Computed tomography of chest and Transthoracic ultrasound for Assessment of Covid -19 Pneumonia

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Abstract

The cell receptor of COVID-19 is angiotensin-converting enzyme-2 (ACV2). COVID-19 starts as interstitial pneumonitis and then affects lung parenchyma. A wide variety of CT findings in COVID-19 have been reported in the different studies, and the CT findings differ according to the stage of the disease and disease severity and associated co-morbidities. In patients with COVID-19 pneumonia, the most common findings in chest CT is GGO, which is usually described as patchy, peripheral, bilateral, and subpleural. Consolidation is defined as an area of increased attenuation which obscures the bronchial and vascular markings and caused by filling the alveolar spaces by fluid, exudates, transudate, blood, or neoplastic cells. Consolidation in COVID-19 pneumonia tends to be patchy or segmental, irregular or nodular, and mainly subpleural and peripheral with reported incidence 2–64% depending on the duration of the illness. Consolidations usually appear after 10–12 days of the onset of symptoms, after the appearance of GGO. Bedside lung ultrasound (LUS) is a widely available diagnostic tool, complementary to physical examination, that can provide a large amount of diagnostic information in several respiratory diseases and settings . In the hands of experienced clinicians, LUS diagnostic accuracy for bacterial pneumonia is similar to chest CT . The advantages of LUS are more obvious in older patients with multimorbidity and restricted mobility, for whom high-quality CXR and CT scans are difficult to obtain. The sonographic signs of interest in COVID-19 include all those which are well known in ARDS. These are the B-lines in various forms, both separate and coalescent, irregular or fragmented aspect of the pleural line, and small peripheral consolidations. Explanations and demonstrations of all these signs can be easily found in the vast existing literature on the topic .However, in the diagnosis of COVID-19 some specificities need to be considered.

Keywords: *Computed tomography , Transthoracic ultrasound , Covid -19 Pneumonia*

1. Introduction

In December 2019, pneumonia associated with the 2019 novel coronavirus (2019-nCoV) was reported in Wuhan, China. Between 4% and 11% of patients with 2019-ncov pneumonia rapidly develop acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications within a short period of time, and eventually deteriorate and die from multiple organ failure [1].

Computed tomography (CT) examinations, which are reproducible and objective, will be used clinically to determine the severity of pneumonia and will constitute an effective tool for defining accurate management. Several studies have reported a relationship between high-resolution CT and the prognosis of pulmonary fibrosis, and have found that radiographic fibrosis scores based on HRCT scan reticulation and honeycomb degree predict mortality. However, the relationship

between CT and the prognosis of 2019-nCoV pneumonia remains unknown [2].

While 2019-nCoV nucleic acid swab tests had up to 41 percent false positives, and lung CT abnormalities were detected in 74% of 2019-nCoV cases [6]. In this study, we retrospectively analyzed patients with suspected 2019-nCoV pneumonia to assess whether imaging CT scores were useful predictors of mortality. This is an observational descriptive study of patients with suspected 2019-nCoV pneumonia, including data of 39 patients from the ICU of Wuhan third hospital from January 31 to February 16, 2020. It describes the CT of 2019-nCoV pneumonia and has scored and quantified the imaging findings [3].

The nucleic acid positive rate (41%) of the suspected 2019-ncov was similar to that of previous studies, but patients with a single negative nucleic acid test could not be excluded from new coronavirus infection. In order to reduce nosocomial cross infection, it is urgently needed to detect multiple pathogens once in a short time in clinic, so as to quickly distinguish cold flu and 2019-nCoV population. Most 2019-nCoV pneumonitis is mild/common viral pneumonia [4].

Light, very light, or no clinical symptoms, but CT can have mild abnormalities, beginning mainly characterized by bilateral subpleural small piece of ground glass opaque light and shadow, ground glass opacity (GGO), also can be in unilateral lung field. With symptoms and signs of normal cases CT performance similar to light, but quickly to GGO lung central extension, later with a consolidation of the lung (small flake and chamber nodules), with time delay and pulmonary interstitial changes, such as septal thickening and thickening of alveolar interval (pavement), lobular core, and a large increase in the number of bronchial pulmonary (lung) beam fuzzy, pleural thickening. The clinical symptoms of severe viral pneumonia progressed rapidly [5].

CT showed that GGO gradually evolved from flaky lung consolidation with a wide range of lesions, accompanied by bronchial gas phase, increased blurring of lung texture, and a small amount of pleural effusion. Pulmonary cavity formation is rare and mediastinal lymph node enlargement is rare. A very small number of people may develop into critically ill cases with diffuse lesions in both lungs and even uniform extensive consolidation ("white lung"). A combination of multiple infections can also be more severe [5]. CT images showed GGO distribution in the marginal areas of the lung in 14 cases (low CT score group), 25 cases were enlarged to the central area of the lung (high CT score), and 16 cases were complicated with consolidation. As the follow-up time was short and no significant fibrosis was observed. The early stage was GGO, and pulmonary consolidation began at a median of 5 days [5].

