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Chest Computed Tomography and Severity Markers in COVID-19

Gisel Viviana Licón Martínez, MD[1], Aranza Elena García Aréstegui, MD[1], Marina Estrada-Rodriguez[1], Katya Lorena Wilhelmy-Ledesma[1], Joaquin Córdova Erberk[1], Gabriel Rocha-González, MD[2], Fernando Augusto Domínguez-García, MD[2], Miguel Angel Gaxiola-García, MD, MSc[3], Hiram Javier Jaramillo-Ramírez, MD[4]

[1]Internal Medicine Department, Mexicali's General Hospital (Hospital General de Mexicali). Autonomous University of Baja California, Faculty of Medicine. Mexicali, Mexico.

[2]Radiology and Imaging Department, Mexicali's General Hospital (Hospital General de Mexicali). Autonomous University of Baja California, Faculty of Medicine. Mexicali, Mexico.

[3]Plastic and Reconstructive Surgery Department, Mexico's Children Hospital (Hospital Infantil de México "Federico Gómez"). Mexico City, Mexico.

[4]Chairman, Internal Medicine Department, Mexicali's General Hospital (Hospital General de Mexicali). Mexicali, Mexico.

ABSTRACT

Background: Computed Tomography chest scan can be a tool for classification of COVID 19 disease. We propose there is a relation between computed tomography severity index and inflammation biomarkers.

Methods: We performed a retrospective analysis of hospitalized COVID 19 patients in Mexicali´s General Hospital, during the period of March 2020 to December 2020. The inclusion criteria was over 18 years old, confirmatory RT- PCR nasal swab and available CT chest scan. We extracted data of medical records; variables studied were age, sex, date of symptom onset, date of admission, chest computed tomography score, RT-PCR result, laboratory values (D-dimer, fibrinogen, ferritin, procalcitonin, C-reactive protein, total leukocytes, lymphocytes), and outcome.

Results: From March 2020 to December 2020, 397 patients were recruited that fulfilled the inclusion criteria from a 700 patient database. Statistically significant differences after *t* tests between survivors and non-survivors were found for C-reactive protein (means 47.1 ± 36 vs. 80.1 ± 54; p = 0.0009), procalcitonin (means 961 ± 279 vs. 1,032 ± 283; p = 0.023), white blood cells (means 10.57 ± 4.46 vs. 12.33 ± 6.22; p = 0.0026) and lymphocytes (means 0.79 ± 0.50 vs. 0.68 ± 0.40; p value= 0.026).

Conclusions: Laboratory and imaging studies are fundamental for stratification and outcome prediction in COVID-19 patients. With these findings we can determine the prognosis of a patient, have a better approach, and search specifically for the relevant severity markers such as fibrinogen, white blood cells, lymphocytes, and C-reactive protein in hospitals with limited resources.

KEYWORDS: Coronavirus infections, Pneumonia, Severity Markers, Computed Tomography, Medical Imaging, Pandemics.

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INTRODUCTION

The first reported cases of coronavirus respiratory disease (COVID-19) occurred in Wuhan, China in December 2019; it manifested as atypical pneumonia or severe acute respiratory syndrome, caused by the respiratory coronavirus 2 (SARS-CoV-2) as named by the World Health Organization (WHO).[1]

As of April 20, 2021, the United States has gathered a total of 31,789,209 cases with a death toll of 568,449.[2] At the same moment Mexico, with a population of over 127 million inhabitants, adds up to 2,311,308 documented COVID-19 cases and 212,127 deaths.[3]

Apart from an antigen-specific confirmatory test (RT-PCR, Reverse Transcription Polymerase Chain

Reaction) obtained by a nasal swab, the diagnosis and treatment protocol for COVID-19 patients requires multiple laboratory and imagenology tests to determine the physiological basal state and to direct treatment adequately.[1, 4]

Computed tomography is used for the diagnosis and follow-up of patients with atypical pneumonia. The estimated sensitivity of chest computed tomography (CT) for COVID-19 patients is around 97%; variations depend on the days of evolution and the severity of the disease. Typical chest CT findings include ground-glass opacity, vascular thickening, and a cobblestone/reticular pattern.[4]

A pulmonary involvement scale has been already devised; this assessment tool has shown a sensitivity of 85.6% and a specificity of 84.5% for prediction of mortality when using a cutoff value.[4] The findings of the chest computed tomography are reported via a semi-quantitative scoring system that estimates the pulmonary involvement based on the affected area.[5] Each of the five lung lobes is visually assessed and scored on a scale from 0 to 5, with 0 indicating no involvement; 1, less than 5% involvement; 2, 5%–25% involvement; 3, 26%–49% involvement; 4, 50%–75% involvement; and 5, more than 75% involvement. The total CT score results from the sum of the five individual lobar scores and ranges from 0 (no involvement) to 25 (maximum involvement).[5] (Table 1) (Figures 1 and 2)

Table 1. Semiquantitative Assessment of Lung Lobes Injuries

Scoring	Range (%)
0	No involvement
1	≤5
2	5 – 25
3	26 – 49
4	50 – 75
5	>75

The result of adding up the scores of the individual lobes constitutes the total score of the Severity Index.

Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-721

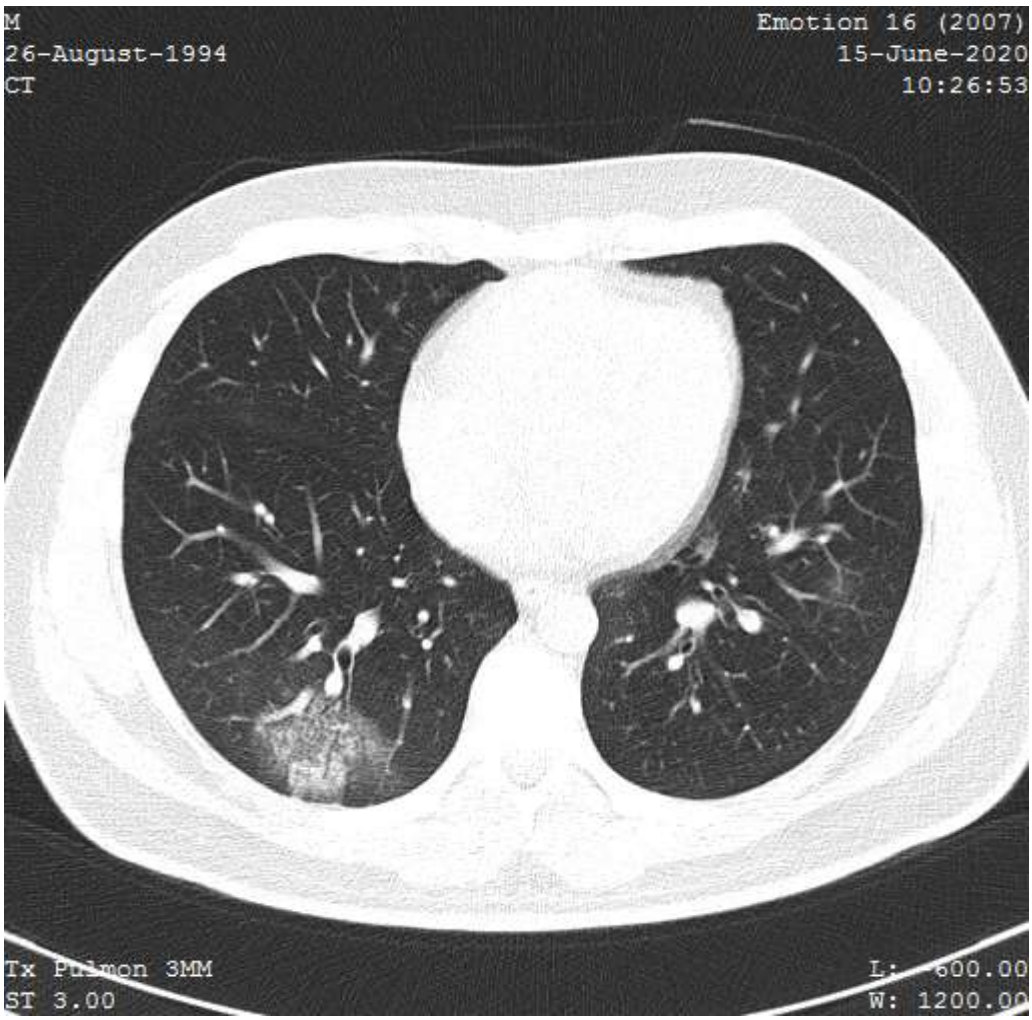

Figure 1. Chest CT-scan of a 26-year-old man with confirmed COVID-19 pneumonia. Representative axial thin-section chest CT image showing focal ground-glass opacity with reticular septal thickening. A total Computed Tomography Severity Index of 3 was calculated.

