DOI: https://doi.org/10.17921/2447-8938.2023v25n4p248-256

Prognostic Effect of Chest Computed Tomography Scan in COVID-19: a Retrospective Study

Efeito Prognóstico da Tomografia Computadorizada de Tórax na COVID-19: um Estudo Retrospectivo

Waldinei Merces Rodrigues[ab]; Ewerton Alexandre Galdeano[b]; Rogério Camargo Cardoso[c]; Marco Aurelio Freitas[b]; Laís Bertoche[b]; Dana T Codreanski[b]; Caroline Von Abel[b]; Ivan Aprahamian[d]; Nilva K. Cervigne*[d]

[a]Faculdade de Medicina de Jundiaí, Department of Internal Medicine, SP, Brazil.
[b]Hospital de Caridade São Vicente de Paulo, Department of Internal Medicine. SP, Brazil.
[c]Icon Diagnostics. SP, Brazil
[d]Faculdade de Medicina de Jundiaí, Department of Internal Medicine, SP, Brazil,
*E-mail: nilva.cervigne@gmail.com

Abstract

The number of COVID-19 disease cases and deaths reached the scale of millions worldwide. Determining risk and prognosis factors are fundamental to allow the development of personalized management strategies. The aim of this study was to correlate lung computed tomographic (CT) findings in patients affected by COVID-19 with the clinical staging of the disease and laboratory findings, and to evaluate whether these findings were effective in predicting disease evolution. Then, laboratory findings and chest CT scans of 309/616 COVID-19 positive patients were analyzed and classified according to the degree of extension of pulmonary involvement. Ground glass opacities predominated in early-phase, while crazy-paving pattern, consolidation, and fibrosis characterized late-phase disease. CT findings were significantly higher among late than early stages (p<0,05), although the indeterminate patterns were significantly associated with early-phase disease(p=0.00216). The ground-glass pattern was significantly associated with TTPA (p=0,0234), and elevated leukocyte counting (p=0,008) and D-dimer levels(p=0.001). ROC curve analysis showed an area of 0.57(95% CI 0·890–0.0623) to early disease stage, 0.764(95%CI 0.817–0.764) to the progressive stage, and 0.816(0.717–0.915) to later stages, suggesting a relevance role of chest CT findings to this disease diagnosis. The data strongly suggested the potential role of chest CT as a technique for enhancing qPCR COVID-19 positiveness capacity by speeding-up diagnosis in symptomatic cases, and predicting the outcome of SARS-CoV2 infected patients. The CT findings were also correlated with laboratory findings and disease severity, and may be of great prognostic value for stratifying the evolution of this infectious disease in hospitalized patients.

Keywords: COVID-19. Pneumonia. Chest Computed Tomography. Diagnostic.

Resumo

O número de casos e mortes pela COVID-19 atingiu a escala de milhões em todo o mundo. A determinação de fatores de risco e prognóstico ainda são de fundamental importância para permitir o desenvolvimento de estratégias de manejo personalizadas. O objetivo foi correlacionar achados tomográficos (TC) pulmonares em pacientes acometidos por COVID-19 com o estadiamento clínico da doença e os achados laboratoriais, e avaliar se os mesmos são efetivos para a predição da evolução da doença. Então, os achados laboratoriais e resultados de TC de tórax de 309/616 pacientes positivos para COVID-19 foram analisados e associados, e classificados de acordo com o grau de extensão do acometimento pulmonar. Opacidades em vidro fosco predominaram na fase inicial da doença, enquanto o padrão de pavimentação em mosaico, consolidação e fibrose caracterizaram a doença na fase tardia. Os achados tomográficos foram significativamente maiores para os estágios tardios em relação aos iniciais (p<0,05), embora os padrões indeterminados tenham sido significativamente associados com a doença em estágio inicial (p=0,00216). O padrão em vidro fosco estava significativamente associado com o TTPA (p=0,0234), a contagem elevada de leucócitos (p=0,008) e os níveis elevados de dímero D (p=0,001). A análise da curva ROC mostrou uma área de 0,57 (95% CI 0,890–0,0623) para o estágio inicial da doença, 0,764 (95% CI 0,817–0,764) para o estágio progressivo e 0,816 (0,717–0,915) para os estágios tardios, sugerindo uma relevância dos achados da TC de tórax para o diagnóstico efetivo dessa doença. Os dados fortemente sugerem o papel potencial da TC de tórax como uma técnica a ser associada ao teste de qPCR positivo para a COVID-19, a fim de acelerar o diagnóstico em casos sintomáticos e prever o desfecho de pacientes infectados. Os achados tomográficos também foram correlacionados com os achados laboratoriais e a gravidade da doença, se mostrando de importante valor prognóstico para estratificar a evolução dessa doença infecciosa em pacientes hospitalizados.

Palavras-chave: *COVID-19. Pneumonia. Tomografia Computadorizada de Tórax. Diagnóstico.*

1 Introduction

The worldwide spread of the new coronavirus pandemic disease, COVID-19, caused by the severe acute respiratory syndrome of coronavirus 2 (Sars-CoV-2), caused more than 767 million cases and close to 7 million deaths reported to WHO until May 31st, 2023, according to Johns Hopkins University survey, in the United States[1-4]; Brazil is also among the countries with the largest number of cases, with more than 37 million records, up to March of 2023.