We found that most of the patients in onset about a week or so weak CT to display the subpleural GGO, even some patients in the earlier CT or negative, weak without interstitial thickening of GGO instructions were fresh, but the fact is that this kind of GGO appear relatively long time after the symptomatic, later to become severe in hospital. Combined with mild cases and common cases are many, although the pharyngeal swab positive nucleic acid, I wonder if, like the common cold, some patients only infected with the upper respiratory tract self-limiting, only a few developed into pulmonary infection, even serious, dangerous patients. Beginning of upper respiratory tract infection, a few progress, a large number of virus particles with breathing into pulmonary gas exchange area, namely, peripheral pulmonary and alveolar mucosa inflammation after adsorption mainly in the alveolar walls, which produce GGO, viral replication after more and stronger immune mechanism against epidemic diseases, inflammation, not just the liquid leakage, fibrous hyperplasia of seepage and gradually form paving stone), the consolidation of the lung, the late pulmonary fibrosis [7].

In partial patient lung pathological changes are very apparent, but upper respiratory tract infection has absorbed, dry cough does not have phlegm, pharynx swab nucleic acid tests can be negative,

false negative at this time. CT score through visual measuring each layer of the proportion of CT image of pathological changes, the score method has been used to evaluate prognosis of idiopathic pulmonary fibrosis, there is no report using CT score to assess 2019 - nCoV pneumonia prognosis, some studies have found that a similar area of grading method to explore its relationship with viral pneumonia of viral load. Patients generally onset the disease 7 to 10 days ago, there was no significant difference in comorbidity and laboratory results, except for PaO2 and Lac in blood gas analysis, there was no significant difference between the high CT score and low CT score groups at the initial level. Our study showed a higher 7-day mortality in high CT score group, indicating that the disease progressed more seriously in the later stages of a high CT score. At present, many cases of 2019-nCoV have occult onset, with one or even multiple negative nucleic acid tests and no clinical symptoms [8].

However, CT images have been positive. These patients may cause familial aggregation infection, which further spreads the epidemic. Therefore, it is necessary to suspect the diagnosis of 2019-nCoV in pneumonia patients with obvious abnormalities in CT. Of course, there might be normal radiological manifestations in some infected patients, and the accuracy rate of diagnosing neocoronavirus infection by CT alone was 76.4%. We also need to combine clinical manifestations with laboratory results. A correlation between lymphoid counts and CT changes, absolute value of lymphocytes reduced progressively, CT performance also deteriorated [9]. Most studies found a decrease in lymphoid absolute count of 2019-nCoV patients. Low lymphoid absolute count may indicate the patient more severe and may get higher mortality. In our study, one dead patient lymphoid absolute count even was close to zero [9].

CT features of novel coronavirus pneumonia (COVID-19):

The cell receptor of COVID-19 is angiotensin-converting enzyme-2 (ACV2). COVID-19 starts as interstitial pneumonitis and then affects lung parenchyma. A wide variety of CT findings in COVID-19 have been reported in the different studies, and the CT findings differ according to the stage of the disease and disease severity and associated co-morbidities [10].

Normal CT chest in patients with COVID-19 pneumonia:

CT plays a very important role in the diagnosis and management of COVID-19 pneumonia. However, multiple studies reported normal CT chest in patients with COVID-19 pneumonia [10, 11, 12].

Reported that 20 out of 36 patients (56%) had normal CT chest within 2 days from onset of symptoms [13].

Reported 21 of 601 (3%) patients with positive RT-PCR had normal CT chest [14].

Reported three of 21 patients with positive coronavirus and normal CT chest, with one of these patients progressed 3 days later and developed a solitary rounded ground-glass lesion. They thought that chest CT lacks complete sensitivity and cannot alone exclude the disease, particularly early in the infection. Also, this may be related to the incubation period of the disease or there may be a prodromal phase where viral infection symptoms appear before the appearance of imaging manifestations [10]. The Centers for Disease Control and Prevention has noted that symptoms of COVID-19 pneumonia may appear in as few as 2 days or as long as 2 weeks after exposure, which is similar to the incubation period of MERS [10].

Ground glass opacity:

Ground glass opacity (GGO) is the non-specific hazy opacification of the lung in the X-ray or computed tomography with no obliteration of bronchial or vascular markings. The presumed pathology includes partial filling of the lung alveoli by fluid, interstitial thickening, or partial

collapse of lung alveoli [15].

In patients with COVID-19 pneumonia, the most common findings in chest CT is GGO, which is usually described as patchy, peripheral, bilateral, and subpleural [16].

In a meta-analysis of 13 studies found that GGO was the most common manifestation, reported in 83.31% of cases [17]. The meta-analysis involved 13 studies; GGO was the main finding in 11 of them. The two studies which did not report GGO were not radiological studies but were clinical studies, and they only reported bilateral abnormalities in the CT chest, and they should be excluded in our opinion [17].

In another meta-analysis by Zhu et al. involving 32 articles and 4121 patients, they reported ground glass opacification as the most common finding (68.1%) [18]. The relative low prevalence of GGO in this meta-analysis is because of the marked heterogeneity in the articles concerned mostly about clinical or laboratory findings. The ground glass opacification is the main CT chest findings in all articles published in radiology journal or other imaging journals [18].

