Integrated Radiologic Algorithm for COVID-19 Pandemic

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A new coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) is contaminating the world; it has originated from China and has been infecting people since December 2019.[1] Like other viruses, SARS-CoV-2 harbors in human cells and results in different degrees of cellular damage. The rapid diffusion and brutal effect of this virus have caused it to be rapidly ranked as a global threat, currently known as SARS-CoV-2 disease (COVID-19)[2] and defined as a pandemic by the World Health Organization on March 11, 2020.

The clinical presentation of COVID-19 might mimic seasonal flu,[3] but it is nothing like that. COVID-19 has a much greater potential for diffuse alveolar damage (DAD), the therapy of which demands advanced respiratory assistance including artificial ventilation. Median age of COVID-19 is around 60 years, and its outcome strictly depends on the preparedness to appropriate clinical management, ranging from 1.4% to 15% mortality in China.[3,4] Mortality in Italy is 8.1% (March 14, 2020).[5] No one country in the world is prepared with sufficient capacity for this scenario, but might be able to adapt rapidly using shared experience. This is the ethical reason for this article that originates from the Italian area of COVID-19 burst in late February 2020.

Early experience on clinical management of COVID-19 came from China.[6] Chinese colleagues taught us about the limited accuracy of biological verification of SARS-CoV-2, and the potential role of medical imaging for triaging a patient referring with severe respiratory symptoms.[7,8]

Advantages of imaging were capacity and dispatch, something that substantially complements the time-consuming process of handling and analyzing biological samples from nasopharyngeal or oropharyngeal swabs.

When COVID-19 was notified in Northern Italy (late February 2020), our regional parliament issued COVID-19 guidelines to organize first-level dedicated triage for respiratory symptoms, integrated with second-level triage including radiography and computed tomography (CT). First impression on this political decision raised some skepticism: no thoracic radiologist would ever propose radiology for management of respiratory virus, because we know its limited accuracy in the etiological definition of DAD and/or organizing pneumonia, namely the main underlying pathologic abnormalities in lung involvement from COVID-19.[9] Indeed, our local first critical impression was substantially in line with the recent position statement of the American College of Radiology (ACR) on March 11, 2020.[10] Nonetheless, we were somehow induced to use imaging and to witness its practical approach in this unique contingency where pretest probability of one specific etiology is substantially higher than any other hypothesis and swab-test results. First, we decided to use both radiography and CT, notably to use mainly radiography and offer supplementary CT in more severe cases or cases in whom radiography was difficult to interpret. This strategy quite overlaps the current ACR recommendation.[10] But practical experience soon showed dilated times for swab analysis (> 24 h) and the need to switch from radiography to CT with the purpose of increasing "both sides" of accuracy in a clinically integrated quick workflow:

- *Rule-out task of radiology*: CT allows some confidence in the definition of alternative diagnosis for severe acute respiratory symptoms and discharging the suspect of COVID-19 in favor of other diagnoses (eg, lobar pneumonia, bronchiolitis, heart failure etc.).
- *Rule-in task of radiology*: CT allows to detect subtle diffuse ground-glass opacities that are variably detected by radiography (think about supine radiography in severely ill patients) and are associated with a wide range of clinical severities (Fig. 1).

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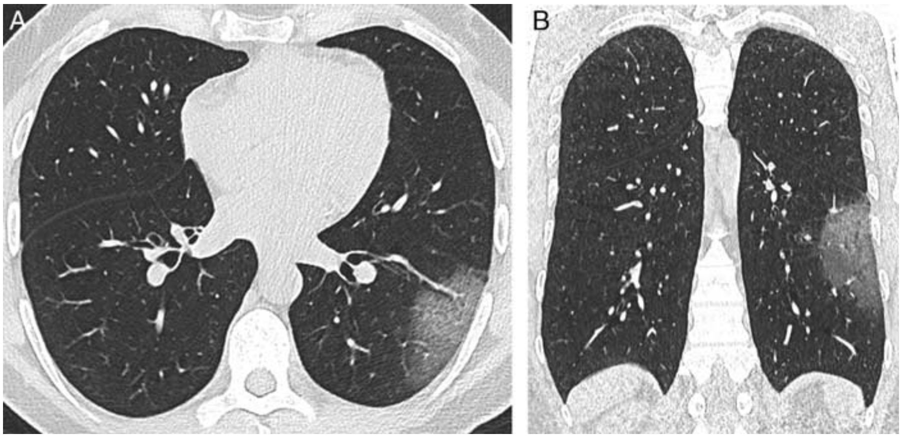

