

Review

Radiomics in COVID-19: The Time for (R)evolution Has Come

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Abstract: The pandemic caused by the new coronavirus in 2019, now called SARS-CoV-2 or COVID-19 disease, has become a major public health problem worldwide. The main method of diagnosing SARS-CoV-2 infection is RT-PCR, but medical imaging brings important quantitative and qualitative information that complements the data for diagnosis and prediction of the clinical course of the disease, even if chest X-rays and CT scans are not routinely recommended for screening and diagnosis of COVID-19 infections. Identifying characteristics of medical images, such as GGO, crazy paving, and consolidation as those of COVID-19 can guide the diagnosis, and can help clinicians in decisions in patient treatment if an RT-PCR result is not available rapidly. Chest radiographs and CT also bring information about the severity and unfavorable evolution potential of the disease. Radiomics, a new research subdomain of A.I. based on the extraction and analysis of shape and texture characteristics from medical images, along with deep learning, another A.I. method that uses neural networks, can offer new horizons in the development of models with diagnostic and predictive value for COVID-19 disease management. Standardizing the methods and creating multivariable models that include etiological, biological, and clinical data may increase the value and impact of using radiomics in routine COVID-19 evaluation. Recently, proposed complex models that may include radiological features or clinical variables have appeared to add value to the accuracy of CT diagnosis by radiomix and are likely to underlie the routine use of radiomic in COVID-19 management.

Keywords: radiomics; COVID-19; SARS-CoV-2; deep learning; imagistics; CT



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1. Introduction

With the aid of high-performance computers, it is now possible to quickly extract countless quantitative features from medical imaging such as digital radiographs, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). The modern concept of radiomics consists in extracting mineable data from high-resolution medical images, starting from the principle that these images contain information about pathological processes that the eye of the medical imagist expert cannot perceive. Radiomics is a subdomain, and an extension, of computer-assisted diagnosis and detection (CAD) systems, the advantage of radiomics being the extraction of a large number of quantitative characteristics that can be analyzed and selected later to generate models with applicability in diagnosis and treatment [1].

The new COVID-19 disease, named from coronavirus 2 acute respiratory syndrome (SARS-CoV-2) and by the year of its first detection (2019), became a major public health emergency of international interest less than 3 months after its onset. There is currently no specific treatment, and low vaccination rates in many countries. China, Italy, Great Britain, France, Spain, and the United States of America have recorded a worrying number of cases and deaths. About 6 months after the start of the pandemic, its epicenter was in Latin America, the most affected country being Brazil with 1,151,479 cases and 52,771 reported deaths on 24 June 2020 [2].

The SARS-CoV-2 Delta strain variant (B.1.617.2), which was identified in India during wave 2, and the more recently identified strain B.1.1.529, called Omicron by the World Health Organization (WHO), is of concern and there are still uncertainties. If we are facing an increased rate of transmission compared to the Delta strain due to a higher affinity for human ACE2 caused by SARS-CoV-2 virus mutations, given the potential severity of the disease, concern remains, especially in countries with low rates of vaccinations. It is therefore obvious that an improvement in imaging diagnosis and a prediction of the evolution with potential severity are topics of interest. Today, 2 years after the onset of the COVID-19 pandemic, nearly 5.5 million deaths have been reported due to complications associated with SARS-CoV-2 infection [3,4].

2. Imagistics in COVID-19

The diagnosis of COVID-19 is confirmed by reverse transcription polymerase chain reaction (RT-PCR); however, the existence of false-negative results, and also some technical difficulties, especially the lack of centers where these determinations can be performed in certain regions of possible pandemic outbreak, make it necessary to develop rapid and non-invasive methods of early diagnosis. Among these non-invasive imaging methods, computed tomography (CT) can bring medical information from the lungs with the screening, diagnosis, and triage value, in the case of the new COVID-19 disease. Unfortunately, it is difficult to discriminate COVID-19 pneumonia from other types of pneumonia, such as influenza, bacterial, and mycoplasma pneumonia [5,6].

Computed tomography (CT) of the chest demonstrated a sensitivity of 97% and a specificity of 25% in a study that included 1014 COVID-19 patients. The correlation between RT-PCR test results and chest CT demonstrated the value of CT medical imaging in the diagnosis of the new coronavirus disease. Adding the advantages of artificial intelligence (AI), using machine learning technology, especially radiomic analysis, in the medical field can maximize the role of medical images in this crisis. Being an infectious disease, there are no gold-standard criteria for the diagnosis of COVID-19, as the RT-PCR test or CT imaging alone as diagnostic methods are not sufficiently accurate for a precision diagnosis [7].