Although most patients with this infectious disease are asymptomatic or have mild clinical symptoms, severe or critical presentations also occur, and have increased especially among older adults, obese patients, and those with associated comorbidities (i.e., hypertension, and diabetes)[5]. The clinical evolution in these individuals progressively leads to dyspnea, hypoxemia, pulmonary involvement, respiratory failure, shock, and death; 20-30% of patients need mechanical ventilation, and mortality reaches 10% of these cases[6-8].

Early detection of COVID-19 is essential to initiate adequate treatment, and isolation, and to avoid adverse outcomes. Gold standard cases confirmation is performed by identifying the viral RNA in nasal secretion through the reverse transcriptase polymerase chain reaction (RT-PCR) technique. However, despite its high specificity, the RT-PCR has some limitations, comprising the quality of the sample collected, the commercial kit available, and the stage of the disease. Thus, false negative results would imply the failure to identify many patients with COVID-19, who would not be adequately isolated, or who could progress to an unfavorable clinical condition in a second moment[9].

Chest computed tomography (CT) scan has been increasingly considered part of the diagnostic investigation of symptomatic individuals with suspected COVID-19, especially in early presentation (i.e., less than 72h). Diagnostic imaging has also been considered a complementary assessment to stage the severity of patients positive for this infectious disease[10]. Chest CT scans can detect findings in almost all patients with COVID-19 pneumonia, including patients with negative RT-PCR results[11-13]. In a meta-analysis by Kim and colleagues (2020), the 63 studies that investigated chest CT comprised 6218 patients, in the first months of the pandemic, chest CT scans showed a sensitivity of 97% compared to 89% for the RT-PCR[14]. However, a chest CT scan may be normal, especially in the early stage of the disease[11,15-17]. As a chest CT scan is recommended for hospitalized patients with symptoms of pneumonia, the number of CT scans in patients under investigation has increased substantially[8].

Previous studies have described the chest CT scan as typical findings of COVID-19 positive patients, especially demonstrating the progressive evolution of lung injuries over time. Typical CT findings include bilateral ground-glass opacities, with or without consolidation in the peripheral portions of the lungs and organizing pneumonia and multi-lobular nodular ground glass[8,16,17]. In an early stage of viral replication (0-4 days), ground-glass opacities are among the predominant lesions. In the progressive stage (5-8 days) the mosaic paving pattern and the reverse halo signal mark the increase in the inflammatory profile in the interstitial cells. At the peak stage of virus infection (days 10-13), consolidations, fibrosis, and diffuse alveolar damage appear[18,19]. However, none of these studies had such a substantial number of patients (ranging between 21 and 81 cases), nor presented as many clinical and laboratory data correlations with the COVID-19 patients' outcomes. Chest CT scans can help in diagnosing this infectious disease, especially in negative RT-PCR patients in which a sensitivity of 75% is observed[(9)]. However, the CT scan has low specificity (25-32%)[15]. Nonetheless, Ai and colleagues reported positive chest CT findings before the results of the RT-PCR in 60% of the cases[7] Additionally, finding a typical imaging pattern may encourage a new diagnostic test (e.g., RT-PCR), when initially negative[20], especially in the persistence of suspected symptoms.

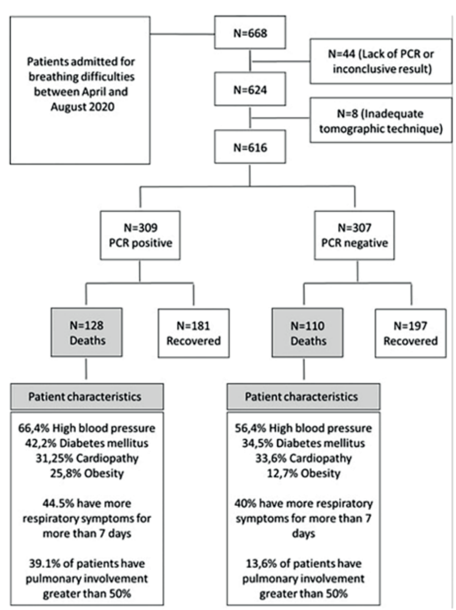
Ultimately, there are mounting arguments for the routine usage of chest CT scans and a standardized imaging description of findings potentially attributed to COVID-19, despite the guidelines not recommending its routine use yet. Thus, the present study aimed to evaluate chest CT findings in a large cohort of patients positive for this infectious disease, and demonstrate its role in diagnosis and prognosis. Altogether, our results strongly suggest chest CT is a technique that may enhance qPCR gold-standard COVID-19 diagnostic capacity, with great prognostic value for stratifying the evolution of most severe cases of this infectious disease.

2 Material and Methods

2.1 Study design and participants

In this retrospective analytical cross-sectional study, data were collected from medical records of patients with clinical suspicion of COVID-19 infection between March and September 2020 at a University-based trauma-center hospital in the Southwestern region of Brazil. Medical records of 616/668 patients admitted to the emergency service were included in the present study; 309 tested negative and 307 patients tested positive for SARS-CoV-2, confirmed by RT-qPCR of nasal swab procedure (Figure 1). All of these 616 patients initially showed typical COVID-19 symptoms and had imaging findings of high-resolution chest computed tomography (chest CT) performed in the hospital.

Figure 1- Patient flow chart showing the diagram of enrolled participants, and criteria of inclusion and exclusion incorporated in the analysis of the present study



Source: research data.

