Research article

CT-based pathological lung opacities volume as a predictor of critical illness and inflammatory response severity in patients with COVID-19

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ABSTRACT

Objective: The aim of the study was to assess the impact of CT-based lung pathological opacities volume on critical illness and inflammatory response severity of patients with COVID-19.

Methods: A retrospective, single center, single arm study was performed over a 30-day period. In total, 138 patients (85.2%) met inclusion criteria. All patients were evaluated with non-contrast enhanced chest CT scan at hospital admission. CT-based lung segmentation was performed to calculate pathological lung opacities volume (LOV). At baseline, complete blood count (CBC) and inflammatory response biomarkers were obtained. The primary endpoint of the study was the occurrence of critical illness, as defined as, the need of mechanical ventilation and/or ICU admission. Mann-Whitney U test was performed for univariate analysis. Logistic regression analysis was performed to determine independent predictors of critical illness. Spearman analysis was performed to assess the correlation between inflammatory response biomarkers serum concentrations and LOV.

Results: Median LOV was 28.64% (interquartile range [IQR], 6.33–47.22%). Correlation analysis demonstrated that LOV was correlated with higher levels of D-dimer (r = 0.51, p < 0.01), procalcitonin (r = 0.47, p < 0.01) and IL6 (r = 0.48, p < 0.01). Critical illness occurred in 51 patients (37%). Univariate analysis demonstrated that inflammatory response biomarkers and LOV were associated with critical illness (p < 0.05). However, multivariate analysis demonstrated that only D-dimer and LOV were independent predictors of critical illness. Furthermore, a ROC analysis demonstrated that a LOV equal or greater than 60% had a sensitivity of 82.1% and specificity of 70.2% to determine critical illness with an odds ratio of 19.4 (95% CI, 4.2–88.9).

Conclusion: Critical illness may occur in up to 37% of the patients with COVID-19. Among patients with critical illness, higher levels of inflammatory response biomarkers with larger LOVs were observed. Furthermore, multivariate analysis demonstrated that pathological lung opacities volume was an independent predictor of critical illness. In fact, patients with a pathological lung opacities volume equal or greater than 60% had 19.4-fold increased risk of critical illness.

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1. Introduction

In December 2019, several cases of pneumonia of unknown etiology were reported in Wuhan (China). Clinical course of the new disease was diverse with symptoms severity ranging from mild disease to fatal respiratory insufficiency. In January 2020, the outbreak was reported in multiples cities of China [1] with cases now confirmed in different regions of the world [2]. The infectious origin of the disease was identified and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of the similarities with the SARS-coronavirus. Therefore, the disease caused by this new agent was officially named as Coronavirus disease 2019 (COVID-19) [3].

Initially, the spread of the disease was associated with regional travelers to Singapore, the Republic of Korea, Australia and some countries in Europe. In the beginning of the spread, cases were reported in Germany, Italy, and Spain, among others [4]. Currently, the Americas represent the region with the highest number of new cases in the world. Up to late June 2020, the Americas contributed with 47% of the new cases of COVID-19 worldwide. United States, Brazil and Mexico concentrate the highest number of COVID-19 fatalities in the region [5]. In September 2021, the Region of the Americas continues reporting the highest number of daily cases and of deaths [28].

COVID-19 has a wide spectrum of clinical manifestations ranging from the asymptomatic status to respiratory failure. Most frequent symptoms include fever, fatigue, myalgia, and anosmia [6]. In 81% of the cases the disease is mild to moderate requiring ambulatory medical management. In the remaining 19% of the cases, a severe disease is observed with 5% of the patients considered as critical [7]. Critical illness is considered in patients with acute respiratory distress syndrome (ARDS), clinically defined by severe hypoxemia, lung edema and acute onset of bilateral infiltrates [8]. The pathogenesis of ARDS is characterized by three phases: exudative, proliferative and fibrotic. Initially, alveolar endothelial and epithelial barriers injury occur secondary to the innate immune response that accumulates a protein-rich fluid with subsequent macrophages recruitment and secretion of pro-inflammatory cytokines leading to recruitment and cellular activation of additional macrophages and T-cells. The last 2 phases correspond to the healing process with an increased risk of morbidity and mortality [9].