Either a parallel test variant, in which the RT-PCR test and the CT imaging are performed simultaneously, or a serial test variant is chosen, in which case the CT scan has the role of a secondary screening test, performed only if the test is initially positive, and an imagistic approach of the disease is a necessary complementary method [8].

Ground glass opacity (GGO) is a typical CT image; however, the radiological diagnosis of accuracy is dependent on subjective evaluation, which is based on the experience of the imagist physician. Using 348 CT scans obtained from 112 patients, Ding et al. classified CT images according to the period from the onset of the initial symptoms into six classes starting from 0–4 days and up to >28 days. The three features of the CT images identified (GGO, crazy paving pattern, and consolidation) were evaluated for each lung lobe. Class 5, representing the 22–28-day interval, was associated with crazy paving pattern, consolidation, and linear opacities. The lower lobe was generally associated with high CT scores, and in class 6, at more than 28 days, CT pathological changes persisted in most cases. The authors note rapid changes in CT images at the onset of the disease, followed by long-term stability of the highlighted lesions [9].

However, some authors consider the diagnostic value of CT imaging in the early stages of COVID-19 disease to be limited. Lymphadenopathy, pneumothorax, and pleural

effusions are rare in COVID-19 disease, but multilobar, bilateral, and peripheral ground-glass opacities are considered characteristic lesions in advanced stages of the disease. Akçay et al. consider that chest CT may be used for early diagnosis in viral infections for patients with normal chest X-rays. The authors proved that the specific lesions show in most cases bilateral involvement of peripheral and diffuse distribution with the pattern of GGO. The British Society of Thoracic Imaging classifies CT imaging characteristics of COVID-19 pneumonia, considering 100% probability for a characteristic appearance with multiple, bilateral opacities, predominantly in the lower lobes, peripheral, with ground glass appearance, crazy paving and peripheral consolidation, air bronchogram, and converse halo sign. The authors of a study from China highlighted thoracic imaging changes in the case of COVID-19 pneumonia associated with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from unilateral opacity to bilateral diffuse opacity. The lesions progressed or coexisted with consolidations for 1–2 weeks. The study identified a sensitivity of 97.2%, and the inclusion of clinical and biological data can generate algorithms that increase the accuracy of the diagnosis [10–14].

In an Italian trial, using CT images obtained from 158 patients, Caruso and collaborators evaluated the sensitivity and specificity of the CT method, obtaining 97% and 56%, respectively. In a subgroup of patients, RT-PCR positive and CT-positive GGO were present in 100% of cases, and in 93% of patients presenting with multilobar and posterior involvement. Bilateral pneumonia was identified in 91% of cases and subsegmental enlargement of vessels > 3 mm was identified by the authors as a COVID-19 pattern, being observed in 89% of cases. Analyzing CT images obtained from three patients diagnosed with COVID-19, the only similar finding in the images was a solitary sub-centimeter GGO adjacent to the broncho-vascular bundles, considered by the authors to be unobservable, and COVID-19 pneumonia had the same node as its starting point [15,16].

Although less performant in the detection of COVID-19 than chest CT, chest radiography is much more accessible and is one of the diagnostic methods used in the first line in the evaluation of suspected COVID-19 patients. In addition, portable X-ray units have the advantage of possibly easier decontamination. The sensitivity of chest radiographs is lower than that of CT, the images may be normal in early and asymptomatic cases of chest X-rays. In COVID-19 cases requiring hospitalization, 69% of patients had an abnormal chest radiograph at baseline, and 80% of patients had pathological changes in chest radiographs during hospitalization, the frequency of changes in hospitalized patients being highest at 10–12 days from the onset of symptoms [17].

Vancheri evaluated X-ray findings to reveal GGO as the most common lesion in the intermediate/late phase of SARS-CoV-2 infection. The most common early lesions were reticular alteration and consolidation increased over time. Most frequently, the lesions were identified bilaterally and peripherally, in the middle and lower lobes. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement are some of the less common findings and usually occur during the course of the disease. Pleural effusion, pericardial, halo sign, lymphadenopathy, cavitations, and pneumothorax occur rarely but may be associated with evolution. In addition, during the course of the disease an increase in the number and size of GGO and their evolution can be observed, along with a tendency to consolidate and the development of crazy paving, reaching maximum severity 10 days after the onset of symptoms. Gradual resolution of opacity consolidation and a decrease in the number of lesions usually occurs after 2 weeks and is associated with a favorable clinical response [18,19].

