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SYSTEMATIC REVIEWS

- 243 Differential diagnosis of COVID-19 at the chest computed tomography scan: A review with special focus on cancer patients

Perrone F, Balbi M, Casartelli C, Buti S, Milanese G, Sverzellati N, Bersanelli M

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Differential diagnosis of COVID-19 at the chest computed tomography scan: A review with special focus on cancer patients

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Abstract

BACKGROUND

Given the several radiological features shared by coronavirus disease 2019 pneumonia and other infective or non-infective diseases with lung involvement, the differential diagnosis is often tricky, and no unequivocal tool exists to help the radiologist in the proper diagnosis. Computed tomography is considered the gold standard in detecting pulmonary illness caused by severe acute respiratory syndrome coronavirus 2.

AIM

To conduct a systematic review including the available studies evaluating computed tomography similarities and discrepancies between coronavirus disease 2019 pneumonia and other pulmonary illness, then providing a discussion focus on cancer patients.

METHODS

Using pertinent keywords, we performed a systematic review using PubMed to select relevant studies published until October 30, 2020.

RESULTS

Of the identified 133 studies, 18 were eligible and included in this review.

CONCLUSION

Ground-glass opacity and consolidations are the most common computed tomography lesions in coronavirus disease 2019 pneumonia and other respiratory

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diseases. Only two studies included cancer patients, and the differential diagnosis with early lung cancer and radiation pneumonitis was performed. A single lesion associated with pleural effusion and lymphadenopathies in lung cancer and the onset of the lesions in the radiation field in the case of radiation pneumonitis allowed the differential diagnosis. Nevertheless, the studies were heterogeneous, and the type and prevalence of lesions, distributions, morphology, evolution, and additional signs, together with epidemiological, clinical, and laboratory findings, are crucial to help in the differential diagnosis.

Key Words: COVID-19; Computed tomography; Differential diagnosis; Cancer; Pneumonia; Radiological findings

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Core Tip: In the coronavirus disease 2019 era, the differential diagnosis of pneumonitis, already challenging in patients with multiple comorbidities and polypharmacological therapy, has become even more challenging. The gold-standard technique for diagnosing coronavirus disease 2019-related pneumonia is still not established. Still, a computed tomography scan is essential for the differential diagnosis of drug-induced pneumonitis, infectious pneumonia, and other conditions such as cancer progression. With this review, we have dealt with frequent radiological diatribes in the radiological diagnosis of coronavirus disease 2019 pneumonitis, with a special focus on cancer patients, for whom clinical elements can be more confounding than helpful as a complement to the correct diagnostic conclusion.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak began in Wuhan, China, in late 2019 and rapidly spread worldwide at the beginning of 2020, when it was declared a global pandemic by the World Health Organization[1,2]. Many jurisdictions in several states carried out public health interventions to contain the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3]. Europe is now experiencing a second wave of contagion[4].

The virus has a specific tropism for the lower respiratory tract, and it is the cause of mild to severe respiratory infection[5].

Imaging has been widely employed to triage the massive load of acute respiratory referral due to COVID-19 by complementing the nucleic acid testing (*i.e.*, the diagnostic reference standard). Typical manifestations of COVID-19 pneumonia on computed tomography (CT) have become known since the early phase of the pandemic: bilateral peripheral opacities with a lower lung distribution, usually consisting of nodular or mass-like ground-glass opacities (GGO) variably associated with areas of consolidation[6,7]. CT abnormalities may be absent in the earliest disease phases and become more extensive in the peak stage (*i.e.*, around day 9 to 13) before resolve or evolve to a more organized phase, possibly leading to fibrotic-like changes[8,9].

Many of the hallmark CT findings are apparent on chest X-ray, which is prone to miss subtle GGO, even if relatively diffuse in extent. Nevertheless, chest X-ray has shown the potential to predict outcomes in relatively advanced disease stages, assess supervening complications, and monitor the disease course[10]. Lung ultrasound was suggested as a fast and feasible approach for triaging COVID-19 patients by identifying peripheral lung abnormalities such as confluent artifactual signs, small hyper-echoic lung regions, thickened pleural lines, and consolidation[11,12]. Though highly sensitive, lung ultrasound is operator-dependent, challenging to perform in obese patients, and has lower specificity than CT[13].

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It is worth emphasizing that the imaging appearance of COVID-19 is non-specific, and the performance of different modalities dramatically relies on the disease prevalence. The typical manifestations may mimic or overlap with other infective and non-infectious diseases, including influenza and acute lung injuries from drug reactions and connective tissue diseases[14]. Identifying findings uncommonly seen in COVID-19 pneumonia such as cavitation, tree-in-bud, and pleural effusion may help suggest an alternative diagnosis, which cannot be prescind from clinical evaluation.

In the present article, we performed a systematic review of the literature focusing on differential radiological diagnosis between COVID-19 pneumonia and other infective and non-infective lung diseases, then discussing possibly helpful clinical elements and finally focusing on this issue in cancer patients.

MATERIALS AND METHODS

We conducted this systematic review according to the Preferred Reporting Items guidelines for Systematic Reviews and Meta-Analysis (PRISMA) Statement[15]. The primary aim was to collect, describe, and discuss all the clinical studies evaluating the different CT findings between COVID-19 infection and other infective or non-infective lung diseases.