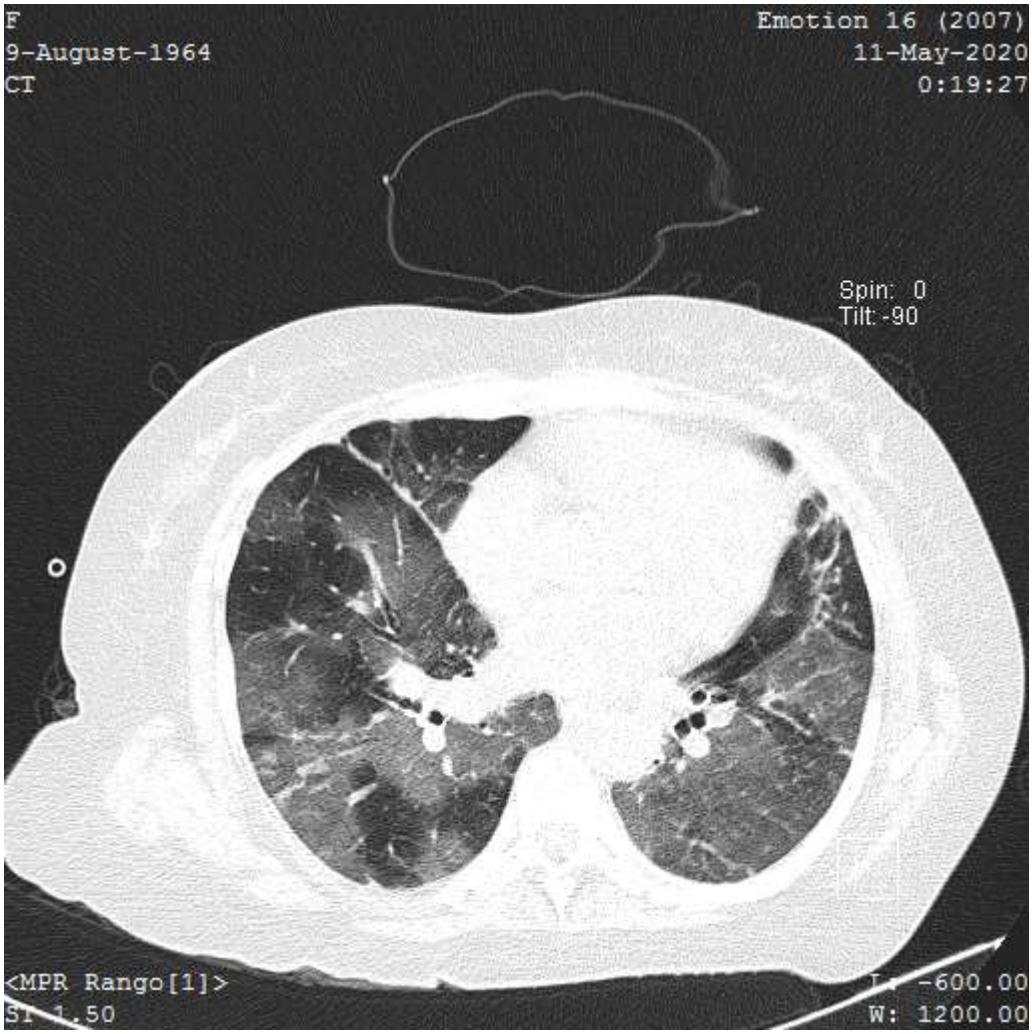

Figure 2. Chest CT-scan of a 56-year-old woman with confirmed COVID-19 pneumonia. Representative axial thin-section chest CT image showing focal confluent ground-glass opacities with diffuse reticular septal thickening. The calculated Computed Tomography Severity Index was 23.

Laboratory indicators of severe disease include leukopenia, lymphopenia, transaminasemia, increased levels of lactic dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, ferritin, and D-dimer, as well as prolonged clotting times and alterations in cardiac enzymes (troponin).[6] CRP levels are elevated in all patients with COVID-19; a mean concentration of 40mg/L is found in patients who survive while a mean of 125mg/L in those who die.[6] Other predictors for a fatal outcome are an increase in LDH and ferritin secondary to hemophagocytic lymphohistiocytosis and cytokine storm, both of which have been reported in patients with severe disease.[6] Those patients who do not survive show higher levels of D-dimer, values above 1μg/L being the strongest independent value for mortality.[6] The treating physician should consider lymphopenia, levels of CRP, ferritin, D-dimer, and cardiac troponins; these allow stratification and severity prediction in hospitalized patients.[6-7] For example, patients with diabetes and COVID-19 pneumonia show elevated levels of ferritin, which is associated with a greater chance of developing serious complications from COVID-19 disease.[8] Conversely, lymphopenia has been observed in patients with cytokine storms 7-14 days after onset of symptoms.[9] There is evidence showing that lymphocytes express the ACE2 (angiotensin-converting enzyme 2) receptor, which is what causes their lysis.[9] This receptor is widely expressed in airway epithelial cells.[10]