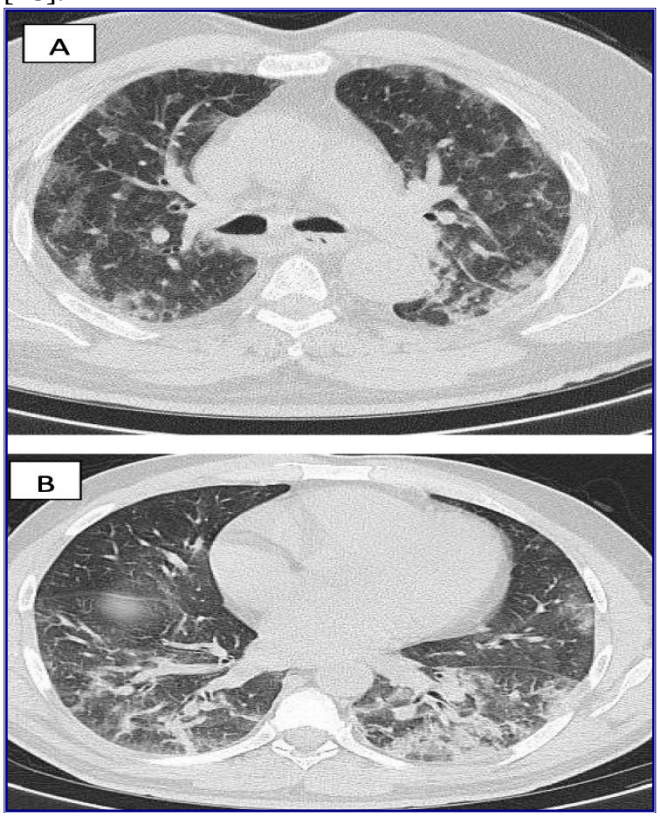

Fig. (1,2): Two different cases with bilateral multiple patches of ground glass infiltration and subsegmental consolidation, lesions mainly peripheral and posterior [20].

For example, Guan et al. in a study including 53 patients with COVID-19 reported GGO in all patients (100%) [19]. Ng et al. reported 86% incidence of GGO, and the rest of the patients had GGO with consolidation [19]. The expert recommendations from the Chinese Medical Association Radiology Branch classified the CT manifestations according to the appearance of GGO into four stages; the early stage is characterized by dilatation of capillaries and engorgement of vessels, mild fluid exudates in the alveoli, and interstitial edema, resulting in single or multiple patchy ground glass opacities. The ground glass opacities are mostly peripheral and subpleural [20]. The second stage is the advanced stage in which the lesions increase in density and size, forming a mixed pattern of GGO and consolidation with or without air bronchogram. The cause

of this appearance is the exudation into the alveolar space and the lung interstitium [20]. The third severe stage in which there is fibrous exudates into the alveoli reflected in the chest CT as wide areas of consolidation with air bronchogram, with the non-consolidated area showing patchy ground glass infiltration [20]. In the 4th dissipation stage, the consolidation and ground glass infiltration gradually resolves, with small areas of residual fibrosis [20]. In some cases, the diffuse ground glass infiltration may give the lungs a white lung appearance [20].

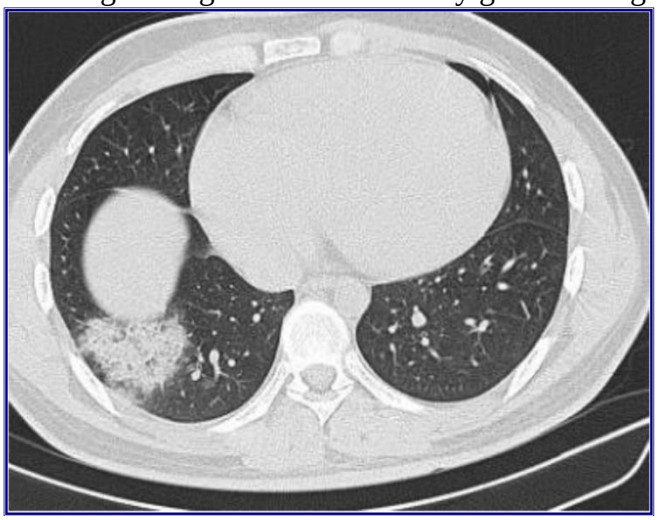

Fig. (3): Patient about 24 days after onset of symptoms. A well-defined area of consolidation/fibrosis seen in the right lower lobe, no other abnormality was noted in both lungs [20].

Consolidation and air bronchogram:

Consolidation is defined as an area of increased attenuation which obscures the bronchial and vascular markings and caused by filling the alveolar spaces by fluid, exudates, transudate, blood, or neoplastic cells. Consolidation in COVID-19 pneumonia tends to be patchy or segmental, irregular or nodular, and mainly subpleural and peripheral with reported incidence 2–64% depending on the duration of the illness. Consolidations usually appear after 10–12 days of the onset of symptoms, after the appearance of GGO [21]. Yuan et al. reported high mortality in patients with consolidation [21]. Li et al. in a series including 83 patients also reported consolidation in patients with severe or advanced disease [21]. In a study by Song et al. the incidence of consolidation was significantly higher in older patients (> 50 years) than younger patients and in patients with symptoms more than 4 days [21].

Air bronchogram, which is defined as air-filled bronchi in an area with high density, has variable incidence in different reports ranging from 28 to 80% of patients [20]. Air bronchogram is usually a sign of advanced disease, usually seen after the second week from the onset of symptoms. Air bronchogram can be seen in both GGO and consolidation [20].

Reticulations:

Reticulations which appear as lineal interlobular or intralobular density are a relatively late finding in patients with COVID-19, and its reported incidence is 48.5–59% [22].

The appearance of reticulations is usually associated with clinical progression of the disease. The cause of reticulations is probably caused by lymphocyte infiltration of the interstitial tissues with interlobular and septal thickening. In some studies, the reticular pattern was a common pattern, considered the third common sign after GGO and consolidation [22].