Search strategy

Two authors (CC and FP) carried out a comprehensive systematic search for published articles on the MEDLINE/PubMed library until October 31, 2020. Given the absence of articles on this topic before December 2019, when the first COVID-19 outbreak started, no upper limit for the search was chosen.

The following search keywords were used: “COVID-19” AND “computed tomography” AND “differential diagnosis.” The reference lists of the included articles and reviews/meta-analyses on our research topic were also reviewed to identify additional relevant papers.

Study selection and eligibility criteria

Retrospective studies, prospective studies, and case reports describing the difference between CT signs caused by SARS-CoV2 infection and other respiratory and non-respiratory diseases were included. Only English-language articles were considered eligible. Studies with insufficient radiological data or focused on non-CT radiological findings (*i.e.*, ultrasound or radiography) were excluded. We planned qualitative analysis only, forecasting a high heterogeneity between the eligible studies, likely preventing quantitative analyses.

Narrative papers, such as commentaries and editorials, were excluded from the formal qualitative analysis, but the most relevant articles discussing the issue were considered in the discussion.

Data extraction and synthesis

The study characteristics (first author, year of publication, type of study, number of patients included, disease of comparison assessed, and main radiological similarities and discrepancies, laboratory findings) were extracted from the included articles by a single author (FP). Two reviewers (FP and CC) initially performed the data extraction, and then it was independently reviewed by an additional reviewer (MB).

Any doubt or disagreement was discussed with a fourth investigator (SB) and resolved with all investigators' consensus.

RESULTS

Literature search

Of the 133 studies found in the search, 104 were initially excluded by title and abstract reading. After reading the full text of the remaining 29 articles, 11 were excluded because they missed relevant radiological information or comparison between different imaging patterns. Overall, 18 studies satisfied the prespecified criteria and were selected for the qualitative analysis. The outline of the search is reported in **Figure 1**.

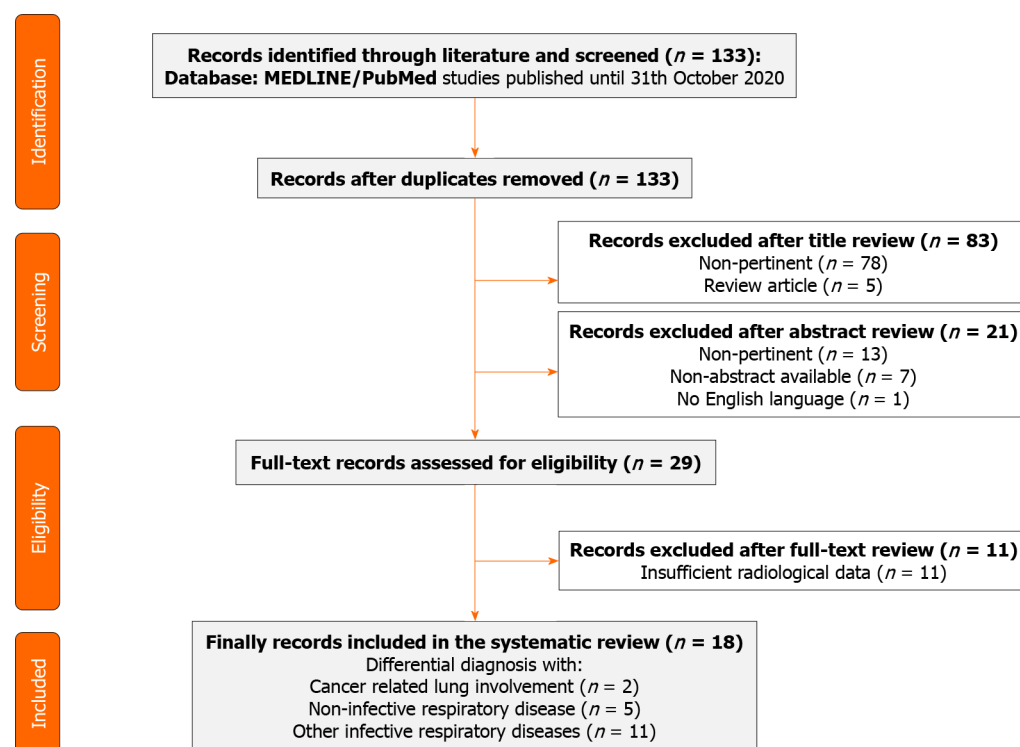


Figure 1 PRISMA flow diagram.

Characteristics of the included studies

Trial characteristics and the main results of the studies included are reported in Table 1. Among the 18 studies included, 5 were case report/case series[16-20], and 13 were retrospective[21-33]. All the studies described the typical radiological characteristics of COVID-19 pneumonia and addressed the radiological differential diagnosis issue. The difference between COVID-19 and non-infective respiratory diseases, namely: Systemic sclerosis and granulomatosis with polyangiitis ($n = 2$)[30,31], fat embolism ($n = 1$)[32], pulmonary contusion ($n = 1$)[33] were evaluated in 5 out of 18 studies. One study evaluated both heart failure-induced pulmonary edema and rheumatic pneumonia ($n = 1$)[16].

On the other hand, 11 studies explored the CT imaging differences between COVID-19 disease and other infective pneumonia. In particular, the differential diagnosis was performed with influenza pneumonia ($n = 3$)[23,30,33], community-acquired pneumonia (CAP) ($n = 3$)[24,25,31], and other non-specified viral or bacterial pneumonia ($n = 5$)[21,22,26,27,32].