Thus, laboratory abnormalities are common; in a study by Guan et al. dealing with 1,099 COVID-19 patients in Wuhan, China, it was reported that at the moment of admission, up to 83% of patients had lymphopenia, 60% had increased procalcitonin levels, and 41% had an increase in LDH.[11]

Elevated levels of D-dimer also show a hypercoagulable state in patients with COVID-19; this can be attributed to various factors such as an inflammatory response, endothelial dysfunction, hypoxia, and comorbidities, among others.[9] Microthromboses in the small pulmonary vessels have been observed in critically ill patients.[9] D-dimer levels greater than 2μg/mL may constitute an effective predictor of mortality as well as the reduction in D-dimer levels is associated with a decrease in the severity of

the disease.[9-11] This marker constitutes a good indicator regarding the effectiveness of patient care.

METHODS

We performed a retrospective analysis of medical records concerning COVID-19 patients in the period from March 2020 to December 2020. Data were extracted from the electronic clinical file; we included patients who were older than 18 years and were hospitalized at a COVID-19 designated hospital, having a confirmatory RT-PCR (Reverse Transcription Polymerase Chain Reaction) nasal swab and an available chest CT scan. The study was approved by the Mexicali´s General Hospital Ethics Committee.

Variables studied were age, sex, date of onset of symptoms, date of admission, chest computed tomography score, RT-PCR result, laboratory values (D-dimer, fibrinogen, ferritin, procalcitonin, C-reactive protein, total leukocytes, lymphocytes), as well as the outcome.

Statistical analysis was performed using Mini Tab 18 and Epi Info version 7.2.4.0. We performed Pearson's correlation test for the quantitative variables. Means derived from continuous variables were compared using Student's *t*-test and Chi-squared test was used for dichotomous variables. The statistically significant *p*-value was set at < 0.05.

RESULTS

From a database of seven hundred patients, we excluded 307 without an identifiable outcome in the electronic medical file. 393 patients in the period from March 24th, 2020 to December 31st, 2020 fulfilled inclusion criteria; of these, 236 (60%) were men and 157(40%) were women.

Age ranged from 20 to 93 years, with a mean of 58 years for the whole sample. The mean age of survivors was 54.1 years, compared with 60.8 years of non-survivors; p<0.0001 after *t*-test. The mean score of the chest CT Severity Index in the whole sample was 20.8 (StdDev 4.9); the mean chest CT Severity Index of the surviving patients was 19.2 compared to 21.8 of non-survivors; p <0.0001 after the *t*-test.

The following laboratory studies were included and compared between survivors and non-survivors: D-dimer, fibrinogen, ferritin, procalcitonin, C-reactive protein, white blood cells and lymphocytes. Table 2 shows mean values for every variable. Statistically significant differences after *t* tests between survivors and non-survivors were found for C-reactive protein (means 47.1 ± 36 vs. 80.1 ± 54; p = 0.0009), procalcitonin (means 961 ± 279 vs. 1,032 ± 283; p = 0.023), white blood (means 10.57 ± 4.46 vs. 12.33 ± 6.22; p = 0.0026) and lymphocytes (means 0.79 ± 0.50 vs. 0.68 ± 0.40; p value= 0.026).

Outcomes were 242 (61.5%) deaths and 151 (38.4%) hospital discharges. Seventy-nine out of 157 women died (50%), while 163 out of 236 men died (69%); Odds Ratio 2.2, p = ≤0.0001.

Table 2. Laboratory values of 393 Patients with confirmatory RT-PCR (Reverse Transcription Polymerase Chain Reaction) nasal swab for COVID-19 and available chest CT scan. Study period: March to December 2020.

Variable	N	Survivors	Deceased	OR	*p**
Age (years)	393	54.11 ± 14.6	60.86 ± 11.8		<0.0001
Men	236 (60%)	73(30%)	163 (70%)	2.2	<0.0001
Women	157 (40%)	78 (49%)	79 (51%)	1	
CT Severity	393	19.26 ± 5.72	21.87 ± 4.08		<0.0001
D-Dimer	193	1,781 ± 1,814	2,108.48 ± 1,981		=0.24
Fibrinogen	342	961 ± 279	1,032 ± 283		=0.0236
Ferritin	40	892 ± 1,056	1,104 ± 1002		=0.5
Procalcitonin	134	1.47 ± 3.5	11.81 ± 89.6		=0.5
C reactive protein	99	47.1 ± 36	80 ± 54		=0.0009
White blood cells	393	10.57 ± 4.46	12.33 ± 6.22		=0.0026
Lymphocytes	393	0.79 ± 0.50	0.68 ± 0.40		=0.026
Total	393	151 (38.4%)	242 (61.5%)		

Variables expressed in means ± SD.
* After Student's *t*-test for continuous variables and Chi-squared test for categorical variables.
SD = Standard deviation.
OR = Odds ratio.