FIGURE 1. CT image in axial (A) and coronal (B) planes showing pure ground-glass opacity in the superior segment of the left lower lobe. This finding might be extremely subtle on radiography or even overlooked (especially with suboptimal quality of radiography, for instance anteroposterior projection). Of note, COVID-19-related abnormalities may be asymmetrical in distribution, making radiography diagnosis even more uncertain.

Still, we are well aware of the diagnostic limits of CT, including the following (and they are):

- *Atypical patterns of COVID-19*: it can be seen when other lung disorders (eg, extensive emphysema, lung fibrosis) are present, or in immune deficiency, the latter being known to determine atypical pulmonary CT findings.[11]
- *Temporal evolution of disease*: early negative CT can be interpreted as absence of pneumonia, but does not tell anything about the presence of infection from SARS-CoV-2.[3] Furthermore, subjects with normal CT may develop severe COVID-related pneumonia shortly (eg, in 2 days).[12]

On the basis of scientific data, knowledge in thoracic radiology, and our Institutional intensive experience with COVID-19 epidemic, we drew and adapted an integrated radiologic algorithm based on the first 702 cases of patients who referred to dedicated COVID-19 radiology protocol after first-level clinical triage in a dedicated emergency unit (Fig. 2A).

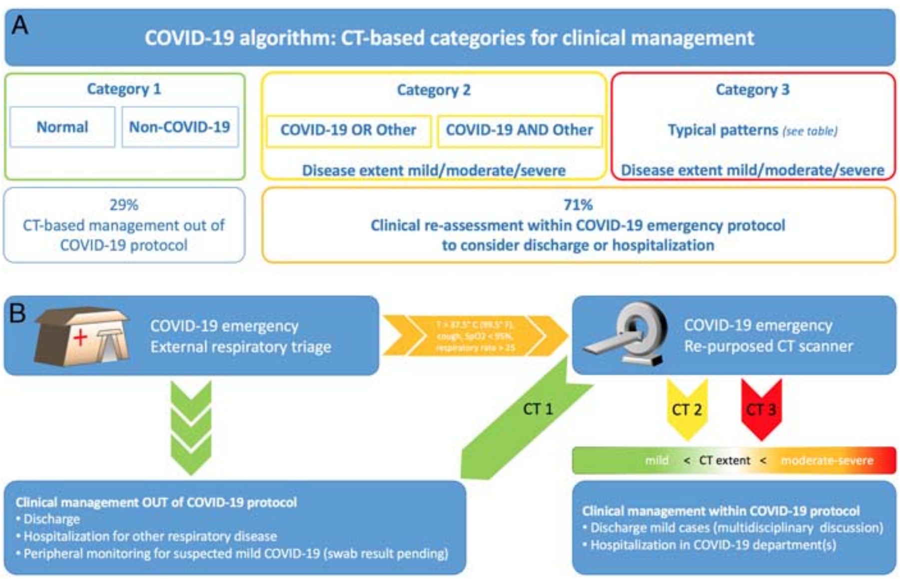

FIGURE 2. Flowchart A, CT diagnostic categories in the COVID-19 protocol. Radiologic integrated contribution is established with 3 major categories that specifically refer to COVID-19: category 1 (green border) encompasses both normal CT and CT with signs of exclusive non-COVID-19 disease; category 2 (yellow border) is meant as indeterminate category that includes 2 main complex scenarios with COVID-19 as alternative or overlapping disease; category 3 encompasses typical patterns recently associated with COVID-19. Both category 2 and 3 are also scored with a CT severity index for description of disease extent, in the attempt of assisting clinicians with the most complete information. Bottom boxes show the proportion of subjects who are discarded from the COVID-19 protocol on the basis of integrated radiologic algorithm (29%), thus reducing the number of patients who are kept in COVID-19 protocol for further clinical assessment. Flowchart B, Integrated COVID-19 protocol with flowchart showing the patient path from the admission to the respiratory triage, selection of those who are to undergo radiology integration based on clinical parameters, CT assessment based on the 3 defined radiologic categories of COVID-19 protocol, and subsequent clinical assessment for appropriate hospitalization or tentative discharge.