Only two studies included cancer patients. One assessed the radiological discrepancies between COVID-19 disease with lung involvement and radiation pneumonitis [28]. In the other study, the differential diagnosis regarded early lung cancer[29].

In the majority of studies, detection of SARS-CoV-2 was performed by RT-PCR on throat/nasopharyngeal swab. The laboratory test was lacking in only one study, in which the final diagnosis was carried out based on clinical and epidemiological findings[20].

In the following paragraphs, the findings of the included studies are reported by topic.

Differential diagnosis between COVID-19 pneumonia and other non-infective respiratory diseases

The radiological difference between COVID-19 pneumonia and heart failure-induced pulmonary edema was evaluated by Dai *et al*[16].

Although GGOs and interlobular septal thickening were CT manifestations shared by both diseases, butterfly signs (patchy high attenuation patterns and large patchy high attenuation patterns in both lungs), peribronchial cuffing, and redistribution of blood flow in both lungs were typical in heart failure pulmonary edema.

Three rheumatologic diseases, namely systemic sclerosis, granulomatosis with polyangiitis, and rheumatic disease, often caused lung involvement with GGOs. Predominant lower lobe distribution associated with reticulations and honeycombing in

Table 1 Summary of the studies included in the systematic review

Ref.	Yr	Type of study	Patients, n	Disease in differential diagnosis	Radiological similarities with COVID-19 disease	Radiological discrepancy with COVID-19 disease	Laboratory findings
Dai <i>et al</i> [16]	2020	Case series	4 pts COVID-19 positive. 1 pts heart failure induced pulmonary edema. 1 pts rheumatic pneumonia.	Heart failure induced pulmonary edema. Rheumatic pneumonia.	Local or multiple GGOs. Patchy high-attenuation patterns. Sporadic or local interlobular septal thickening. Patchy GGOs and consolidations; interlobular septal thickening.	Butterfly sign. Peribronchial cuffing. Redistribution of blood flow in both lungs.	Normal WBC count, D-dimer, hs-CRP. RT-PCR for SARS-CoV-2 negative. Normal WBC and lymphocyte count, high hs-CRP, D-dimer, rheumatoid factor. RT-PCR for SARS-CoV-2 negative.
Orlandi <i>et al</i> [17]	2020	Case report	-	Systemic sclerosis ILD	Bilateral GGOs with or without consolidations. Reticulations.	Limited to lower lobes. Honeycombing pattern.	RT-PCR for SARS-CoV-2 negative
Shenavandeh <i>et al</i> [18]	2020	Case report	1	Granulomatosis with polyangiitis	GGOs and consolidation	Nodules and mass lesions	-
Chen <i>et al</i> [20]	2020	Case report	1	Pulmonary contusion	GGOs and consolidation	More consolidations. Less combined with pleural effusion and subpleural atelectasis. Different time evolution of lesions.	High WBC count and mild decreased of lymphocyte count
Mazouz <i>et al</i> [19]	2020	Case report	1	Fat embolism	Bilateral GGOs	Central and peripheral involvement	High CRP, alkalosis with hypoxemia, normal lymphocyte count. RT-PCR for SARS-CoV-2 negative.
Zhang <i>et al</i> [29]	2020	Retrospective	157 pts COVID-19. 374 pts with early lung cancer.	Early lung cancer	Air bronchogram. Cystic change.	Less lobes and segments involved. Unilateral oval lesions. Pure or mixed GGOs. Lobulated sign, pleural retraction and vessel convergence sign. Less lymphadenopathies and pleural effusion.	Higher WBC and lymphocyte count, lower D-dimer level.
Zeng <i>et al</i> [28]	2020	Retrospective	112 pts COVID-19 positive or suspected. 4 pts with radiation pneumonitis.	Radiation pneumonitis	GGOs with consolidation. Air bronchogram. Irregular intralobular or interlobular septal thickening. Fibrosis in late stage.	Onset within 6 mo after radiation. Slow evolution. Lesions confined to radiation fields.	High WBC count, D-Dimer, CRP and PCT, marked lymphopenia. RT-PCR for SARS-CoV-2 negative.
Himoto <i>et al</i> [27]	2020	Retrospective	21 pts COVID-19 positive. 15 pts with viral or bacterial pneumonia.	Pneumococcal pneumonia, Moraxella pneumonia, Legionella pneumonia, not-specified bacterial or viral pneumonia. Pneumocystis pneumonia and interstitial pneumonia.	Bilateral peripheral GGOs. No cavitation, airway abnormalities, pleural effusion, and mediastinal lymphadenopathy.	Less lobes involved. No rounded morphology lesions.	RT-PCR for SARS-CoV-2 negative
Luo <i>et al</i> [22]	2020	Retrospective	30 pts COVID-19 positive. 43 pts with viral or bacterial pneumonia.	Influenza pneumonia, Pneumocystis carinii pneumonia, Mycoplasma pneumonia and CAP.	GGOs with or without consolidation	Less lobes involved. Peribronchovascular distribution. Centrilobular nodules. Bronchial wall thickening.	WBC and lymphocyte count normal, but lower in COVID-19 positive patients. RT-PCR.