The inclusion criteria comprised the diagnostic suspicion for COVID-19 of patients over 18 years of age, which consisted of fever and respiratory symptoms such as cough and dyspnea, mild upper airway symptoms, and close contact with anyone positively confirmed for this infectious disease. The exclusion criteria consisted of Individuals whose imaging evaluation has not been achieved with adequate quality (i.e., positioning and intensity of ionizing radiation) generated by patient breathing or movements that would avoid adequate analysis of the chest CT images and patients with inconclusive RT-qPCR test results. This study was approved by the Research Ethics Committee of the medical school and by the Ethics Committee of the university hospital (CAAE: 30990920.3.0000.5412).

2.2 Procedures and Clinical Workflow

Suspected COVID-19 patients were subjected to an RT-qPCR test by nasal and oral swab between the 3rd and 7th day of symptom onset. For each patient, clinical data, and laboratory exams, including age, sex, complete blood count, CRP, d-dimer, fibrinogen, coagulogram, and presence of comorbidities such as cardiovascular disease, hypertension, chronic pulmonary disease, diabetes, and chronic liver disease were collected during hospitalization. Additional information such as time of utilization of mechanical ventilation, admission to the intensive care unit (ICU), and progression to death or discharge from the hospital was recorded. Disease outcome severity was defined as critical if the patient had any of the following outcomes: utilization of mechanical ventilation and admission to the ICU, or death. If the patient did not have any of these critical outcomes, the disease severity was defined as non-critical. These individuals had a unique chest CT scan to determine the presence or absence of viral pneumonia realized once between the 1st and the 14th day of symptom onset. CT scans were performed in the Somaton Force (Siemens) 32-channel CT scanner with patients in a supine position and without the injection of intravenous contrast. Technical parameters used were: tube voltage of 120 Kv; tube current modulation from 100 to 250 mAS; pitch spiral factor of 0.98; and 1.0 mm collimation.

After the acquisition, chest imaging was reconstructed with a 1.0 mm slice thickness using a high spatial frequency reconstruction algorithm and stored in the PACS system. Images were visualized in both the parenchyma (width: 1200 HU, level -700 HU) and mediastinal (width: 350 HU, level 40 HU) formats. The decontamination of the room on the surface was performed with 62-71% ethanol or 0.1% sodium hypochlorite. Intervals of 40 to 60 minutes were performed between examinations of new patients.

2.3 Analysis of the chest CT imaging

Two radiologists analyzed the images independently: one with 25 years of experience in chest radiology (CR) and the other with 30 years of experience in radiology in internal medicine (WMR). Phenotypic findings on CT scans were described using the criteria defined in the Fleischner Society glossary of terms[21,22]: (a) ground-glass opacities, (b) ground-glass pattern, (c) ground-glass location, (d) consolidation, (e) multi-lobed involvement, (f) bilateral distribution, (g) consolidation location, or ground glass, (h) thickening of the interlobular septa, (i) reverse halo signal, (j) crazy paving, (k) reticular pattern, (l) pleural effusion, (m) cardiomegaly, (n) hepatic steatosis.

2.4 Statistical analysis

Data were analyzed using the R Statistical Software version 4.0.3, and *p*-values lower than 0.05 were considered statistically significant. Continuous variables were expressed as mean value ± standard deviation (SD). The Mann-Whitney test was used for single comparisons, while the Kruskal-Wallis test was used for multiple comparisons. The frequencies of demographic and clinical characteristics of populations were expressed as the number (percentage) of occurrences and were compared using the 2-tailed χ^2 test or Fisher's exact test, so as for the frequencies of CT features in early- versus late-phase and for comparisons between mortality rate both versus age ranges and clinical stages.

A two-sample test for equality of proportions with continuity correction was used to compare chest computed tomographic findings characterized as typical, atypical, undetermined, and negative pulmonary lesion patterns among COVID-19 patients in association with the disease outcome. Multiple adjusted logistic regression models were used for correlations between CT findings versus laboratory determinants and clinical parameters, to evaluate the association with the disease outcome. Univariate analysis between mortality and other variables including sex, age, CT findings, and D-dimer levels was also performed, and statistically significant variables were used as independent variables in multivariate analysis to identify independent predictors of death in positive patients.

The analysis of the receiver operating characteristic curve (ROC) was constructed using data from tomographic findings for positive and negative COVID-19 patients, according to Hosmer and Lemeschow, 2000[23]. The area under the curve (AUC) was estimated to assess the diagnostic sensitivity of tomographic findings during each one of this infectious disease evolution stage. The α level for statistical significance for this analysis was set at $p<0.05$.

3 Results and Discussion

3.1 Characteristics of the population

The present study aimed to correlate clinical, laboratory, and tomographic findings for patients with suspected COVID-19 disease. Between March and October 2020, a total of 1,667 COVID-19 suspected patients were admitted to the

São Vicente de Paulo hospital. Out of initially 668 patients in our dataset, 44 (6.5%) were discharged for qPCR inconclusive results and 8 for poor quality CT scan imaging. Then, 309/616 (50.16%) patients presented qPCR positiveness for COVID-19, of which 128/309 (41,4%) hospitalized patient died. The main symptoms related to the disease were fever (53.07%), dyspnea (74.43%), myalgia (27.8%), dry cough (67.31%), and 40.45% required ventilatory assistance (intubation orotracheal). The most prevalent comorbidities were systemic arterial hypertension (66.44%), heart disease (31.25%), diabetes mellitus (42.20%), obesity (25.80%), and COPD (6.47%). These findings agree with the literature data.

Three hundred and seven (307) out of 616 patients were COVID19-qPCR negative, with a death rate prevalence of 35.8% (110/307). The causes of death in the group of patients without the infectious disease included systemic arterial hypertension (56.4%), diabetes (34.5%), and heart disease (33.6%). Clinical data and chest CT scans from a total of 616/668 suspected patients, 274 men and 342 women, were collected and analyzed. The demographic characteristics of the population are described in Table 1.