FIGURE 3. Axial CT image of a clearly different diagnosis, namely cavitary consolidation in the right upper lobe in a patient presenting at the respiratory triage during this COVID-19 epidemic.

PROPOSED INTEGRATED RADIOLOGIC ALGORITHM

The basic rationale of this radiologically integrated algorithm is the use of CT to safely triage the massive load of acute respiratory referral during a specific period of pandemic, now called COVID-19. This algorithm is based on practical experience in this contingency and absolutely does not find application out of the aforementioned dramatic scenario.

The classification of CT findings was defined by 3 major categories:

(1) Negative for COVID-19.
(2) Indeterminate for COVID-19.
(3) Typical pattern of COVID-19.[13]

Category 1—Negative for COVID-19

Category 1 includes both normal CT and CT signs certainly attributable to a specific disease, with the aim of ruling out from the dedicated COVID-19 protocol. This category was meant and assigned with *absolute caution*, to minimize false negatives. We observed 16% (111/702) cases with normal CT despite decent clinical symptoms and blood gas abnormality. Further, 13% (90/702) cases were highly consistent with other disorders (Fig. 3). Overall, category 1 allowed to exclude 29%

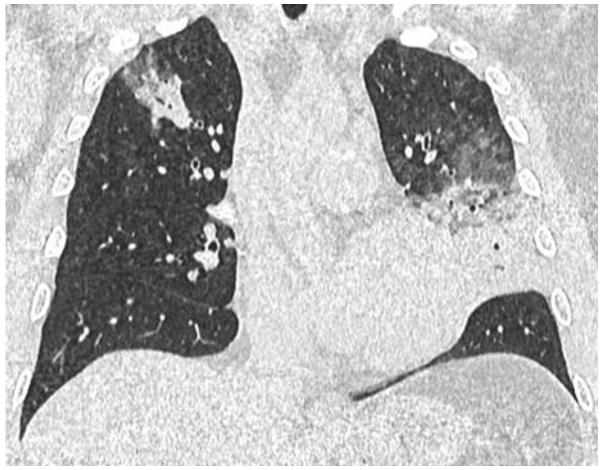

FIGURE 5. Coronal reformation of CT image showing multifocal opacities with ground-glass and consolidative component, with some perilobular distribution. Prospective reporting was category 2, including the potential diagnosis of bacterial pneumonia or COVID-19. Two days after CT, the swab was positive for SARS-CoV-2.

of referrals from the COVID-19 protocol: a substantial help in the process of patient selection for dedicated respiratory care. Among those with completely negative CT, we report 5% (6/111) later onset of CT findings of COVID-19 (within 1 wk, CT performed for further clinical worsening), which is an important limitation of the different clinical-radiologic phases of this disease (Fig. 4).

The amount of negative CT might be explained by diseases that are not visible at CT (eg, acute exacerbation of chronic obstructive pulmonary disease). This specific aspect of the current algorithm will be thoroughly analyzed in due time.

Category 2—Indeterminate for COVID-19

Category 2 included 2 subsets of CT indeterminate scenarios:

- Differential diagnosis between COVID-19 *OR* other disease (Fig. 5).
- Potential overlap of COVID-19 *AND* other disease (Fig. 6).