Xie <i>et al</i> [26]	2020	Retrospective	12 pts COVID-19 positive. 16 pts COVID-19 negative.	COVID-19 negative	Bilateral multiple lung involvement, large irregular/ patchy opacities, rounded opacities and linear opacities, crazy-paving patterns, interlobular septal, pleural and peribronchovascular interstitial thickening, air bronchograms, tree-in-bud patterns.	More central distribution of lesions. Less frequent rounded opacities.	Higher level of neutrophil count in COVID-19 negative. RT-PCR.
Bai <i>et al</i> [21]	2020	Retrospective	219 pts COVID-19 positive. 205 pts with viral pneumonia.	Viral pneumonia	Bilateral, multiple GGOs, consolidation, nodules. Septal thickening.	More central + peripheral distribution. More air bronchogram, pleural thickening, pleural effusion and lymphadenopathy.	Higher WBC and lymphocyte count in patients with viral pneumonia. RT-PCR.
Chi <i>et al</i> [32]	2020	Retrospective	17 pts COVID-19 positive. 51 pts with viral or bacterial pneumonia.	Influenza A and B. Adenovirus. Chlamydia pneumonia. Mycoplasma pneumonia.	-	INFLUENZA A: scattered and patchy shadows and nodular shadows in both lungs. INFLUENZA B: subpleural patchy shadows. ADENOVIRUS: consolidation near the pleura. CHLAMYDIA PNEUMONIAE: multiple GGOs and consolidations in both lungs. MYCOPLASMA PNEUMONIAE: bronchial wall thickening, centrilobular nodules, GGOs and consolidation.	Higher WBC count, RT-PCR
Li <i>et al</i> [24]	2020	Retrospective	43 pts COVID-19 positive. 49 pts with CAP.	CAP	-	More nodular or consolidation shadows with or without patchy GGOs. Less fine mesh changes, small vessels dilatated, bronchiectasis and lesion with long axis parallel to the pleura.	RT-PCR
Liu <i>et al</i> [25]	2020	Retrospective	165 pts COVID-19 positive. 118 pts with CAP.	CAP	-	More central distribution. More frequent single lesion. GGOs rapid changes in consolidation. Fibrous cord and bronchial wall thickening.	Normal WBC count, higher lymphocyte count and CRP. RT-PCR.
Zhou <i>et al</i> [31]	2020	Retrospective	149 pts COVID-19 positive. 97 pts with CAP.	CAP (<i>Streptococcus pneumoniae</i>)	-	More consolidation lesions, bronchial wall thickening, centrilobular nodules and pleural effusion. Less GGOs, crazy paving sign and abnormally thickened interlobular septa.	High WBC count, neutrophils count and CRP. Rt-PCR.
Liu <i>et al</i> [23]	2020	Retrospective	122 pts COVID-19 positive. 48 pts with influenza pneumonia.	Influenza pneumonia	GGOs with consolidation. Nodules. Linear opacities. Interlobular septal thickening tree-in-bud sign.	More nodules, pleural effusions and tree-in-bud sign. Central + peripheral distribution.	RT-PCR for influenza or SARS-CoV-2.
Zhao <i>et al</i> [33]	2020	Retrospective	31 pts COVID-19 positive. 18 pts with influenza pneumonia.	Influenza pneumonia	-	More consolidations and pleural effusions.	RT-PCR
Wang <i>et al</i> [30]	2020	Retrospective	13 pts COVID-19 positive. 92 pts with influenza pneumonia.	Influenza pneumonia	GGOs and GGOs with consolidation	Inferior lobe involved. Cluster-like GGOs. Lesion with vague margin. Bronchial wall thickening.	Normal WBC count. Low lymphocyte count in Influenza B. No significant difference between two groups. RT-PCR.

pts: Patients; GGO: Ground-glass opacity; ILD: Interstitial lung disease; CAP: Community acquired pneumonia; WBC: White blood count; hs-CRP: High

sensitivity C-reactive protein; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PCT: Procalcitonin; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein.

advanced cases distinguished systemic sclerosis-related interstitial lung disease from interstitial pneumonia, as reported by Orlandi *et al*[17].

According to Shenavandeh *et al*[18], pulmonary nodules, mass lesions, and consolidation caused by lung hemorrhage and infarction due to small vessel vasculitis were typical for granulomatosis with polyangiitis.

Finally, extensive patchy exudates and consolidations in both lungs, faint GGOs on edge, and interlobular septal thickening were characteristic features for rheumatic pneumonia observed by Dai *et al*[16].

Although GGOs and consolidation characterized pulmonary contusion (usually caused by traffic accidents, falls, bumps, and crashes), a higher proportion of consolidations often associated with bilateral pleural effusion and subpleural atelectasis was observed when compared to COVID-19 disease. In addition, the radiological evolution was different in the two illnesses. No signs or few sheet shadows may be observed in pulmonary contusion 4-6 h after injury. The lung returned to normal after 7-10 d. Otherwise, in the case of COVID-19, the radiological pattern was long-lasting[20].

As in COVID-19 disease, bilateral GGOs with multilobe central and peripheral involvement were observed by Mazouz *et al*[19] in the case of fat embolism.

Differential diagnosis between COVID-19 pneumonia and cancer-related lung lesions

One out of two studies including cancer patients investigated the difference between COVID-19 disease and pulmonary toxicities caused by radiotherapy. GGOs with partial consolidation, lung fibrosis characterized by linear scarring, air bronchograms, irregular intralobular or interlobular septal thickening were typical radiation pneumonitis features. With the onset within 6 mo after completing radiotherapy and limited distribution to the irradiation field, CT lesions were distinguished from COVID-19 pneumonia by Zeng *et al*[28].

