounded shape) and absence of typical SSc-ILD abnormalities (i.e. RET).

This study was the first to analyse the CTs parameters that may identify the radiological features for a differential diagnosis between SSc-ILD and COVID-19 pneumonia. The strength of this study is the number of patients that were examined, and the high number readers and considered variables. However, limitations are the low number of COVID-19 superimposed on SSc-ILD, the presence of

COVID-19 CT images at different stages of the disease as well as SSc-ILD with diverse disease duration and different ILD stage.

In conclusion, the CT differential diagnosis between COVID Pneumonia and SSc-ILD is today possible. A specific expertise is however recommended. If an overlap of both diseases is suspected, the differential diagnosis may be challenging, especially in the early phase of COVID-19 pneumonia. In these cases, the presence of consolidation in the lower lobes and the presence of fibrosis inside GGO may help in differentiating the diseases and drive the physician toward an early diagnosis either of SSc-ILD progression or overlapping of COVID-19 in SSc-ILD.

Our results and considerations should be confirmed on a much larger cohort of patients with both diseases. Moreover, based on our results, a future research agenda should include ILD secondary to other autoimmune diseases such as inflammatory myositis.

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Table 1. Inter-reader agreement

CT PARAMETER	nRAD COHEN'S K (LCL95%-UCL95%)	RAD COHEN'S K (LCL95%-UCL95%)	nRAD VS RAD p-VALUE	Chest RAD COHEN'S K (LCL95%-UCL95%)	n-chest-RAD COHEN'S K (LCL95%-UCL95%)	n-chest-RAD VS chest-RAD p-VALUE
WHOLE LUNG PARENCHYMA						
Right lung involvement	0.15(0.14-0.16)	0.60(0.58-0.63)**	<.0001	0.63(0.6-0.67)**	0.64(0.53-0.75)**	0.9221
UPPER ZONE						
CONSOLIDATION						
Presence	0.25(0.24-0.27)	0.60(0.56-0.64)*	<.0001	0.66(0.6-0.72)**	0.39(0.2-0.58)	0.0081
Fibrosis	-	0.35(0.32-0.39)	.	0.63(0.58-0.68)**	0.35(0.21-0.48)	0.0001
GGO						
Fibrosis in focal lesions	-	0.63(0.53-0.73) **	.	0.63(0.53-0.73)**		
RETICULATIONS						
Central/Peripheral	0.12(0.11-0.13)	0.60(0.56-0.64)**	<.0001	0.61(0.55-0.66)**	0.59(0.41-0.78)*	0.8741
Fibrosis	-	0.46(0.43-0.49)*	.	0.65(0.6-0.7)**	0.45(0.31-0.58)*	0.0065
LOWER ZONE						
CONSOLIDATION						
Presence	0.28(0.27-0.3)	0.62(0.58-0.66)**	<.0001	0.71(0.65-0.77)**	0.46(0.27-0.64)*	0.0124
Central/Peripheral	0.15(0.14-0.16)	0.55(0.52-0.59)*	<.0001	0.62(0.57-0.67)**	0.46(0.28-0.63)*	0.0755
Anterior/Posterior	0.17(0.16-0.18)	0.56(0.52-0.59)*	<.0001	0.62(0.57-0.67)**	0.47(0.31-0.63)*	0.0968
RETICULATIONS						
Presence	0.25(0.23-0.26)	0.71(0.67-0.75) **	<.0001	0.75(0.69-0.81)**	0.58(0.39-0.76)*	0.0714
Bilateral/Simmetrical	0.16(0.15-0.17)	0.66(0.62-0.69)**	<.0001	0.70(0.65-0.76)**	0.52(0.37-0.67)*	0.0208
Fibrosis	-	0.51(0.48-0.54)*	.	0.74(0.69-0.8)**	0.39(0.25-0.53)	<.0001
PLEURAL AND MEDIASTINAL INVOLVMENT						

Table 1. Inter-reader agreement

CT PARAMETER	**nRAD COHEN'S K** (LCL95%-UCL95%)	**RAD COHEN'S K** (LCL95%-UCL95%)	**nRAD VS RAD** p-VALUE	**Chest RAD COHEN'S K** (LCL95%-UCL95%)	**n-chest-RAD COHEN'S K** (LCL95%-UCL95%)	**n-chest-RAD VS chest-RAD** p-VALUE
Pleural effusion	0.19(0.18-0.2)	0.56(0.53-0.59)*	<.0001	0.65(0.6-0.7)**	0.44(0.3-0.58)*	0.0060
Dilated oesophagus	0.27(0.25-0.28)	0.60(0.56-0.64)**	<.0001	0.59(0.53-0.65)*	0.55(0.36-0.74)*	0.6974

Legend: Total detailed results of inter-reader agreement.

*Discrete inter-readers agreement; ** Good inter-readers agreement

nRAD: non radiologist clinicians; RAD: radiologists; Chest-RAD: chest radiologists, with at least more than 5 years of experience; n-chest-RAD: radiologists without chest experience.

Table 2. Readers Diagnostic performance

READERS	CORRECT DIAGNOSIS			RAD vs nRAD	Chest-RAD vs non -chest RAD
	COVID-19	SSc-ILD	TOT (CI)		
nRAD	75.95% (499/657)	78.95% (510/646)	77.5% (75.13%- 79.74%)	p=0.0008	
RAD	86.61% (304/351)	81.06% (270/333)	83.92% (80.95%-86.59%)		
Chest-RAD	88.40% (221/250)	84.58% (203/240)	86.53% (83.18%-89.43%)		p=0.0034
Non-Chest-RAD	82.18% (83/101)	72.04% (67/93)	77.32% (70.77%-83.01%)		

Legend

nRAD: non radiologist clinicians; RAD: radiologists; Chest-RAD: chest radiologists, with at least more than 5 years of experience in chest imaging ¸ Non-Chest-RAD: radiologists without experience in chest imaging.