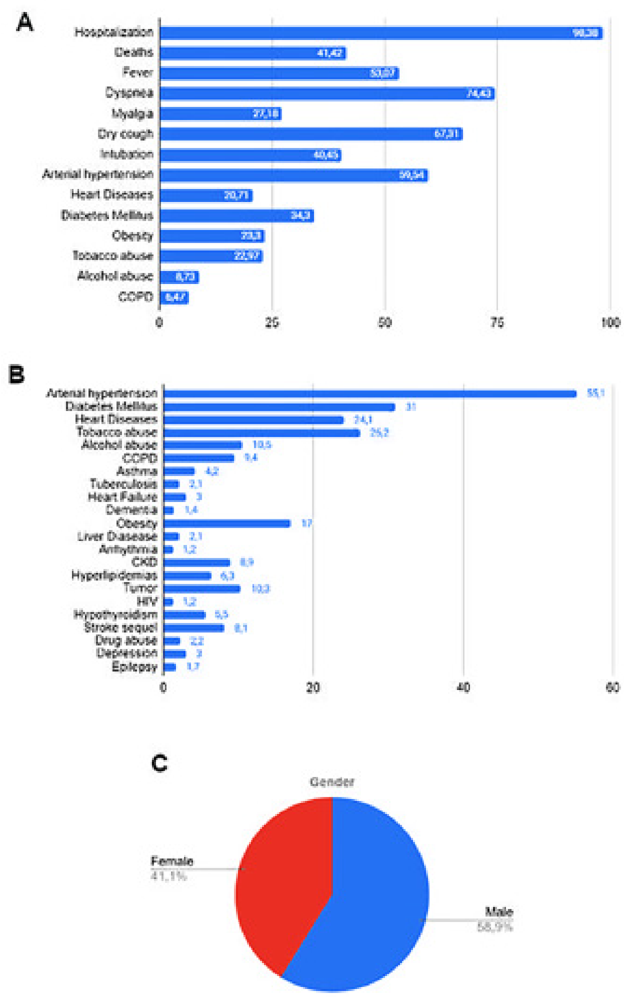
Table 1 - characteristics of positive Covid-19 patients population used in the present study

Characteristics	Value (%)
N of patients	616
Age mean (range)	61.8 (18 – 99)
Sex	
Male	342 (55.5%)
Female	274 (45.5%)
RT-PCR	
Positive	307 (49.8%)
Negative	309 (51.2%)
Death	
Yes	238 (38.6%)
No	378 (61.3%)
Clinical Symptoms	
Fever	282 (45.8%)
Dyspnea	447 (72.55)
Cough	415 (66.3%)
headache	35 (5.6%)
Anosmia	28 (4.5%)
Comorbidities	
Diabetes	191(31%)
Hypertension	340 (55.2%)
Obesity	105 (17%)
cardiopathy	158 (27.2%)
Tomography findings	
Ground Glass	375 (60.8%)
Crazy paving	130 (21.1%)
Inverted halo	134 (21.7%)
consolidation	190 (30.8%)
Steatosis liver	130 (16.7%)

Source: research data.

We sought to evaluate the diseases secondarily associated with this population. Among the most relevant symptoms carried by positive patients were fever, dyspnea, myalgia, and dry cough (Figure 2A). The distribution of patients diagnosed with COVID-19 by RT-PCR test (n=309) showed 182 men and 127 women (Figure 2C), with an average age of 64.01 ± 12 years, with short hospitalization rates and deaths. The comorbidities arterial hypertension (*p*=0,035), heart failure (*p*=0,019), obesity (*p*=0.006), cancer (*p*=0.008), HIV (*p*=0.012), and Stroke (*p*=0.0002) were among the most frequent (Figure 2B) and were significantly present within this population (table 2).

Figure 2 - Demographic and clinical-epidemiological description of Covid-19 suspects used for the present study



Source: research data.

Table 2 - Secondary diseases related to suspected Covid-19 patients

Secondary Diseases Related to Suspected COVID-19 Patients	Absolute Frequency (n)	Relative Frequency (%)	*p*-Value
Arterial hypertension	345	55.1	0.035*
Diabetes Mellitus	191	31	0.09
Heart Diseases	149	24.1	0.05
Tobacco abuse	162	26.2	0.07
Alcohol abuse	65	10.5	0.18
Chronic Obstructive Pulmonary Disease (COPD)	58	9.4	0.17

Secondary Diseases Related to Suspected COVID-19 Patients	Absolute Frequency (n)	Relative Frequency (%)	*p*-Value
Asthma	26	4.2	0.15
Tuberculosis	13	2.1	0.09
Heart Failure	19	3	0.019*
Dementia	9	1.4	0.49
Obesity	105	17	0.006*
Liver Disease	13	2.1	0.25
Arrhythmia	8	1.2	0.07
Kidney Failure chronic (CKD)	55	8.9	0.24
Hyperlipidemias	39	6.3	0.52
Tumor	64	10.3	0.008*
HIV	8	1.2	0.012*
Hypothyroidism	34	5.5	0.84
Stroke sequel	50	8.1	0.0002*
Drug abuse	14	2.2	0.17
Depression	19	3	0.34
Epilepsy	11	1.7	0.066

* p<0,05.

Source: research data.