The study on cancer patients conducted by Zhang *et al*[29] focused on the similarities and discrepancies between COVID-19 pneumonia and early lung cancer. Although GGOs, air bronchogram, and cystic changes were present in both diseases, some differences were observed. Pure and mixed GGOs were most frequent in lung cancer, while COVID-19 patients tended to have more than one type of lung lesion. Contrary to COVID-19 pneumonia, characterized by patchy and bilateral lesions, unilateral and oval lesions were predominant in lung cancer patients. Air bronchogram was prevalent in COVID-19 patients, in contrast with cystic changes in lung cancer patients. Some radiological features were present only in COVID-19 pneumonia, such as reticular pattern, subpleural linear opacity, bronchial dilatation, centrilobular nodule, and the tree-in-bud sign. On the other hand, lobulated signs, pleural retraction, and vessel convergence signs were present in lung cancer patients but absent in those with COVID-19. More lobes and segments were involved in COVID-19 pneumonia compared to early lung cancer.

Differential diagnosis between COVID-19 pneumonia and another infective pneumonitis

In a retrospective study, Himoto *et al*[27] used five chest CT criteria to distinguish COVID-19 pneumonia from other infective respiratory diseases, such as Pneumococcal pneumonia, Moraxella pneumonia, Legionella pneumonia, not-specified bacterial or viral pneumonia, Pneumocystis pneumonia, and non-specific interstitial pneumonia. The differential patterns evaluated were: (1) GGO-predominant lesions; (2) GGO- and peripheral-predominant lesions; (3) bilateral GGO-predominant lesions; (4) bilateral GGO- and peripheral-predominant lesions; and (5) bilateral GGO- and predominant peripheral lesions without nodules, airway abnormalities, pleural effusion, and mediastinal lymphadenopathy. Compared to other infective respiratory diseases analyzed, COVID-19 pneumonia had bilateral GGO- and peripheral-predominant lesions without airway abnormalities, mediastinal lymphadenopathy, and pleural effusion [27].

Luo *et al*[22] developed an imaging score to distinguish COVID-19 pneumonia and non-COVID-19 pneumonia (Influenza pneumonia, Pneumocystis carinii pneumonia, Mycoplasma pneumonia, and CAP). Seven positive signs were identified: posterior part/lower lobe predilection, bilateral involvement, rounded GGO, subpleural band-

like GGO, crazy-paving pattern, peripheral distribution, and GGO with or without consolidation. Only one-lobe involvement, only central distribution, the tree-in-bud sign, and bronchial wall thickening were considered negative signs. The score ranged from -4 to 7 and was significantly higher in the COVID-19 group than in the non-COVID-19 group. Both diseases shared GGOs with or without consolidation. The tree-in-bud sign was observed in non-COVID-19 patients only. Rounded and subpleural bandlike GGO were more common in COVID-19 patients.

Similarly, other authors found that pure/mixed GGOs, interlobular septal thickening, crazy-paving patterns, halo signs, and consolidation were common both in COVID-19-positive and negative patients. The unique CT finding, potentially typical of COVID-19 disease, was a peripheral distribution of the pulmonary lesions[26] and a high proportion of rounded opacities. Bronchial wall thickening was a characteristic sign of *Mycoplasma pneumoniae*[32].

Although GGOs and consolidations were present in both other viral pneumonia (adenovirus, influenza, parainfluenza, rhinovirus, and others) and COVID-19, central plus peripheral distribution, air bronchogram, pleural thickening, pleural effusion, and lymphadenopathy were more frequent in viral pneumonia[21].

Two studies investigated the differential radiological manifestations of COVID-19 lung disease and CAP. By using a new radiological model, Li *et al*[24] observed that CAP was characterized more often by nodular or consolidation shadows with or without patchy GGOs and more rarely by subtle mesh changes, dilated small vessels, bronchiectasis, and lesion with the long axis parallel to the pleura compared to COVID-19 pneumonia. Moreover, lymphadenopathy, pleural effusion, pleural and bronchial wall thickening, fibrous tissue, lung cavity, and bullae were detected by other authors in CT scans of CAP affected patients, while these findings were absent or more rarely in COVID-19 patients[25]. Similar radiological signs were observed by Zhou *et al*[31] in *Streptococcus pneumoniae* CAP.

Consolidation, nodules, pleural effusion, and tree-in-bud signs were the radiological manifestation in influenza pneumonia in the analysis by Liu *et al*[23] and Zhao *et al* [33]. The distribution of the lesions (bilateral lobe *vs* inferior lobe), their margin (clear *vs* vague), and the GGO lesion involvement pattern (patchy or GGO associated with consolidation *vs* cluster-like involvement) distinguished COVID-19 from influenza pneumonia, according to Wang *et al*[30].

DISCUSSION

The current review focuses on the differential diagnosis between COVID-19 disease and other respiratory and non-respiratory disorders.

Since the early phase of the pandemic, radiological imaging has been employed to assess the suspicion of COVID-19 pneumonia in patients selected by clinical triage, demonstrating the potential for a standardized assessment of the degree of pulmonary involvement and prognostication purposes. Moreover, it has been used as a tool capable of complementing the limited sensitivity and time-consuming laboratory testing process for the SARS-CoV-2 infection detection[34-37].