Table 3. Discriminating CT parameters.

CT PARAMETER	LEVEL	COVID-19	SSC-ILD	OR (95%CL)	p-VALUE	AURC (95%CL)	PREDICTIVE CAPABILITY	
FOCAL GGO with FIBROSIS UPPER ZONE	Absence	14(27.45%)	34(70.83%)	Reference	.			
	No	37(72.55%)	6(12.5%)	0.07 (0.03 - 0.21)	<.0001*	0.82 (0.75 - 0.90)	Good	
	Yes	0(0%)	8(16.67%)	7.15 (0.33 - 156.76)	0.2120			
GGO with FIBROSIS LOWER ZONES	Absence	5(9.8%)	4(8.33%)	Reference	.			
	No	42(82.35%)	4(8.33%)	0.129 (0.025 - 0.667)	0.0145	0.908 (0.849 - 0.967)	Exellent	
	Yes	4(7.84%)	40(83.33%)	11 (2.131 - 56.794)	0.0042			
RETICULATIONS LOWER ZONE	No	49(96.08%)	7(14.58%)	Reference	.			**Associated with SSc-ILD**
	Yes	2(3.92%)	41(85.42%)	109.59 (24.31 - 494.08)	<.0001*	0.91 (0.85 - 0.96)	Exellent	
RETICULATIONS SIDE LOWER ZONE	Absence	49(96.08%)	7(14.58%)	Reference	.			
	Bilateral, asymmetric	0(0%)	2(4.17%)	33.02 (0.74 - 1474.71)	0.0712	0.91 (0.85 - 0.96)	Exellent	
	Bilateral, symmetric	2(3.92%)	39(81.25%)	104.28 (23.08 - 471.10)	<.0001*			
RET with FIBROSIS LOWER ZONE	Absence	49(96.08%)	7(14.58%)	Reference	.			
	No	1(1.96%)	2(4.17%)	11 (0.94 - 129.11)	0.0563	0.92 (0.86 - 0.97)	Exellent	
	Yes	1(1.96%)	39(81.25%)	173.8 (28.06 - 1076.39)	<.0001*			
CONSOLIDATION LOWER ZONE	No	8(15.69%)	44(91.67%)	Reference	.			
	Yes	43(84.31%)	4(8.33%)	0.02 (0.00 - 0.07)	<.0001*	0.88 (0.82 - 0.94)	Good	
CONSOLIDATION SIDE LOWER ZONE	Absence	8(15.69%)	44(91.67%)	Reference	.			
	Unilateral	10(19.61%)	3(6.25%)	0.06 (0.01 - 0.27)	0.0002*	0.90 (0.84 - 0.96)	Exellent	
	Bilateral, asymmetric	16(31.37%)	0(0%)	0.01 (0 - 0.11)	0.0007*			
	Bilateral, simmetric	17(33.33%)	1(2.08%)	0.02(0.00 - 0.11)	<.0001*			
CONSOLIDATION C/P DISTRIBUTION LOWER ZONE	Absence	8(15.69%)	44(91.67%)	Reference	.			**Associated with COVID-19 pneumonia**
	Central	1(1.96%)	0(0%)	0.06 (0.00 - 6.24)	0.2402	0.89 (0.82 - 0.95)	Good	
	Peripherical	32(62.75%)	3(6.25%)	0.02 (0.00 - 0.08)	<.0001*			

Table 3. Discriminating CT parameters.

	No prevalence	5(9.8%)	0(0%)	0.02 (0.00 - 0.45)	0.0147*		
	Patchy	5(9.8%)	1(2.08%)	0.05 (0.01 - 0.42)	0.0055*		
CONSOLIDATION A/P DISTRIBUTION LOWER ZONE	Absence	8(15.69%)	44(91.67%)	Reference	.		
	mostly anterior	4(7.84%)	0(0%)	0.02 (0.00 - 0.60)	0.0242*	0.88 (0.82 - 0.95)	Good
	mostly posterior	33(64.71%)	3(6.25%)	0.02 (0.00 - 0.08)	<.0001*		
	no predominance	6(11.76%)	1(2.08%)	0.04 (0.01 - 0.34)	0.0027*		
GGO ROUNDED LOWER ZONE	Absence	5(9.8%)	4(8.33%)	3.32 (0.74 - 14.81)	0.1165	0.81 (0.73 - 0.89)	Good
	RoundedRounded	38(74.51%)	9(18.75%)	Reference	.		
	Non rounded	8(15.69%)	35(72.92%)	16.93 (5.96 - 48.04)	<.0001*		

Legend:

Detailed results of all CT parameters analysed.

*P<0.05

C/P: Central /Posterior ; A/P: Anterior/Posterior; GGO: Ground glass opacities; Absence: absence of the alteration for which the sub analysis should have been performed

Table 4. Multivariate analysis with backward selection method results

CT PARAMETER	LEVEL	OR (95%CL)	p-VALUE	AURC (95%CL)
CONSOLIDATION LOWER ZONE	No	reference		0.97 (0.94-1.00 CI)
	Yes	69.41 (7.81-616.801)	0.0001	
GGO with FIBROSIS LOWER ZONE	Absence	21.65 (1.51-310.0)	0.0236	
	No	119 .61 (12.13-999.99)	<0.0001	
	Yes	reference		
FOCAL GGO with FIBROSIS UPPER ZONE		excluded	0.99	
RETICULATIONS LOWER ZONE		excluded	0.89	
ROUNDED GGO LOWER ZONE		excluded	0.97	

Legend

GGO: Ground glass opacities; Absence: Absence of the alterations for which the sub analysis should have been performed