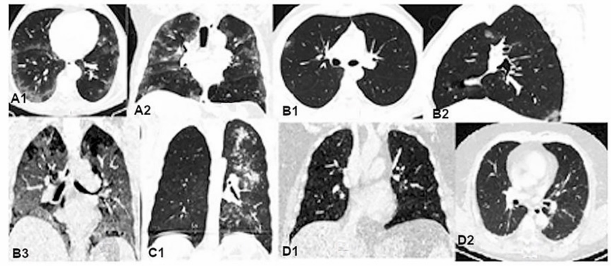
Our findings indicated that cardiac disease and diabetes and obesity were among the main disease associated with COVID-19 patients, with average age of approximated 62 years-old, during the first pandemic wave, suggesting these patients might be at higher risk of complications from COVID-19. According to Covino et al.[25] the patients aged ≥80 years are the most at risk of a poor outcome for COVID-19, however conclusions of the study also pointed that another common disease, dementia, appears to be one of the most relevant risk factors for death on those patients.

By contrast, another study showing the characteristics of patients with COVID-19 and seasonal influenza showed that individuals with COVID-19 less frequently had heart failure or chronic respiratory disease in all age groups, except those younger than 18 years[26]. They conclude that SARS-CoV-2 appeared to have a higher potential for respiratory pathogenicity, leading to more respiratory complications in patients with fewer comorbidities, and it was associated with a higher risk of mortality, particularly in these adolescents, although any conclusions for this age group should be treated with caution considering the small number of deaths.

3.2 Tomographic aspects of positive Covid-19 patients

Chest CT scans were analyzed for 274 men and 342 women (Figure 3). After analyzing the distribution of lung lesions, the findings were grouped into a) typical (ground glass, peripheral, multilobular changes, round pattern, and signs of mosaic pavement and reverse halo) (Figure 3A1-A2); b) undetermined (changes in ground glass, focal, unilobular and non-peripheral or diffuse alveolar damage) (Figure 3B1-B3); c) atypical (isolated consolidations, centrilobular nodules, cavitations and signs of budding tree) (Figure 3C1) negative (without infectious findings, or other findings such as hydrostatic edema, pleural effusion or tumors) (Figure 3D1-D2).

Figure 3 - The illustration shows the distribution and type of lesions in the lung of patients with Covid-19 analyzed by Chest CT scan



Bilateral, peripheral ground-glass opacities and symmetrical distribution (A1 and A2); scattered focal ground-glass opacities in the upper right lobe and lower left lobe (B1 and B2); ground-glass opacities with diffuse, central, and peripheral distribution (B3); consolidations with endobronchial dissemination in the left upper and lower lobes (C1); chest tomography without abnormalities, negative (D1 and D2).

Source: research data.

The database was divided into two distinct groups, according to the patient's evolution (only positive cases of COVID-19 were confirmed through the RT-PCR test), 1. patients who did not die (n=180) and 2. patients who died (n=125). After removing the observations that there was no record of the variables, the final basis for the hypothesis of the Exact Fisher test contained the information of 305 patients. The variable death response, which contains the outcome of the patient's evolution, shows that patients died in 41% of the cases. Regarding the classification of tomographic outcomes, patients who died had 57% of typical lung lesions pattern, 52% of atypical lesions, 44% of indeterminate patterns, and only 34% had no presence of lesions in the lungs (negative).

As in previous reports on computed tomography, ground glass findings were predominant (80.3%), followed by a peripheral distribution (59.22%), involvement of multiple lobes (65.3%), and reticular opacities (62.1 %). The CT severity can aid in the diagnosis and treatment of positive patients. CT scans can monitor the progression or improvement of lung lesions according to the time evolution, which can alter therapy. We identified different patterns of lesions according to time between patients with a non-severe and severe disease with a peak of severe disease occurring at approximately 9 to 10 days[24].

On the other hand, most patients who were alive had no lesions in the lungs (66%), while the presence of typical (43%), atypical (48%), or indeterminate (56%) lesions patterns were present in a smaller portion of this group of patients. The comparison between the evolution of patients to death or not, between the tomographic patterns analyzed is described in Table 3. Of note, the result of the logistic regression showed statistical significance for the tomographic pattern variables of peripheral distribution (*p*=0.00611) and the interaction between the early stage and the indeterminate tomographic pattern (*p*=0.02157) related to the evolution of the patients to death.

Table 3 - The comparison between the evolution of patients to death or not, among the tomographic image patterns analyzed

Death	Radiological result	
	Grounded glass opacity/ULRL	
	YES	NO
Yes	41%	42%
No	59%	58%
	Grounded glass opacity/ LLRL	
	YES	NO
Yes	39%	46%
No	61%	54%
	Grounded glass opacity/ MLRL	
	YES	NO
Yes	54%	23%
No	46%	77%
	Grounded glass opacity/ULLL	
	YES	NO
Yes	40%	46%
No	60%	54%
	Grounded glass opacity/LLLL	
	YES	NO
Yes	39%	45%
No	61%	55%
	Opacity in consolidation/ ULRL	
	YES	NO
Yes	41%	41%
No	59%	59%
	Opacity in consolidation/ LLRL	
	YES	NO
Yes	57%	39%
No	43%	61%
	Opacity in consolidation/ MLRL	
	YES	NO
Yes	40%	41%
No	60%	59%
	Opacity in consolidation/ ULLL	
	YES	NO
Yes	50%	40%
No	50%	60%
	Opacity in consolidation/ LLLL	
	YES	NO
Yes	39%	42%
No	61%	58%
	DP - peripheral location	
	YES	NO
Yes	41%	41%
No	59%	59%
	DP - multiple lobes	
	YES	NO
Yes	39%	45%
No	61%	55%
	DP - focused	
	YES	NO
Yes	42%	41%
No	58%	59%
	DP - rounded	