Table 3 shows Pearson's correlation values between chest computed tomography and inflammatory markers. Procalcitonin showed a moderate correlation with the Computed Tomography Severity Index. A weak correlation was found between the Computed Tomography Severity

Index and the variables white blood cells, fibrinogen, and age; these correlations were statistically significant.[12]

Table 3. Correlation between Severity Markers and Computed Tomography Severity Index

Severity Marker	r	*p*	Correlation
Lymphocytes ($\times10^3/\mu L$)	-0.077	0.129	Negligible correlation
tablWhite blood cells ($\times10^3/\mu L$)	0.148	0.003	Weak correlation
Fibrinogen (g/L)	0.178	0.001	Weak correlation
D-dimer (μg/mL)	0.038	0.602	Negligible correlation
Procalcitonin (ng/mL)	0.58	0.502	Moderate correlation
C-reactive protein (mg/L)	0.062	0.539	Negligible correlation
Ferritin (μg/L)	0.011	0.946	Negligible correlation
Age (years)	0.106	0.036	Weak correlation
Correlations graded according to reference 12.			

DISCUSSION

The present study was carried out at a COVID-19 designated and government-sponsored hospital with an installed capacity of 150 hospital beds for the attention of a population of over one million inhabitants. Amidst the COVID-19 pandemic, patients from all socioeconomic statuses were treated at our institution; besides this, our geographic location at the border with the United States conditioned a considerable flow of patients.

We intended to determine the relationship between a chest computed tomography Severity Index and serum severity markers. From all the evaluated serum severity markers, elevated levels of C-reactive protein predicted higher mortality with a statistically significant *p*-value. In the same way, a higher Severity Index reported in the lung CT scan is associated with a fatal outcome.

Different studies have documented a high concentration of C-reactive protein in COVID-19 patients; this is associated with the severity of the disease and the degree of pulmonary damage.[13-14] CRP levels and the diameter of the largest lesion on the CT scan increase as the disease progresses.[13] In a study carried out at the Wenzhou People's Hospital, Shanghai, China including 76 patients with a positive test for SARS-CoV2 confirmed by RT-PCR, a direct relationship of CRP as a biomarker of severity was observed.[14] When the CT scan classification increased from mild to moderate or severe, the CRP concentration increased.[14] Unexpectedly, in our study, the correlation between C-reactive protein levels and the Severity Index obtained by CT-scan was negligible. This contrasts with a report from Tan et al. where the authors found a strong correlation (r = 0.62) between these two variables.[15] These differences may be due to unequal sample sizes or a still non-identified confusing factor. Conversely, as we expected, age is a demographic predictor of mortality; older patients had an increased risk of death, as well as higher Severity Index reported in the CT scan.

Our results, if generalized to similar hospitals with finite resources, may help to optimize laboratory and imagenology studies, which are fundamental for stratification and outcomes prediction in the COVID-19 population.

The relevance of this study is that with these findings we can determine the prognosis of a patient, have a better approach, and search specifically for the necessary severity markers such as fibrinogen, white blood cells, lymphocytes, and C-reactive protein.

Other severity indexes exist and are used in other pathologies such as pancreatitis (e.g. the Ranson Severity Score, or the Acute Physiology and Chronic Health score); they have shown correlation with the CT-scan of the involved region, as was the case in our study.[16] Additionally, a significant correlation was found in a study by Saeed et al. between a CT-scan derived severity score and male gender, raised inflammatory markers, maximum oxygen requirement, length of hospital stay, need of intubation, as well as clinical outcome.[17] This demonstrates a pivotal role for CT scans in assisting physicians during the management of severely ill patients.[16,17] The CT-Severity Index used in COVID-19 has a great potential for assessing the extent of pneumonia and discriminating between moderate, severe, and critical types.[18]

Finally, our study bears some limitations: concerning data acquisition, some registers about severity markers were lost for a few patients and thus analysis and interpretation were hindered. In the same way, the

interpretation of the chest computed-tomographies was performed by different radiologists; interobserver agreement couldn't be determined.

A valuable opportunity for systematization of care arises by the design of a hospital protocol that ensures that all patients undergo the same laboratory tests; this looking for quality improvement in patient care and promotion of research.

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