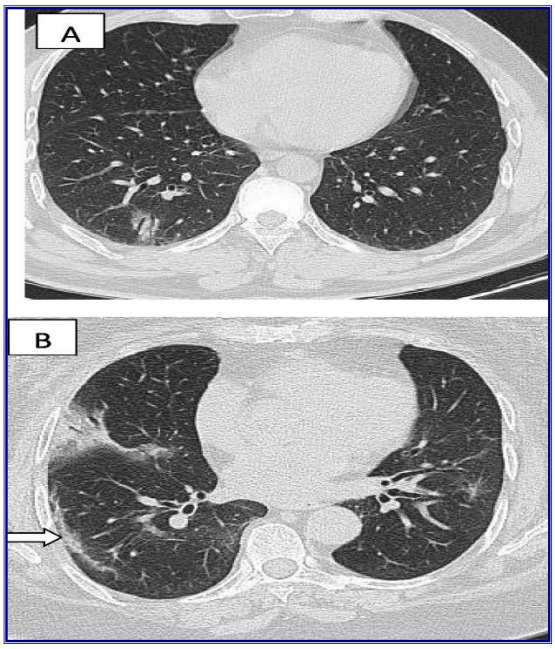

Fig. (4): a Ground glass infiltration with air bronchogram. **b** Small area of consolidation with air bronchogram. Note the presence of sub-pleural line (white arrow) [20].

Crazy paving sign:

The crazy paving signs represent thickened interlobular septa superimposed on GGO. This sign represents alveolar edema and interstitial inflammatory reaction.

In the meta-analysis of Bao et al, the crazy paving sign had an incidence of 14.81% (95% CI 6.61–25.99%) [16]. On the other hand, some articles reported higher incidence like the study performed by Guan et al., who reported 89.4% incidence of crazy paving sign, and they thought this sign was due to hyperplasia of interlobular and intralobular interstitial [19]. Interestingly, though the crazy paving sign is a sign of progressive disease and its appearance may indicate that the disease is entering the peak stage, yet it is the first CT sign to resolve in the absorptive stage while the consolidation, and GGO may persist for up to 26 days [19].

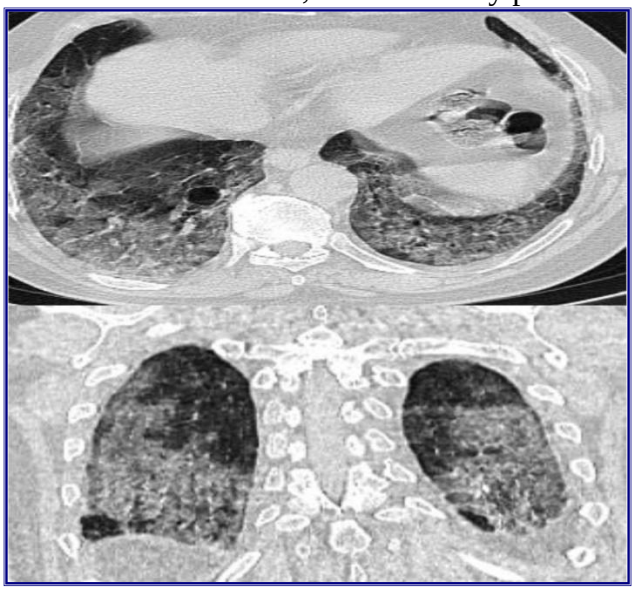

Fig. (5): Axial and coronal CT images of patient with COVID-19, 10 days after the onset of

symptoms, showing extensive ground glass infiltration with crazy paving infiltration. The appearance of crazy paving appearance indicates a progressive disease[21].

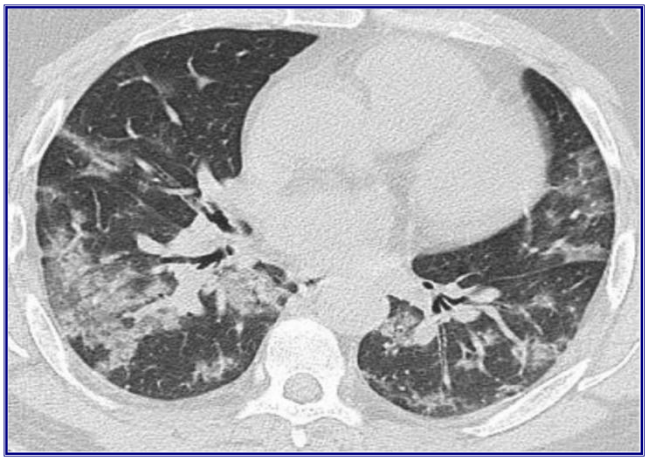

Fig. (6): Patient with advanced COVID-19 and crazy paving appearance [24].

Halo sign:

Halo sign is defined as ground glass opacity surrounding a nodule or mass. Previously, this sign is considered a manifestation of fungus infection, viral pneumonia, or hypervascular metastasis [23].

In a recent study by Bai et al., they reported a halo sign in 26% of patients with COVID-19 pneumonia and 21% of cases with other viral pneumonia, and they found it a non-helpful sign in differentiating COVID-19 pneumonia from other viral pneumonia [24].

Inverted (reversed) halo sign or atoll sign:

The reversed halo sign represents an area of GGO surrounded by a near complete ring of consolidation [25].