Death	Radiological result	
	YES	NO
Yes	31%	44%
No	69%	56%
	AC– mosaic pavement	
	YES	NO
Yes	44%	40%
No	56%	60%
	AC- reverse halo	
	YES	NO
Yes	36%	44%
No	64%	56%
	AC- larger vases caliber	
	YES	NO
Yes	8	117
No	9	171
	AC- reticular opacity	
	YES	NO
Yes	37%	47%
No	63%	53%
	AC- dilation	
	YES	NO
Yes	50%	41%
No	50%	59%
	AC- involvement >50%	
	YES	NO
Yes	46%	38%
No	54%	62%

ULRL: upper lobe of right lung; LLRL: lower lobe of right lung; MLRL: middle lobe of right lung; ULLL: upper lobe of left lung; LLLL: lower lobe of left lung; DP: distribution pattern; AC: associated characteristics.
Source: research data.

Chest computed tomography involves a significant portion of the abdomen, showing the liver parenchyma. As the examinations were performed without the use of intravenous iodinated contrast, it was possible to assess liver density in all the patients, and a large percentage of hepatic steatosis was significantly demonstrated in these patients (33.6%).

3.3 Evaluation of Chest CT as a potential prognostic marker

To evaluate whether the Chest CT was a good potential prognostic marker for determining disease outcomes in PCR$^+$ COVID-19 patients, as well as to determine the relevance of the tomographic findings during the evolutionary stages of the disease, the two groups of patients who died or did not (alive) were compared by logistic regression (Table 4). For that, we considered the groups containing Chest CT to be taken at an early (day 0 to 5), intermediate/progressive (day 6 to 9), and peak/later stage (day 10 and after) of COVID-19 infection. The results showed that the peak stages of the disease were significantly associated with typical consolidation lung lesion pattern in alive individuals (p=0.016), and with the periphery distribution pattern in dead individuals (*p*=0.03) positively infected (Table 4). Also, the indeterminate lesions pattern verified in the Chest CT scans analyzed was significantly related to COVID-19 early stage (p=0.02157).

Table 4 - Distribution of the Chest computed tomographic lesions patterns in Covid-19 positive patients in association with the disease outcome

Radiological Characteristics	Distribution pattern	Alive	Dead	*p*-Value
Ground-glass	Early stage	18.55%	81.45%	-
	Progressive stage	9.89%	90.11%	0.116
	Peak Stage	8.33%	91.67%	0.083
Consolidation	Early stage	54.03%	45.97%	-
	Progressive stage	53.85%	46.15%	0.11
	Peak Stage	65.28%	34.72%	0.016*
DP - Periphery	Early stage	45.16%	54.84%	-
	Progressive stage	37.36%	62.64%	0.31
	Peak Stage	29.17%	70.83%	0.03*
DP - Multilobes	Early stage	37.90%	62.10%	-
	Progressive stage	31.87%	68.13%	0.44
	Peak Stage	27.78%	72.22%	0.19
DP - Focal	Early stage	93.55%	6.45%	-
	Progressive stage	92.31%	7.69%	0.93
	Peak Stage	95.83%	4.17%	0.74
DP - Rounded	Early stage	78.23%	21.77%	-
	Progressive stage	76.92%	23.08%	0.951
	Peak Stage	76.39%	23.61%	0.904
AC – Mosaic Pavement	Early stage	72.58%	27.42%	-
	Progressive stage	68.13%	31.87%	0.57
	Peak Stage	68.06%	31.94%	0.61
AC – Reverse Halo	Early stage	66.13%	33.87%	-
	Progressive stage	59.34%	40.66%	0.38
	Peak Stage	58.33%	41.67%	0.34
AC – Vases Caliber	Early stage	92.74%	7.26%	-
	Progressive stage	95.60%	4.40%	0.77
	Peak Stage	95,83%	4.17%	0.54

DP: Distribution Pattern; AC: Associated characteristics; *$p<0.05$ (Fisher Exact test).

Source: research data.

It has been demonstrated in the literature that patients over 60 years of age and comorbidities are prognostic factors in patients with COVID-19, especially heart disease, diabetes mellitus, COPD, and obesity. However, the hepatic steatosis factor was a condition that demonstrated a worse prognosis in our patients, a fact that is generally associated with obesity, although a portion of the population with steatosis does not present significant obesity.

Our analysis to determine the Chest CT characteristics relevance as a prognostic marker for the progression of this infectious disease and outcome showed significance in the association of the indeterminate Chest TC pattern and disease early stage (p=0.02157), meaning that among patients who are in the early stage of presenting symptoms of COVID-19, the classification of lung lesions through Chest CT as 'indeterminate' matters to the outcome of the death of this disease

Then, we sought to determine the importance of some clinical (dyspnea, cough, sore throat, fever, headache, myalgia, and anosmia) and laboratory (leukocytes, lymphocytes, APTT, and D-Dimer) determinants for the prognosis of patients with 'COVID-19+ and Chest CT typical patterns (Ground-glass and consolidation)' *vs.* 'COVID-19+ and negative Chest CT lesions' by logistic regression analysis. For that, we used a data basis from a total of 361 different patients, who pursued a complete record of the clinical and laboratory variables verified. The results demonstrate that the variables myalgia (p=0.01557), cough (p=0.03501), and the activated partial thromboplastin time (APTT) (p=0.0234) were statistically significant in patients with COVID-19 containing typical ground glass pulmonary lesion identified by Chest CT (Table 5). Also, the variables ground glass and APTT were significant to determine the prognosis of this infectious disease (p=2.88E^{-12}).