This category includes any CT finding that does not safely suggest exclusive alternative diagnosis. We observed

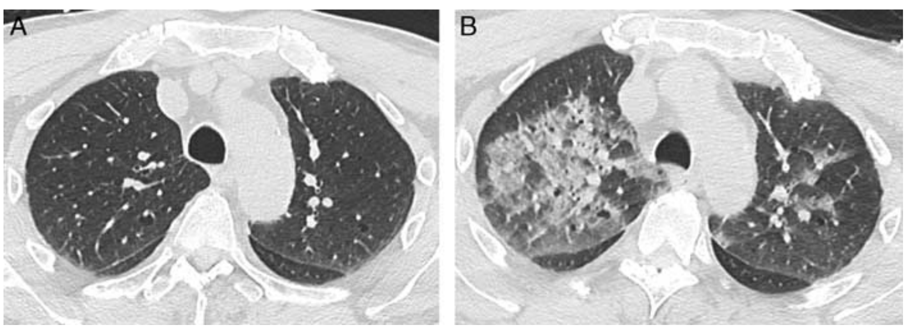

FIGURE 4. Temporal evolution in a patient presenting with respiratory symptoms on March 5, showing negative CT for COVID-19 (A) and negative swab, then returning to respiratory triage 7 days later with onset of typical CT pattern of COVID-19 with bilateral part-solid opacities (B) confirmed by a positive swab a further 2 days later.

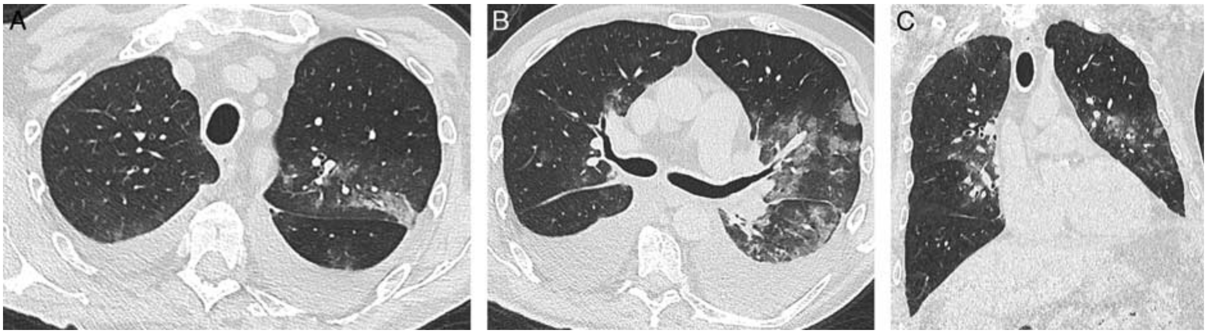

FIGURE 6. CT image in axial (A, B) and coronal (C) plane showing ground-glass opacities with heterogeneous distribution on axial plane (both central and subpleural), as well as some perilobular distribution, associated with massive bilateral pleural effusion. Prospective reporting was category 2 for potential overlapping of COVID-19 and supervening heart failure. One day after CT, the swab was positive, and heart failure was confirmed by evolution after diuretic therapy. Noteworthy, we observed elderly and cardiopathic patients displaying overlapping of COVID-19 and heart failure with potential overlapping of ground-glass opacities from infection and edema.

10% (72/702) patients with differential diagnosis and 9% (66/702) patients with potential overlap. Overall, category 2 was assigned in 19% of cases. In our experience, this category ranged through the historical period, with less indeterminate cases in the early days after COVID-19 outbreak (5/40 patients, namely 13% of all patients undergoing CT), then progressively increasing with more days into the epidemic of this area (11/51 patients, namely 22%). Again, several epidemiological considerations of these categories are strictly applicable in the epidemiological setting of such specific contingency.

Comparison with prior CT will be very helpful in defining the differential with overlapping patterns and prompt appropriate classification, especially in oncologic patients and patients with immune deficiency.

Category 3—Typical Pattern of COVID-19

Category 3 includes a number of typical patterns of COVID-19 with a range of disease phases and severity. Category 3 was assigned in 52% (363/702) of cases, and it always prompted clinical assessment for further stratification of risk and optimal management, within the available facilities of COVID-19 protocol (over 350 extra/converted beds).