Such a practical approach has found application in an unprecedented pandemic scenario, where the prevalence of the disease was extraordinarily high, with the awareness that the imaging findings of COVID-19 pneumonia were non-specific as reflecting the diffuse alveolar damage and organizing pneumonia with features shared by a broad spectrum of disorders[38,39]. Despite the increasing knowledge about radiological imaging's role in the pandemic, the actual diagnostic performance of different imaging modalities is still unclear, with reported specificities and sensitivities depending on several factors, from the duration of symptoms to the pre-test probability of the disease. Without articulating the relative merit of X-ray or lung ultrasound *vs* CT, the latter is generally recognized as more sensitive for early parenchymal disease, disease progression, and differential diagnoses, including acute heart failure and pneumonia caused by other pathogens[40]. Remarkably, caution is warranted when analyzing data about the specificity and sensitivity of CT in detecting COVID-19 pneumonia, as some of the most cited studies from the radiology literature seem to suffer from limitations that may lead to overreaching conclusions[16,41-43]. Among the studies included in the present analysis, Bai *et al*[21] recruited the most extensive study population in which differences between COVID-19 and viral pneumonia were evaluated[21]. Though these authors concluded that radiologists are likely to distinguish COVID-19 from viral pneumonia on chest CT with high specificity (*i.e.*, up to 94%), the lack of training information or specific diagnostic criteria in

their study suggests that such results could have been overestimated.

Similarly, other studies included in the present analyses should be interpreted with caution due to limitations such as selection bias or the relatively limited number of patients. Given this awareness, it is noticeable how some CT imaging findings, namely mucoid impactions, centrilobular nodules, lobar consolidation, and significant pleural effusion, have been consistently found to be less frequent in COVID-19 than in other types of pneumonia (Figures 2-4). Thus, they are potentially helpful in everyday practice to complement clinical data in triaging acute respiratory patients[22,23,25,31,44]. Notably, radiologists need to have consciousness of ancillary findings that can be encountered in association with typical pulmonary features of COVID-19 pneumonia, possibly mimicking diseases other than COVID-19 (*e.g.*, centrilobular solid nodules: polyhedral in shape and close to enlarged vessels within ground-glass opacities in COVID-19 pneumonia, while rounded or branching in minor airway diseases)[45].

Imaging findings typical of interstitial pneumonia may be found in asymptomatic COVID-19 patients[46]. Interestingly, incidental GGO showing accumulation of fluorine-18 fluorodeoxyglucose at the positron-emission tomography scan has been described in cancer patients with SARS-CoV-2 infection, raising the suspicion of tumor progression in cases of a false-negative RT-PCR result[47-49]. In those situations, an approach that includes a comparison with recent chest CT findings, as well as a close follow-up, would be appropriate.

When dealing with cancer patients, COVID-19 needs to be considered among diseases that may confound staging or treatment response assessment[50]. For obvious reasons, special attention will need to be given to patients being screened or treated for lung cancer. In our experience, different etiopathogenetic factors can coexist, and their respective inflammatory phenomena can be overlapped in the same patient, as shown in Figure 5, collecting the different CT patterns of five cancer patients who underwent differential diagnosis for pneumonitis.

Besides cancer progression, COVID-19 pneumonia has been investigated as a mimic of early lung cancer, both potentially displaying as single or multifocal GGOs [29]. Unsurprisingly, in their retrospective study, Zhang *et al*[29] found a single location and nodular morphology as significantly more frequent in lung cancer than in COVID-19[29]. Although the authors are alert about the consequences of an inappropriate surgical approach in these patients, it is reasonable to assume that evaluating the temporal evolution of CT findings, symptoms, and molecular test results would allow avoiding such a diagnostic and therapeutic pitfall in most cases.

Radiotherapy and oncologic treatment, such as target therapy and immunotherapy, may induce lung toxicity, mimicking COVID-19 illness. Zeng *et al*[28] recruited suspected COVID-19 patients diagnosed with cancer and treated with radiation to explore the differential diagnosis between COVID-19 pneumonia and radiation pneumonitis. The location, extent, and distribution of the lung CT abnormalities were considered useful to differentiate these two entities, with acute radiation-induced pneumonitis usually displaying GGOs or consolidation in the irradiated lung in contrast to the predominantly peripheral, subpleural opacities described in COVID-19 pneumonia. Otherwise, the differential diagnosis between COVID-19 and immune-related pneumonia is likely to be less straightforward. The issue is highly relevant, especially considering the expanding immune checkpoint inhibitor indications and their potential to induce unique pulmonary toxicities[51,52]. Pneumonitis is a rare but potentially severe side effect of immune checkpoint inhibitors, involving 2.7% of the patients treated with anti-programmed cell death 1 and anti-programmed death-ligand 1 monotherapy and 6.6% of the patients receiving the combination of anti-programmed cell death 1 and anti-cytotoxic T-lymphocyte antigen 4[53]. Several clinical and radiological presentations have been described. Dyspnea and cough are the most frequent symptoms, while fever occurs in 12% of cases[54]. These clinical manifestations could be further confounding for the differential diagnosis. From a radiology perspective, COVID-19 and immune-related pneumonia have a range of imaging manifestations that can substantially overlap, particularly in cases of organizing pneumonia pattern (*i.e.*, the most common pattern seen across all tumor treatments and regimens) and when leading to diffuse GGO and consolidation as a result of diffuse alveolar damage[51,52]. The varying sensitivity of molecular confirmation of SARS-CoV-2 infection and the low specificity of both entities' clinical manifestation renders even more complicated the correct diagnosis, mostly requiring a multidisciplinary discussion before deciding on patient management[55]. However, the simultaneous presence of other immune-related adverse events, such as diarrhea, skin toxicities, and thyroid alterations, with or without a high level of inflammatory factors (*i.e.*, interleukin-6, C-reactive protein) involved in the cytokine storm (the latter also shared with COVID-19), could lead to the hypothesis of pneumonitis most likely