The proposed mechanisms in COVID-19 pneumonia is either disease progression with development of consolidation around an area of GGO or a consolidated area with resolution of the central area leaving an area of decreased density [26, 27].

The reversed halo sign is usually seen in relatively long-time onset of symptoms, and the presence of this sign suggests that organizing pneumonia may be one of the mechanisms of lung injury in COVID-19 pneumonia [28, 29].

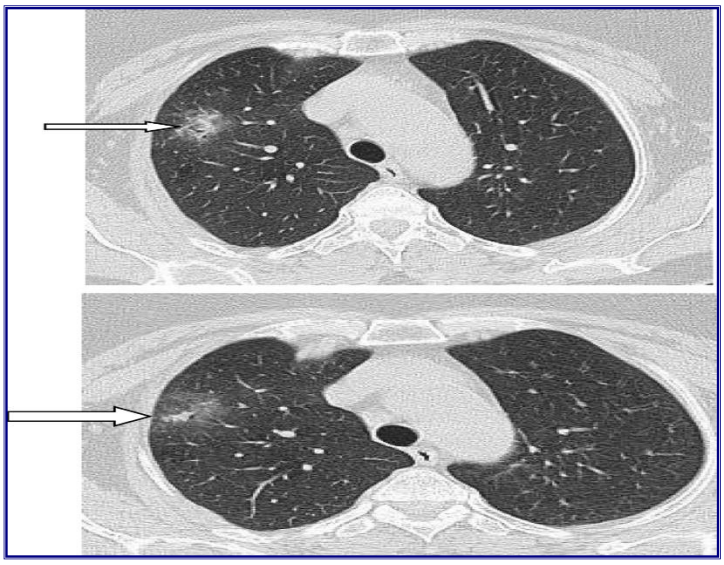

Fig. (7): Another patient with patches of ground glass infiltration and halo sign [26].

Subpleural transparent line:

Subpleural transparent line is defined as a thin and transparent line between the areas GGO or consolidation and the visceral pleura, and it was reported in 53.2% in one study [30].

Another study by Zhou et al. involving 100 patients reported the incidence of a transparent line to be 45.3% in the early stage, 47.7% in the advanced stage, and 6.5% in the absorption stage, and they suggested that the presence of this sign indicates an advanced stage [31].

Pleural changes:

Pleural thickening and pleural effusion are relatively less common findings in patients with COVID-19. The reported incidence of pleural thickening is about 27–32% [18, 10].

The incidence of pleural effusion is less common (2–5%). There is agreement between studies that the presence of pleural effusion carries a poor prognosis and reflects high viral load and high virulence [32, 33].

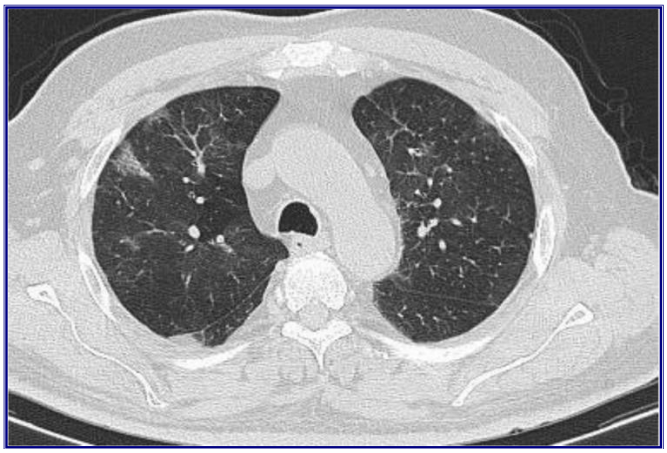

Fig. (8): Pleural thickening in the right side in patient with COVID-19 pneumonia. Virulence [27].

Fibrosis:

Lung fibrosis and fibrous strips have been reported in patients with COVID-19, with a reported incidence of about 17% [34].
Some authors consider it a sign of regression of disease severity and carries a good prognosis [34].
But other authors consider it a sign of severe disease [35] or a warning sign of the development of interstitial fibrosis [36].
Anatomical lesion distribution:
Bao et al. in a meta-analysis involved 13 studies; the disease was bilateral in 81.8% of patients [16]. The lesions are more common in the peripheral areas (76.95%). Few lesions were located in the central (peribronchovascular) area. The lower lobes are more commonly involved; the right lower lobe and left lower lobe were the most commonly involved, 87.21% and 81.41% respectively, and both lower lobes in 65.22%. The upper lobes were involved in 65.22% and 69.43% for the right and left sides respectively. There are about 39.54% of patients with all lobes affected and 20.51% patients with four lobes affected [16].
In general, the disease most commonly affects both lungs, the lower zones more commonly affected and the right middle lobe is the least involved one. Also, patchy multifocal distribution is more frequent compared with diffuse disease, but unilateral or unifocal affection can occur. The peribronchial distribution is rare and considered atypical [20, 37].

COVID-19 Reporting and Data System (CO-RADS) classification:
Based on the CT findings, the level of suspicion of COVID-19 infection is graded from very low or CO-RADS 1 up to very high or CO-RADS 5 and the severity and stage of the disease is determined with remarks on comorbidity and a differential diagnosis.
Regular updates will be provided. CO-RADS-1 has a high negative predictive value in patients with complaints for four or more days.