Table 5 - Analysis showing the correlation of clinical and laboratory parameters with the presence of typical lung lesions patterns

Clinical Parameters		Point parameter estimation	*p*-Value	Odds	Lower bound (95%)	Upper bound (95%)
Signs and symptoms	Fever	0.341	0.1914	14.063	-	-
	Myalgia	0.890	0.01557*	2.430	0.288	1.207
	Dyspnea	0.436	0.1235	15.462	-	-
	Sore throat	1.277	0.177	35.869		-
	Cough	0.751	0.03501*	2.110	0.248	1.254
Lung Injuries	Ground Glass pulmonary lesion	19.891	2.88E-12*	7.309	1.43	5.547
	Consolidation pulmonary lesion	0.072	0.7813	10.749	-	-
Laboratory	Leucocytes count	-0.043	0.112	0.958	-	-
	APTT	1.351	0.0234*	3.861	0.182	2.519
	D-Dimer	-0.00007874	0.2059	0.999	-	-

APTT: activated partial thromboplastin time.

Source: research data.

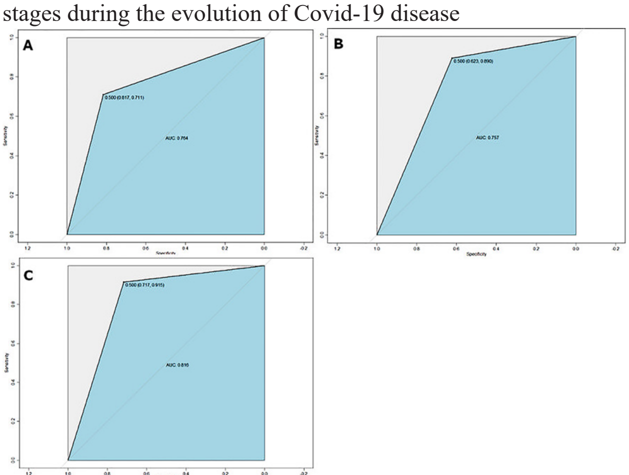
Other variables that were relevant for prognosis by the Exact Fishes hypothesis test were not significant for the model due to the high correlation with the ground-glass variable, but have relevant odds ratios, which confirms the importance of the diagnosis. Only the variables dyspnea, sore throat, fever, and D-Dimer did not show dependence on the ground-glass variable. Additionally, the interaction between the progressive stage and leukocyte count included in the model also showed statistical significance (p=0.00478), so there is a relevant difference in the leukocyte count of patients when considering the progressive stage of the disease.

3.3 Chest CT characteristics predict diagnosis for Covid-19 patients

The analysis of the ROC curve (Operating Characteristic Curve) was performed to assess the diagnostic accuracy of the chest CT for the different stages during the evolution of COVID-19 disease. Of the 616 patients in the initial database, 44 were removed from the database because they did not have information on the time of onset of symptoms, resulting in a base of 572 patients for this analysis. Then, patients were divided into three distinct groups (as for disease stages), according to the time since the onset of first symptoms: 1. Early-stage - patients who were experiencing symptoms for up to a maximum of 5 days; 2. Progressive stage - patients who were experiencing symptoms for more than 5 days and up to a maximum of 9 days; and 3. Peak stage - patients who have been experiencing symptoms for more than 9 days.

Our data showed that in the early stage of symptoms, the tomographic characteristics of Chest CT had high sensitivity (81.7%) and moderate specificity (76.4%) for detecting the disease (AUC=0.764; CI: 95%, 0.817 ~ 0.711, p<0.05) (Figure 4A). In the progressive stage of symptoms, the tomographic characteristics had the highest sensitivity detected, 89%, but moderate specificity of 62.3% (AUC = 0.757; CI: 95%, 0.623 ~ 0.890, p<0.05) (Figure 4B). Finally, the tomographic characteristics showed a moderate sensitivity of 71.7%, but the highest specificity detected, 91.5%, for the diagnosis of COVID-19 when performed at the peak stage of the symptoms of the disease (AUC = 0.816; CI: 95%, 0.717 ~ 0.915, p<0.05) (Figure 4C).

Figure 4 - Chest CT scan diagnostic accuracy to discriminate patients PCR positive and negative for Covid-19, at different stages during the evolution of Covid-19 disease



Showing the Operating Characteristics Curves at (A) Early Stages, (B) Progressive Stages, and (C) Peak or later stages.
Source: research data.

The Roc analysis was performed to determine whether the Chest CT by itself was a relevant diagnostic marker and if that would be more sensitive and specific at the beginning, middle, or end of the disease. When comparing the 3 curves by the AUC, it appears to be at the peak of the symptoms stage that the tomographic characteristics have the greatest diagnostic power for COVID-19, compared to the early and progressive stages. In this last stage, sensitivity is medium, greater than progressive, and less than the peak of the disease, which was shown to have the highest specificity among the three periods.

As for any retrospective study, some limitations of the present study are worth considering, such as the data being collected from a group of patients admitted during a pandemic period, while many protocols were being applied and modified the means that more knowledge about the virus SARS-CoV2 was acquired. Then, much of the data collected did not maintain the same level of information as laboratory tests collected through the medical records. Also due to the collection within the peak of the pandemic period, a high prevalence of coronavirus infection and low prevalence of other viral infections, make a group control for bias decrease.