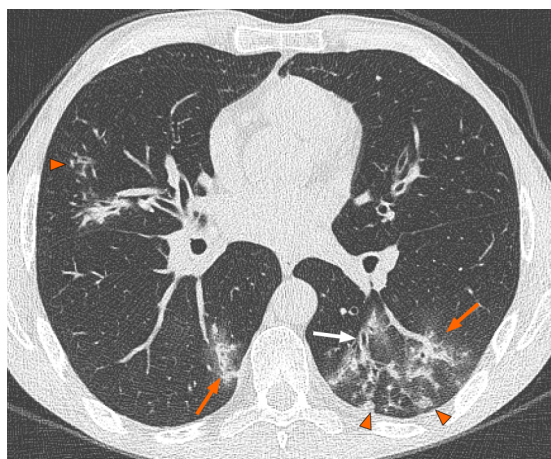


Figure 2 Axial computed tomography image of a 36-year-old man shows nodular (arrowheads) and peribronchovascular branching (orange arrows) opacities along with bronchial wall thickening (white arrow), which suggest a diagnosis other than coronavirus disease 2019 pneumonia. The patient was diagnosed with *Mycoplasma pneumoniae* pneumonia.

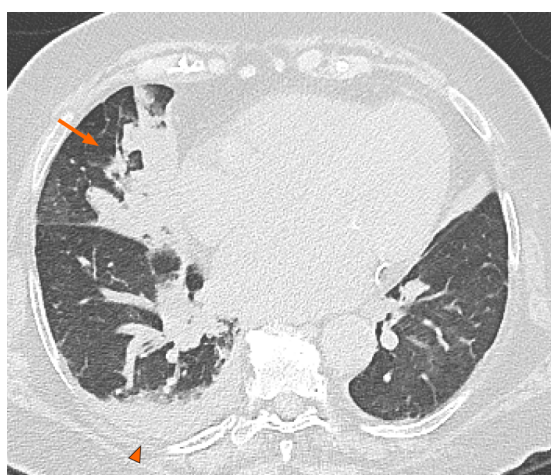


Figure 3 Axial computed tomography image shows right lung consolidation (arrow) and unilateral pleural effusion (arrowhead) in a 64-year-old man with bacterial pneumonia.



Figure 4 Axial computed tomography image in a 50-year-old woman diagnosed with bronchopneumonia shows confluent centrilobular nodules (arrows) and consolidation (arrowheads) mostly located in the lower lobes.

due to immunotherapy.