A retrospective analysis of images of patients in Shanghai (China) with incipient COVID-19 disease (<4 days after the onset of symptoms) described CT lesions including lesion distribution, maximum axial section size, and attenuation category (from I to IV), pleural effusion signs in relation to lesions such as bronchogram, and vessel expansion, mediastinal lymphadenectasia > 1 cm in short axis diameter. CT score is defined as size (in centimeters) X attenuation category weight (from 1 to 3; 1 for category I, 2 for category II/III and 3 for category IV). Attenuation categories are defined as type I-pure GGOs,

type II GGOs + consolidation, type III GGOs with interlobular septal thickening, and type IV-consolidation [20].

The standardization of suspected pulmonary involvement in CT imaging has resulted in the design of a score called COVID-19 Reporting and Data System (CO-RADS), in order to facilitate communication and reporting between specialists. Based on unenhanced chest CT images, the score is applicable to cases with moderate and severe forms of the disease, proposing a scale from 1 to 5 according to the BI-RADS score used in the imaging evaluation of breast cancer [21,22].

3. From Imagistics to Radiomics

Radiomics is one of the most interesting and challenging directions in radiology research, involving data and artificial intelligence (AI), but also offers optimistic perspectives through image transformation in mathematical numbers. The central idea behind radiomics is currently limited by difficulties in data standardization. Multidimensional quantities extracted from sets of CT or MRI images, PET-CT, and radiographs and ultrasonographs are transformed into mineable data with potentially applications in medicine. The radiomic process can be divided into distinct stages, starting with image acquisition and reconstruction, image segmentation, extraction of radiomic characteristics, evaluation of the significant value of the features, and model construction. Each stage of radiomic analysis is essential for building robust and reliable models in order to be transferred into clinical practice for diagnosis and prognosis, radiomics being a method of noninvasive disease monitoring and assessment of disease response to treatment. After defining the texture parameters, among which shape characteristics, texture, and grey levels matrix must be maintained, it is necessary to select the parameters useful for a radiomic approach. Principal component analysis, random forest, linear regression, logistic regressions, non-linear support vector machine, neural network, and cluster analysis are the most widely used methods in the selection of significant radiomic features [23–26].

With the development of radiomics, another field of AI has shown potential to increase the accuracy of COVID-19 detection. Deep learning is different from radiomics, being based on the development of deep artificial neural networks that were inspired by biological neural networks. Neural networks can learn an algorithm from existing data by training themselves to recognize some features of new objects and data introduced in the analysis system. Unlike deep learning, radiomics extracts the spatial aspect of the tissue of interest's shape and texture on different types of images, converting the characteristics of textures and patterns to gray levels, analyzing the relationships between neighboring pixels, and spectral properties in regions of interest for medical images. Radiomics features such as first order entropy or gray level cooccurrence matrix (GLCM) entropy are measures of tissue heterogeneity [27–29].

Rapid and accurate diagnosis of COVID-19 is essential and radiographs and CT images are the most used in attempts to improve the use of radiomic and deep learning algorithms in the management of this disease. In order to develop a radiomic model to discriminate cases of COVID-19 from non-COVID-19 pneumonia cases, Chen and collaborators selected as significant 80 imaging semantic features and 70 clinical variables extracted from 70 COVID-19 patients and 66 non-COVID-19 pneumonia patients. Dividing patients into two cohorts (98 patients in the primary cohort and 38 patients in the validation cohort) and using chi-square, Student, and Kruskal–Wallis H tests, the authors constructed three models based on multivariate logistic regression. These radiomic models were built using semantic and clinical radiological features by multivariate logistic regression. Predictably, GGO and consolidation in the periphery are significant variables for differential diagnosis. In addition to these COVID-19-specific lesions, the size of the lesion (1–3 cm) was also considered significant. The authors thus demonstrate the value of a multivariable model including both clinical and semantic imaging data in the differential diagnosis of pneumonia of COVID-19- or non-COVID-19 etiology [30].