CO-RADS* **Level of suspicion COVID-19 infection**		
		CT findings
CO-RADS 1	No	normal or non-infectious abnormalities
CO-RADS 2	Low	abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indeterminate	unclear whether COVID-19 is present
CO-RADS 4	High	abnormalities suspicious for COVID-19
CO-RADS 5	Very high	typical COVID-19
CO-RADS 6	PCR +	

CO-RADS 5 has a very high positive predictive value given the high a priori-chance in this epidemic.
The interobserver variation of CO-RADS 2-4 is still high and has a poor negative and predictive value.
The interpretation of the CT findings has to be combined with the clinical symptoms and the

duration of the symptoms as a CT can be negative in the [38].

Chest CT-Severity Score Assessment (CT-SS):
A chest CT severity score was calculated by assessing the degree of lobe involvement for each of the five lung lobes separately as follows:
0% (no involvement),
1%–25% (minimal involvement)
26%–50% (mild involvement)
51%–75% (moderate involvement)
76%–100% (severe involvement).
Corresponding scores for each degree of lobe involvement were classified from lobe score 0 (no involvement) to lobe score 4 (severe involvement). The overall lung "total severity score" was calculated by adding the five lobe scores reaching a range of possible scores from 0 to 20 [39].

Follow-up CT scans were judged to show progression, resolution, or no change of pulmonary lesions. Any disagreements between the two radiologists were resolved through their consensus [39].

Transthoracic ultrasound for Assessment of Covid-19 Pneumonia:
Bedside lung ultrasound (LUS) is a widely available diagnostic tool, complementary to physical examination, that can provide a large amount of diagnostic information in several respiratory diseases and settings. In the hands of experienced clinicians, LUS diagnostic accuracy for bacterial pneumonia is similar to chest CT [40].
Recently, it has been suggested that point-of-care LUS can be useful for both diagnosing and monitoring COVID-19 patients. COVID-19 pneumonia-related pulmonary abnormalities are often located in the subpleural regions of the lung, thus increasing the likelihood of insonation during ultrasound examinations. As reported by studies in small case series, COVID-19 pneumonia can be associated with multifocal B lines, bilateral subpleural consolidations, and pleural thickening, which reflect abnormalities detectable on chest CT. However, a correlation between LUS and CT findings in patients urgently hospitalized for severe COVID-19 pneumonia remains to be determined [41].

Sonographic signs and patterns of COVID-19 pneumonia:
The sonographic signs of interest in COVID-19 include all those which are well known in ARDS. These are the B-lines in various forms, both separate and coalescent, irregular or fragmented aspect of the pleural line, and small peripheral consolidations. Explanations and demonstrations of all these signs can be easily found in the vast existing literature on the topic. However, in the diagnosis of COVID-19 some specificities need to be considered [42].
B-lines in COVID-19 pneumonia are visualized in all their possible forms. We may describe COVID-19 pneumonia as a storm of clusters of B-lines, both in separate and coalescent forms, sometimes giving the appearance of a shining white lung. They can arise from one point of the pleural line and from small peripheral consolidations and spread down like rays maintaining their brightness until the edge of the screen without fading. These artifacts represent the typical signs

of the disease, but can be also observed in other interstitial diseases of various etiologies [43].
However, we are observing that one peculiar aspect of these artifacts is invariably visualized in the early phases of COVID-19 pneumonia (unpublished data). It is a shining band-form artifact spreading down from a large portion of a regular pleural line, often appearing and disappearing with an on–off effect in the context of a normal A-lines lung pattern visible on the background. In our opinion, this sign is demonstrative of a very acute phase of GGO lesions during the early spread of the active disease, when limited areas of lesions alternate with preserved lung parenchyma. Other Chinese authors called this sign "waterfall", without further characterizing it [43].
They did not differentiate this vertical artifact from other less specific signs, like coalescent B-lines arising from peripheral consolidations or from a very irregular pleural line. We think that the name "light beam" can well describe this artifact, as a large beam of light sometimes appearing and disappearing during respiration. Identifying this band-form sign as the one arising from a large portion of a regular pleural line helps characterizing the LUS pattern. As a technical note, it is crucial to use a convex probe with a large emission surface and low frequency to visualize the light beam more reliably. It is also important to position the focus at the level of the pleural line to prevent misinterpretations of the vertical artifacts [32].
LUS patterns: All the LUS signs of COVID-19 pneumonia, including the light beam, can be observed in a variety of different lung conditions. However, what gives specificity to LUS is the distribution of the pattern and the current epidemiological milieu. Bilateral patchy distribution of multiform clusters, where all these signs are represented and sharply alternated to "spared areas", is typical of the disease. Included in the clusters, evidence of the light beam is crucial to assign a diagnosis of high probability. Any other combination of signs should be considered at intermediate probability and should demand further testing. Finally, some patterns allow ruling out the disease and orientating towards alternative diagnoses. For instance, a regular pleural line with more uniform, symmetric and gravity-related distribution of B-lines with a stronger correlation to the severity of dyspnea, is typical of cardiogenic pulmonary edema. Diffuse irregularities of the pleural line without the typical patchy distribution are more typical of chronic diffuse interstitial pulmonary diseases, like fibrosis. Isolated large lobar consolidation with or without effusion and with dynamic air bronchograms indicates bacterial infection. Large pleural effusion with atelectatic consolidation of the base of the lung and signs of peripheral recruitment during inspiration suggest a compressive origin of the lung condition. The presence of echoic septa or other images inside the effusion demonstrates a different origin of the infection, as SARS-CoV-2 does not yields complex exudative effusions [30].
Correlation with the patient condition: The power of LUS in orientating the management of patients during this COVID-19 outbreak is consistently increased by correlating LUS patterns with clinical information. The early approach should be differentiated in three main subgroups of patients, or phenotypes. (1) Patients with respiratory symptoms, ranging from those complaining of mild exertional dyspnea to those with severe respiratory distress; it should be noted that patients with COVID-19 tend to appear less symptomatic than expected when gas analysis or quick exercise testing are performed; (2) patients without respiratory symptoms, suspected for a mild form of SARS-CoV-2 infection; (3) patients with pre-existing chronic cardio-pulmonary diseases, mainly severe COPD, pulmonary fibrosis, lung cancer, cor pulmonale, heart failure [30].
Three main principles justify this differentiation. (A) A negative LUS examination in patients of the phenotype 1 allows ruling out COVID-19 pneumonia with very high sensitivity and reallocate the patient; sometimes, even an intermediate pattern that is disproportionate to the severity of a