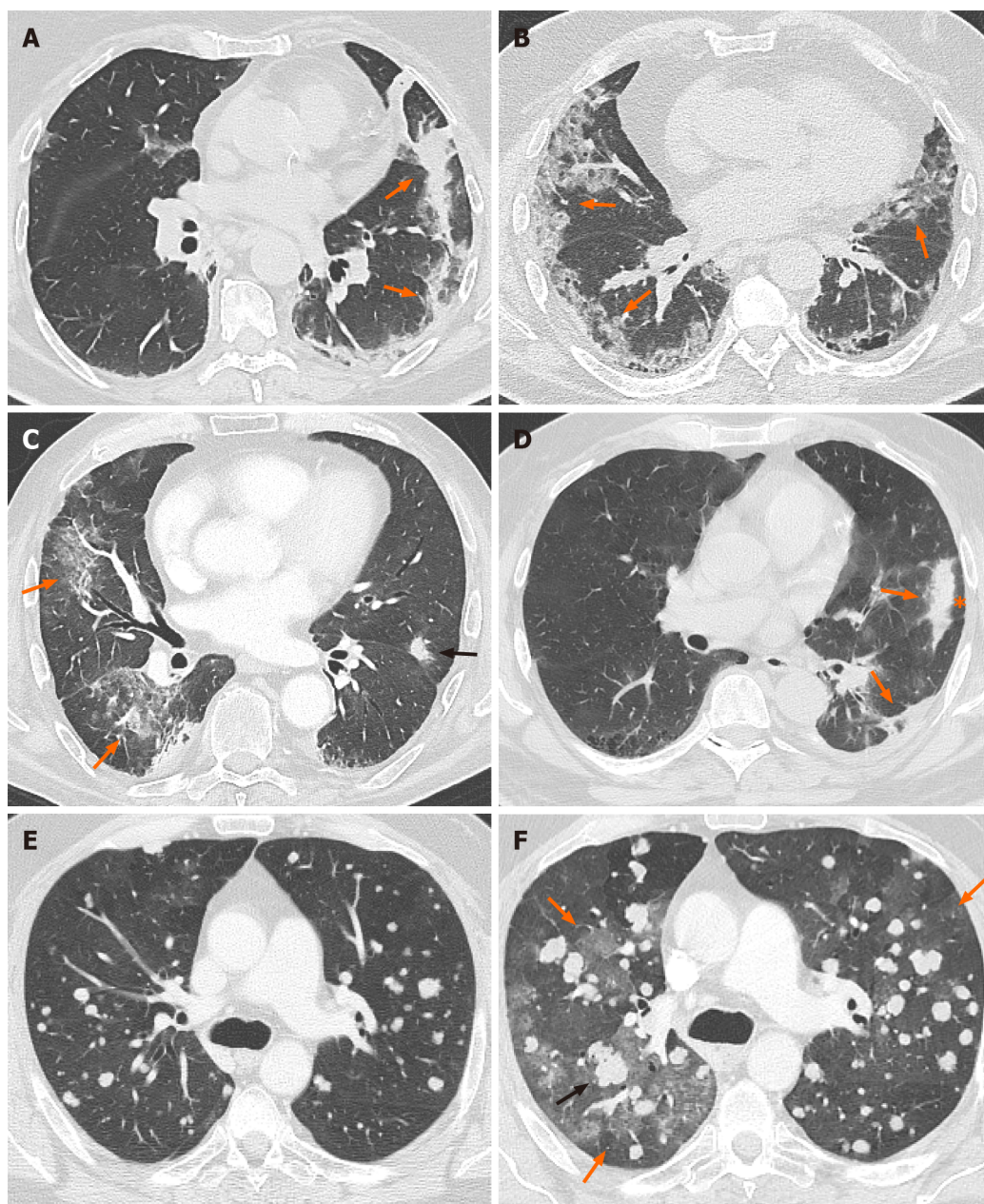


Figure 5 Axial computed tomography image. A: Axial computed tomography (CT) image of a 45-year-old patient with coronavirus disease 2019 showing left peripheral consolidation with peribubular distribution (arrows) suggesting organizing pneumonia; B: Axial CT image showing bilateral ground-glass opacities distributed in the subpleural regions (arrows) in a renal cancer patient confirmed with coronavirus disease 2019 pneumonia; C: Axial CT image showing multifocal ground-glass opacities in the right lung (orange arrows) and nodular consolidation (black arrow) in a renal cancer patient diagnosed with immune-related pneumonitis after treatment with nivolumab; D: Axial CT image of a patient suffering from immune-related pneumonitis showing multifocal, bandlike consolidation in the left lower lobe (arrows) with peripheral sparing (asterisk) suggesting organizing pneumonia; E and F: The last is a case of immune-related pneumonitis in a patient undergoing ipilimumab plus nivolumab for metastatic soft tissue sarcoma, whose baseline axial CT image (E) shows bilateral solid metastatic nodules; the axial CT image obtained after starting immunotherapy (F) shows new multifocal ground-glass opacities (orange arrows) with interval enlargement and an increasing number of pulmonary nodules (black arrow).

In addition to immune checkpoint inhibitors, other anticancer drugs such as tyrosine kinase inhibitors (*i.e.*, gefitinib, erlotinib, crizotinib, osimertinib, panitumumab, cetuximab, and others), mTOR inhibitors (everolimus, temsirolimus), and chemotherapy (topotecan, bleomycin, gemcitabine, and others) can induce an interstitial pneumonitis[56]. To date, neither radiological nor clinical features can help the physician in the differential diagnosis. The rapid development of cardiovascular complications, such as acute pericarditis, left ventricular dysfunction, acute myocardial injury, embolic complications due to coagulopathy, such as disseminated intravascular coagulation, venous thromboembolism, or massive pulmonary embolism, with or without detection of the virus, can address the diagnosis of COVID-19[57].

Although lymphopenia and a high level of D-dimer and C-reactive protein are often identified in COVID-19 patients, these laboratory findings are not unique and are inadequate to address the proper diagnosis, especially in cancer patients.

Our systematic review has several limitations, including the mostly retrospective nature and the heterogeneity of the included studies.

CONCLUSION

The patient's global view of epidemiological, clinical, radiological, and laboratory elements could help the physician overcome the diagnostic difficulties in the COVID-19 era.

ARTICLE HIGHLIGHTS

Research background

Several radiological features are shared by coronavirus disease 19 (COVID-19) pneumonia and other infective or non-infective pulmonary diseases.

Research motivation

The differential diagnosis of COVID-19 pneumonia is a radiological challenge.

Research objectives

To identify crucial radiological features of COVID-19 pneumonia reported by the literature and their differential diagnosis.

Research methods

We performed a systematic review with a descriptive aim.

Research results

Ground-glass opacity and consolidations are the most common computed tomography lesions in COVID-19 pneumonia and other respiratory diseases. Of the identified 133 studies, 18 were eligible and included in this review. Single lesion associated with pleural effusion and lymphadenopathies distinguishes COVID-19 pneumonia from early lung cancer. Only two studies included cancer patients, and the differential diagnosis with early lung cancer and radiation pneumonitis was performed. The onset of the lesions in the radiation fields only allows the differential diagnosis between COVID-19 pneumonia and radiation pneumonitis.

Research conclusions

Computed tomography scan is essential for the differential diagnosis of drug-induced pneumonitis, infectious pneumonia, and other conditions such as cancer progression.

Research perspectives

The focus on patients with cancer evidenced a wide lack of data in this field, suggesting at least retrospective collection of data in this population.

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