Negative RT-PCR testing is the key criterion for hospital discharging for patients diagnosed with COVID-19. Periodic repetition of RT-PCR tests leads to increased expenses and prolonged hospitalizations, without being able to estimate the time of recovery and healing. A group of researchers from China have proposed a radiomic algorithm that can predict the negation of RT-PCR tests during treatment using radiomics and clinical features in order to assess the optimal time for retesting. Using a deep learning algorithm for lesion segmentation that automatically extracted radiomic features from images obtained from 203 patients with mild COVID-19, the authors used Spearman regression and correlation analyses to select the strongest feature predictors of RT-PCR negativity. The authors found a correlation between RT-PCR negation with a longer interval from the onset of symptoms and CT examination and selected nine CT radiomic features for model construction. In conclusion, the study demonstrated the ability of a model that includes both clinical and radiomics variables to predict RT-PCR negation during treatment for COVID-19 disease.

Another topic of interest in the management of the disease produced by the new SARS-CoV-2 is the evaluation of prognosis and the stratification of risk. The development of a model based on a radiomic signature using CT chest imaging would be a non-invasive tool that can modify, based on data initially obtained in the early stages of the disease, the management and surveillance of patients with severe evolution potential. Wu et al. propose a radiomic model that individually predicts progression with possible death, need for hospitalization in intensive care units (ICU), and need for mechanical ventilation in patients with COVID-19, using CT images obtained from 492 patients. Given the differences between the time interval from the onset of symptoms to the CT scan moment, the authors divided the images into two categories, considering one and two weeks as the cutoff values. For the first group of patients, automatic image segmentation was used and in the second set, a minimal image pre-processing was performed. Using three prognostic models: clinical, radiomic (RadScore), and combined clinical-radiomic (CrrScore), the study predicted cumulative outcome and 28-day outcome. In an early-phase group CrrScore demonstrated predictive power for both endpoints. RadScore demonstrated superiority by its ability to predict progression in both patient groups. The authors recommend radiomic signature as a method of predicting poor prognosis if CT imaging is performed within 7–14 days and CT images performed within the first 7 days of onset of symptoms require a model that includes radiomic and clinical features for creating a valid predictive model. Vaid and collaborators created a deep learning model with convolutional neural networks (CNN) which automatically extracted and analyzed the characteristics of COVID-19 disease from the antero-posterior images of chest radiographs. The model demonstrated the possibility of disease detectors with an accuracy of >96.3% [29,31,32].

CoroNet is a deep convolutional neural network model that uses X-ray chest images and was proposed by researchers in New Delhi, India to automatically detect COVID-19 infection. COVID-19 pneumonia images and X-ray pneumonia chest images obtained from two publicly available databases were used to train the model. Overall accuracy was 89.6%, but where COVID-19 was identified from a set of four diagnostic classes (COVID-19 pneumonia, bacterial pneumonia, viral pneumonia, and healthy patients). When the number of diagnostic classes was reduced to three COVID-19 pneumonia vs. other pneumonia vs. healthy patients, the accuracy of detection was 98.2%. The authors believe that more data and minimal pre-processing will increase CoroNet's accuracy in the differential diagnosis of COVID-19 pneumonia with other types of pneumonia [33].

Hamid Abdollahi considered that all suspected SARS-CoV-2 people should be investigated imagistically within the department's capabilities through the same imaging protocols and using the same scanners, and the protocols could be optimized by medical physicists and physicians specializing in medical imaging to improve image quality and minimize patient exposure to irradiation. Thus low-dose protocols can be implemented in cases where chest CTs are required. For the quantitative analysis of images, Lung-RADS and CO-RADS proposed by the American College of Radiology and by the COVID-19 working group of the Dutch Radiological Society, respectively. For extracting and selecting

features an open-source Python package called Pyradiomics may be a suitable choice. Segmentation is a challenge, the author's recommendation being three-dimensional automatic segmentation algorithms if CT images are used. The concept of variation of radiomic characteristics brings attention to a new possible biomarker (delta-radiomics) for COVID-19 disease, less used in studies. Delta-radiomics dynamic evaluation can bring important data about the clinical evolution with impact on the therapeutic approach [34].