respiratory distress may be useful to orientate to another diagnosis; anyway, LUS can exclude the diagnosis of pneumonia but cannot exclude SARS-CoV-2 infection; (B) in phenotype 2, even intermediate LUS signs allow diagnosis of COVID-19 pneumonia that needs to be confirmed by viral swab testing; the degree and distribution of the typical patterns in combination with clinical information allow establishing the severity of the disease and the risks of discharging home the patient; (C) in phenotype 3, any LUS pattern that cannot be considered at high probability, for instance due to absence of multiple light beams, remains doubtful. Diagnosis cannot be concluded without a combination of swab test and often CT scan [43].

Finally, correlation with timing of the onset of symptoms should be always considered. When the LUS pattern is the result of several days of disease, it is potentially less evolutive than similar patterns observed at a very early phase. The correlation of the LUS pattern with some blood exams is also useful. The typical blood assays picture in COVID-19 is based on the evaluation of leukocyte count, lactate dehydrogenase, procalcitonin, and others. The leukocyte count, which is almost invariably reduced in COVID-19, is especially helpful. Negative serum procalcitonin allows to support the diagnosis of COVID-19 in patients showing LUS signs of pneumonia [44].

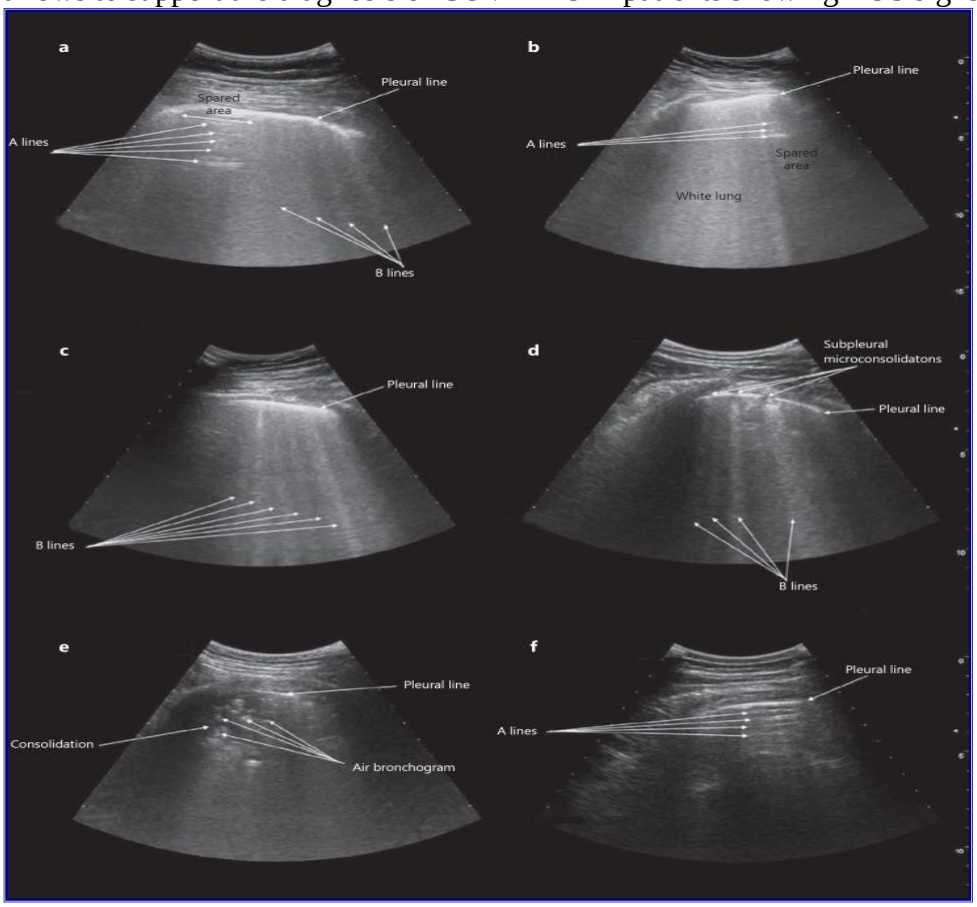

Fig. (9): Appearance of COVID-19-related alveolar-interstitial pneumonia at bedside lung ultrasound. a Nonconfluent B lines (comet-tail artifacts) with spared areas of normal lung parenchyma showing A lines (horizontal artifacts). b Confluent B lines with "white lung" pattern and spared areas of normal lung parenchyma showing A lines. c Diffuse, nonconfluent B lines reflecting homogeneous interstitial involvement of lung parenchyma. d Subpleural microconsolidations with indentation of pleural line, associated with a nonconfluent focal B-line pattern. e Overt subpleural consolidation with air bronchograms. f Spared area showing A lines

corresponding to a region of normally ventilated lung parenchyma without alveolar-interstitial involvement. [46].