CT pattern was included in the attempt of depicting different phases of the disease and, hopefully, to assist the clinician in recognizing early and potentially evolving scenarios from more mature and potentially more stable scenarios. We observed classical peripheral ground-glass opacity and crazy paving pattern, also recognizing the spectrum of the DAD-related initial phases at CT, essentially exudative (Fig. 7), or organizing (Fig. 8). Furthermore, in keeping with previous findings, we observed multiple ground-glass nodules (of variable size) randomly distributed in the lungs.

Potential Utility of Disease Extent by Visual Assessment

CT severity index of COVID-19 was elaborated to stratify among subjects with category 2 or 3 disease. Both morphology and extent were categorized.

The degree of lung parenchymal involvement (defined as "extent") was included in the attempt to assist the clinician in the hospitalization, and was classified into mild, moderate, and severe (Table 1, Fig. 9). The supervening massive situation ought to try and define some very low-risk strata among category 2 and 3 patients by definition of extremely small findings on CT to be integrated with clinical parameters and to allow early discharge from hospital with peripheral follow-up (general practitioners are involved in peripheral monitoring of COVID-19) (Fig. 2B). Mild extent in both category 2 and 3 was based on the subjective experience of the first 702 cases, with the aim of stratifying a group of low-risk patients to discharge and

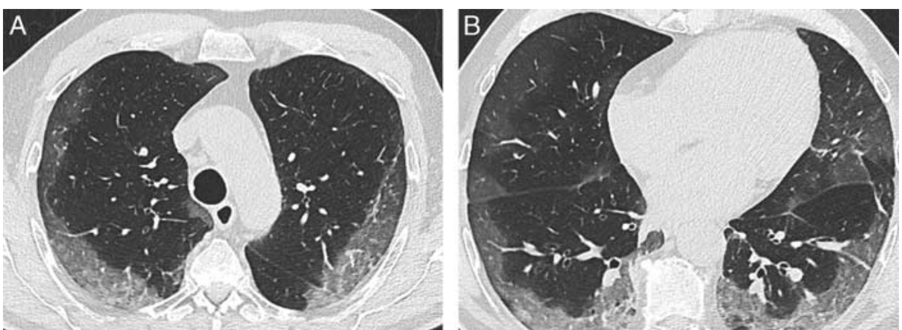

FIGURE 7. A and B, Axial CT images showing large ground-glass opacities mostly distributed in subpleural regions, with severe extent involving all lobes. These CT findings are recognized among the range of typical CT patterns for COVID-19.

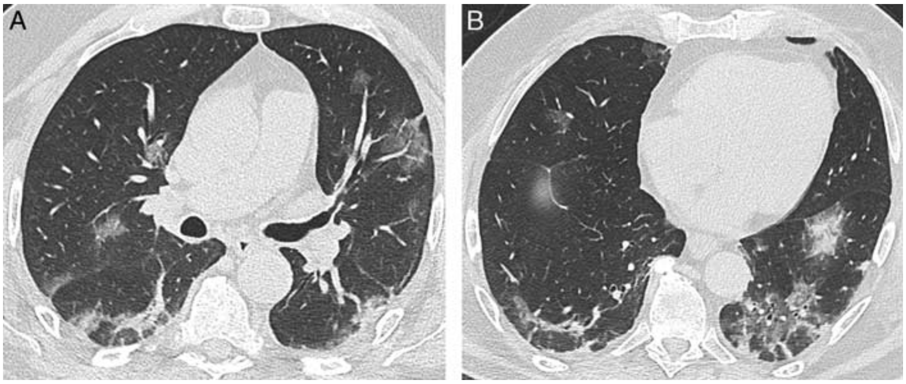

FIGURE 8. A and B, Axial CT images showing multifocal parenchymal opacities with both ground-glass component and consolidation, notably with perilobular distribution and signs of distortion suggesting organizing pneumonia.

potentially further carving the number of patients admitted in the dedicated COVID-19 respiratory protocol for respiratory assistance. If the reporting radiologist is undecided between mild and moderate disease, multidisciplinary discussion is suggested.