4 Conclusion

Chest computed tomography has the potential to bring diagnostic information in earlier stages of COVID-19 disease progression, as well as predict the prognosis of such infection according to the pre-existing comorbidities and associated findings. These results strongly suggest the use of CT as an adjuvant method for the initial diagnosis and in the management of hospitalized patients positive for this infectious disease.

References

1. Lu R, Zhao X, Li J, Niu Pehiua, Yang B, Wu Honglong. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565-74. doi: https://doi.org/10.1016/S0140-6736(20)30251-8

2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song. et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382(8):727-33. doi: 10.1056/NEJMoa2001017

3. Jernigan DB; CDC COVID-19 Response Team. Update: Public Health Response to the Coronavirus Disease 2019 Outbreak - United States, February 24, 2020. MMWR Morb Mortal Wkly Rep 2020;69(8):216-9. doi: https://www.cdc.gov/mmwr/volumes/69/wr/mm6908e1.htm

4. Schalekamp S, Huisman M, van Dijk RA, Boomsma M, Jorge PJF, Boer WS, et al. Model-based Prediction of Critical Illness in Hospitalized Patients with COVID-19. Radiology 2021;298(1):E46-E54. doi: 10.1148/radiol.2020202723

5. Homayounieh F, Ebrahimian S, Babaei R, Mobin HK, Zhang E, Bizzo BC, et al. CT Radiomics, radiologists and clinical information in predicting outcome of patients with COVID-19 Pneumonia. Radiol Cardiothoracic Imaging 2020;2(4):e200322. doi: 10.1148/ryct.2020200322

6. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation

of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020;296(2):E32-E40. doi: 10.1148/radiol.2020200642

7. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061-1069. doi: 10.1001/jama.2020.1585

8. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology 2020;295(1):202-207. doi: 10.1148/radiol.2020200230

9. Li J, Lin Z, Xiong N. Effective Chest CT–Based Diagnosis for Coronavirus Disease (COVID-19). Am J Roentgenol 2020;215(3):W37-W8. doi: 10.2214/AJR.20.23548

10. Akl EA, Blazic I, Yaacoub S, Frija G, Chou R, Appiah JA, et al. Use of Chest Imaging in the Diagnosis and Management of COVID-19: a WHO Rapid Advice Guide. Radiology 2021;298:E63-E69. doi: 10.1148/radiol.2020203173

11. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): relationship to duration of infection. Radiology 2020;295(3):200463.

12. Caruso D, Zerunian M, Polici M, Pucciareli F, Polidori T, Rucci C, et al. Chest CT Features of COVID-19 in Rome, Italy. Radiology 2020;296(2):E79-E85. doi: 10.1016/j.clinimag.2020.10.035

13. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. AJR Am J Roentgenol 2020;215(1):87-93. doi: 10.2214/AJR.20.23034

14. Kim H, Hong H, Yoon SH. Diagnostic performance of CT and reverse transcriptase polymerase chain reaction for Coronavirus disease 2019: a meta-analysis. Radiology 2020;296(3):E145-E55. doi: 10.1148/radiol.2020201343

15. Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L. et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020;323(14):1406-7. doi: 10.1001/jama.2020.2565

16. Pan F, Ye T, Sun P, Gui S, Li L, Zheng D, et al. Time course of lung changes at chest ct during recovery from Coronavirus disease 2019 (COVID-19). Radiology 2020;295(3):715-21. doi: 10.1148/radiol.2020200370

17. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of Chest CT for COVID-19: comparison to RT-PCR. Radiology 2020;296(2):E115-E117. doi: 10.1148/radiol.2020200432

18. De Smet K, De Smet D, Ryckaert T, Laridon E, Heremans B, Vandenbulcke R, et al. Diagnostic performance of chest CT for SARS-CoV-2 infection in individuals with or without COVID-19 Symptoms. Radiology 2021;298(1):30-7. doi: 10.1148/radiol.2020202708.

19. Rosa MEE, Matos MJR, Furtado RSOP, Brito VM, Amaral LTW, Beraldo GL. et al. COVID-19 findings identified in chest computed tomography: a pictorial essay. Einstein (São Paulo) 2020;18:eRW5741. doi: http://dx.doi.org/10.31744/einstein_journal/2020RW5741

20. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M. et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. J Thorac Imaging 2020;35(4):219-27. doi: 10.1097/RTI.0000000000000524.

21. Silva CIS, Marchiori E, Souza Júnior AS, Muller NL. Illustrated brazilian consensus on the terminology of descriptors and fundamental standards of chest CT. J Bras Pneumol 2010;36(1):99-123. doi: https://doi.org/10.1590/S1806-37132010000100016

22. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Mullet NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. Radiology 2008;246(3):697-722. doi: 10.1148/radiol.2462070712

23. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, 2000. doi: 10.1002/0471722146

24. Wang X, Hu X, Tan W. Multicenter study of temporal changes and prognostic value of a CT visual severity score in hospitalized patients with Coronavirus disease (COVID-19). AJR Am J Roentgenol 2021;217(1):83-92. doi: 10.2214/AJR.20.24044

25. Covino, M, De Matteis, G, Santoro, M. Clinical characteristics and prognostic factors in COVID-19 patients aged ≥80 years. Geriatr Gerontol Int 2020;20:704-8. doi: https://doi.org/10.1111/ggi.13960.

26. Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, Quantin C. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. Lancet Respir Med 2021;9(3):251-9. doi: 10.1016/S2213-2600(20)30527-0.