On hospital admission, COVID-19-related alveolar-interstitial pneumonia was associated with LUS abnormalities reflecting chest CT alterations. The most frequent ultrasound presentations were focal areas of the interstitial syndrome (either nonconfluent or confluent B lines) with possible presence of small, multiple, subpleural consolidations and indentation of the pleural line. In some cases, overt consolidations with air bronchograms could be detected, while pleural effusion was present in only few cases [45]. The LUS score, calculated according to type, extension, and severity of ultrasound abnormalities, showed a statistically significant correlation with analogous CT severity score and oxygen saturation in room air [45].

These findings are coherent with expert opinions and case series previously published in the literature. However, the significant correlation between ultrasound and CT scores allows to make a step forward in defining a role for LUS in the clinical management of COVID-19 pneumonia. In patients urgently admitted with respiratory symptoms and fever, the integration of clinical and anamnestic data with LUS findings could represent an important aid for diagnosis of COVID-19 and for addressing patients to the most appropriated care path, especially in situations where CT diagnostics are not immediately available [46].

The use of LUS for triaging patients with symptoms compatible with pneumonia in the prehospital setting or at the moment of first emergency department evaluation. This application of LUS could be particularly useful considering that, during the pandemic peak, many COVID-19 patients, especially if older and multimorbid, may have atypical clinical presentation and no evident history of a contact with individuals who tested positive for SARS-CoV-2 [47]. Early LUS evaluation of patients with respiratory symptoms in the emergency department can result in significant changes in patient management, and this could be particularly useful in the COVID-19 pandemic, where misdiagnoses may have relevant consequences in terms of infection spread [47].

The use of ultraportable handheld devices could be of particular interest in this emergency setting, as recently demonstrated for interventional applications. The correlation between LUS and CT visual scores in COVID-19 supports the implementation of this technique and the design of larger, prospective studies evaluating the importance of LUS in different settings of COVID-19 care [48].

The ultrasound imaging findings of COVID-19 pneumonia are similar to those previously described in cases of viral pneumonia of different etiology, including H1N1 and H7N9 influenza viruses. In that situation, LUS was effectively used for the diagnosis of the acute respiratory distress syndrome, monitoring of the response to intensive care treatments, and for the detection of bacterial superinfections [49]. Such applications could also be useful in the context of COVID-19 pneumonia and should be carefully evaluated in future studies. Notably, we observed higher LUS scores in patients with consolidation or diffuse GGO abnormalities detectable on HRCT than in individuals showing patchy GGO [49].

Although the findings of our study support the use of bedside LUS in the evaluation of patients with suspect COVID-19, ultrasound should not be considered as a substitute for chest CT for several reasons. First, the correlation between the severity of ultrasound abnormalities and CT visual score was suboptimal, albeit statistically significant. This suggests that ultrasound may be less accurate than CT for the stratification of the severity of lung involvement in COVID-19. Moreover, the false-negative and false-positive rates of LUS findings in COVID-19 pneumonia

in comparison with CT have not been elucidated yet. The interobserver agreement of LUS is also uncertain in COVID-19 pneumonia, although it was demonstrated as good to excellent in several other respiratory diseases [40]. The limited availability of ultrasound equipment dedicated to isolated patients may also be an important barrier for the use of this technique in the context of COVID-19 patients [40].

We must also acknowledge that the ultrasonographic signs of COVID-19 pneumonia can be present in other respiratory and cardiovascular diseases, including pulmonary fibrosis and congestive heart failure. Confluent or nonconfluent B lines with pleural line thickening and subpleural nodules are the key abnormalities associated with idiopathic or secondary pulmonary fibrosis. Diffuse B lines also represent a well-known index of pulmonary congestion usually responding to diuretic treatment [49]. The integration of the clinical and epidemiological context with ultrasound findings is therefore necessary for the differential diagnosis between COVID-19 pneumonia and other conditions with similar ultrasonographic appearance. The detection of pleural effusion, which is rare in COVID-19 (<6% of cases according to a recent meta-analysis of CT findings) and very frequent in congestive heart failure, may represent an important element for the formulation of a correct diagnosis [49].

From this perspective, LUS represents a technologic complement to physical examination to evaluate the diagnostic suspicion in patients with a clinical history compatible with COVID-19 pneumonia. This is the framework in which LUS examinations were performed in the present study. LUS should therefore be considered as a guide, and not a substitute, for the prescription of more consolidated diagnostic techniques, such as CXR and CT. It is also noteworthy that neither LUS nor traditional imaging can be able to detect SARS-CoV-2 infection when pulmonary involvement is not present. Similarly, none of these diagnostic techniques can help to distinguish viral pneumonia caused by other respiratory viruses from COVID-19 pneumonia. Thus, integration of imaging with clinical and anamnestic data is always mandatory to reach a correct diagnosis even in the context of a pandemic. LUS could also represent a promising tool for monitoring the evolution of pulmonary involvement of COVID-19 after baseline traditional imaging (CXR or CT) [50].

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