These codes allow very quick reporting time by the thoracic radiologist, notably well below 2 minutes in the majority of cases, with some extra time needed when atypical cases are read (observed 19% in overall workload). The number of dedicated CT scanners will depend on the size of the center (24/7 service granted by 2 dedicated scanners in our center, with further 4 scanners for non-COVID-19 clinical activity). Further details of CT workflow management will apply, including times for sanitation of the CT room and any room where patients are supposed to wait to supply a continuous flow.[14]

We are sharing this algorithm to let colleagues know, discuss, and prepare in advance with a strategy that we would have never thought about until 4 weeks ago, but now we see it as one good option to manage the humongous wave of admittance for acute respiratory symptoms and the consecutive overload of the intensive care unit. Now, we are using these diagnostic categories and integrating them with clinical data to face the admittance overflow and to control hospitalization, potentially selecting for discharge those with limited disease. Future studies will clarify the prognostic value of this integrated algorithm.

TABLE 1. CTc Ategories of the Proposed in Tegrated Radiologic Algorithm for COVID-19 Pneumonia

		EXTENT Definition*
Category 1	NORMAL	
	NON-COVID DISEASE—Report alternative diagnosis	
Category 2	INDETERMINATE FOR COVID	
	Differential diagnosis COVID-19 OR other disorders	
	Up to 3 focal abnormalities (up to about 3-4 cm in maximum diameter)	Mild
	More than 3 focal abnormalities (above 3-4 cm in maximum diameter)	Moderate/severe
	Suspected overlap COVID-19 AND other disorders	
	Up to 3 focal abnormalities (up to about 3-4 cm in maximum diameter)	Mild
	More than 3 focal abnormalities (above 3-4 cm in maximum diameter)	Moderate/severe
Category 3	TYPICAL	
	Pure patchy ground-glass opacities	
	Up to 3 focal abnormalities (up to about 3-4 cm in maximum diameter)	Mild
	More than 3 focal abnormalities (above 3-4 cm in maximum diameter)	Moderate/severe
	Focal ground-glass opacities admixed with "early" consolidation	
	Up to 3 focal abnormalities (up to about 3-4 cm in maximum diameter)	Moderate/severe
	More than 3 focal abnormalities (above 3-4 cm in maximum diameter)	Moderate/severe
	Diffuse ground-glass opacities (distribution may be heterogenous)	Severe
	Ground-glass admixed with perilobular opacities or consolidation with signs of distortion†	Severe

*Differential between "moderate" and "severe" is entirely subjective and will not impact on the decision for hospitalization (Fig. 8).
†This category was chosen in the presence of conspicuous organized consolidation, despite the predominant pattern still being ground-glass.

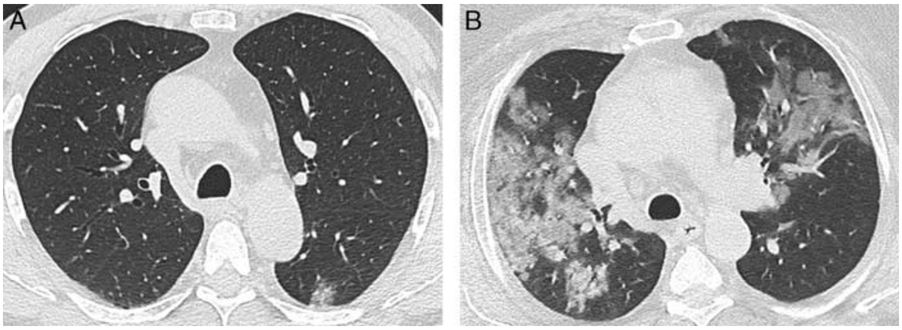

FIGURE 9. Axial CT images showing mild (A) and moderate/severe (B) extent of pulmonary involvement in patients admitted to COVID-19 protocol, later confirmed with positive swab for SARS-CoV-2. Noteworthy, differentiating between mild and moderate/severe (Table 1) might be relevant to assist integrated clinical management. Otherwise, the difference between moderate and severe extent is subjective and is not meant to influence the decision about hospitalization (Table 1).

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