The concept of proposing complex clinical and radiomic models with higher predictive and diagnostic powers has been successfully tested in both laboratory animal research and clinical trials. The study proposed by Liu et al. seeks to assess the differential diagnostic power between COVID-19 and non-COVID-19 pneumonia and succeeds in demonstrating the superiority of the combined clinical and radiomic model over the clinical model in differential diagnosis. The study included 115 confirmed COVID-19 patients and 435 cases of non-COVID-19 pneumonia. A model was created from eight radiomic features and five clinical variables. The validation of the results was performed by two radiologists according to the CO-RADS standardization. The concept of a complex diagnostic tool is also proposed by Yang, who created a model for differential diagnosis including radiomic features, traditional radiological features, quantifying features, and clinical variables. The Support Vector Machine (SVM) model was created based on semi-automated features outlined in 326 chest CT images, with groups of patients with COVID-19 and non-COVID-19 pneumonia being comparable. Assessed individually, the characteristics of the four groups that made up the complex model showed much lower accuracy in performing differential diagnosis, except for radiomic features [21,35].

The prediction of mechanical ventilation and mortality using computational analysis of digital radiographs for COVID-19 patients was proposed in a study that included 515 patients treated at the Stony Brook University Hospital and the Newark Beth Israel Medical Center. Three machine learning methods (linear discriminant analysis, quadratic discriminant analysis, and random forest) analyzed the radiomic features extracted from digital radiographs, but the authors also propose deep learning algorithms. The author concludes that a combined model that would associate radiomics analysis with the subjective assessment of the CT images by an expert physician would provide superior predictive power to any individual method. In COVID-19 patients, the association of subjective analysis with the radiomic model demonstrates increased predictive power regarding the mortality and the need for mechanical ventilation of COVID-19 patients [36].

In a retrospective study that included 301 lung lesions from 60 COVID-19 patients and 74 patients with atypical pneumonia, lesions were evaluated by CT to discriminate atypical pneumonia from COVID-19 pneumonia. The authors then proposed a comparative assessment for each type of lesion by the radiomic method. Of the 301 lesions, 150 were GGO, 52 crazy paving, and 99 consolidation. For radiomic analysis, localization, size, and shape first- and second-order features were extracted. In comparing the two lots of patients, significant differences between radiomics features were identified for GGO and consolidation. In the case of crazy paving, only one radiomic feature was different between atypical pneumonia and COVID-19 pneumonia CT images. Overall, radiomics demonstrated 80% accuracy in the diagnosis of COVID-19 pneumonia and 81.1% in the diagnosis of atypical pneumonia. An accuracy of 81% in the detection of COVID-19 was also demonstrated by Santone and collaborators, radiomics being considered a tool that should help the pathologist and the radiologist in the diagnosis of COVID-19 disease [37,38].

A set of 833 quantitative features from 157 COVID-19 patients were used to propose a radiomic model for early prediction of COVID-19 pneumonia prognosis (clinical stage, death, and complications). Least Absolute Shrinkage and Selection Operator (LASSO) was used to reduce and filter features and build a radiomic signature. A predictive accuracy for death, stage, complication, and ARDS of 0.846, 0.918, 0.919, and 0.852, respectively, initially obtained with the help of the radiomic signature was improved after identifying the cut-off value for each end point. Thus, CT imaging radiomics demonstrates its value in the early prediction of the evolution of COVID-19 disease [32].

4. Conclusions

Medical imaging provides important quantitative and qualitative information that complements information related to the diagnosis and dynamic evolution of COVID-19 disease. The identification of characteristic patterns from medical images such as GGO, crazy paving, and consolidation can guide the diagnosis if an RT-PCR result is not available in a short time, and can bring information about the severity and potential of an unfavorable evolution. Radiomics, based on the extraction and analysis of shape and texture characteristics from medical images, along with deep learning, a method based on neural networks, can offer new horizons in creating models with diagnostic and predictive value in COVID-19 disease management. Early prediction of cases with possible poor evolution allows the medical team to improve the follow-up and clinical management of these cases. Standardizing the method and creating multivariable models that include etiological, biological, and clinical data may increase the value and impact of using radiomics in routine COVID-19 evaluation. Delta-radiomics, the variation of some radiomic features during treatment, is a potential biomarker that is less used in the evaluation of COVID-19. Due to its huge potential and non-invasive nature, radiomics must be optimized for routine use in the medical approach to COVID-19 disease. Recent proposals of complex models that may include radiological features or clinical variables appear to add value to the accuracy of CT diagnosis by radiomics and are likely to underlie the routine use of radiomics in COVID-19 management. We estimate that the context created by the increase in the number of cases with the Omicron variant of COVID-19 will lead to the initiation of radiomics studies that will evaluate the power of differential diagnosis between the initial variants of SARS-CoV-2 virus and the new Delta and Omicron variants.

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