Immune dysregulation is an important factor that contributes to progression of severe COVID-19. Initially, the innate immune response reacts against viral infection with the activation of monocytes, macrophages and dendritic cells, leading to the release of IL6 and subsequent release of further cytokines producing an immune phenomenon known as “cytokine storm”, characterized by a hyper inflammation phase [10].

In recent studies, elevated serum levels of IL6, D-dimer, ferritin and pro-calcitonin have been reported to be associated with severe COVID-19 secondary to a hyper inflammation state that is related to the need of mechanical ventilation and finally death [11] (Figure 1). Therefore, immune reduction of IL6 release has become a therapeutic option regulating the inflammatory response and prevention of COVID-19 progression [12].

Currently, chest imaging is an important instrument to assess patients with COVID-19. Chest-CT is an effective imaging method for detection of pulmonary injury [13], with typical findings including bilateral ground-glass opacities with peripheral distribution, crazy-paving, and the inverted halo sign [14] (Figure 2).

Similarly, chest CT findings have been reported to be associated with disease severity and progression [15, 16]. Quantitative and semi quantitative methods have been proposed to assess severity of lung injury [17]. Extensive pathological lung opacities have been documented in patients with severe stages of COVID-19. However, the association between abnormal chest CT findings and immune response dysregulation and clinical course of patients with COVID-19 is still not well understood.

Therefore, the purpose of this study is to assess the association between lung CT-based segmentation volumes and inflammatory response severity on outcomes of patients with COVID-19.

2. Materials and methods

2.1. Study population

After an institutional review board approval was obtained (Centro Medico Nacional 20 de Noviembre ethical committee, approval number 04.064–2020), we performed a retrospective, single center, single arm study of a prospectively maintained database. Because of the observational nature of our study, a waiver to the informed consent was approved by the IRB.

All the patients included in the study attended our institution with symptoms suspicious for COVID-19. At the triage consultation, patients were directed, to the respiratory emergency room (ER). As part of the baseline assessment, severity of symptoms were classified according the National Early Warning Score (NEWS) 2 [18] and Quick SOFA (qSOFA) scales [19]. Overall, patients with a NEWS-2 score higher than 4 and/or qSOFA score higher than 1 were admitted to the hospital. Furthermore,
At hospital admission patients underwent RT-PCR testing and non-contrast enhanced chest CT scanning. Electronic chart review was performed to collect baseline characteristics, including demographics, comorbidities and RT-PCR results.

Patients were not eligible to participate in our study if baseline chest CT was not performed at our institution, or technically limited chest CT exams that precluded adequate lung segmentation, or clinical evidence of other viral respiratory infections and/or incomplete clinical information that would not allow primary endpoint analysis.

2.2. CT-scanning protocol

Chest CT imaging was performed with two CT scanners (Siemens SOMATOM drive and Siemens SOMATOM emotion scanners, Siemens Healthineers, Germany). CT images were acquired with patients lying supine at the end of full inspiration tolerated by the patient. Scanning field of view extended from the apex to the base of the lungs. The following acquisition parameters were followed: 80–120kV tube voltage with tube current of 50–350 mAs, pitch of 0.99–1.22 mm, matrix of 512 × 512, slice thickness of 5 mm, field of view of 350 × 350 mm, lung window width between -1500 HU and -700HU. Chest CT images were reconstructed with a 1 mm slice thickness without inter slice gap, using filtered-back-projection reconstruction based on SOMATOM definition. Multiplanar reconstructions were based on axial 1 mm images.

2.3. CT-based lung segmentation

To perform lung segmentation analysis, lung window 1-mm slice thickness images were imported into the Alma Medical Workstation 5.0. Then, volume of interest (VOI) was defined for each lung according to threshold-based automated methods. Thresholds were defined in a manual chosen attenuation range [27]. An experienced radiologist reviewed VOI definition to adjust and finalize the definition of lung boundaries.

Finally, semiautomatic methods were used to delineate intrapulmonary sub organ structures [27] including the airway, blood vessels, and lesion boundaries. After segmentation was finalized, post-processed images were submitted for volumes calculation, as follows:

Homogenous non-pathological region- Normal lung volume (NLV): automatic segmentation based on thresholds defined by a range of Hounsfield Units between -1000 and -600. Structures other than non-pathological lung parenchyma were excluded using the semi-automated region-based tool. Finally, the segmentation was evaluated and approved by an expert radiologist.

Pathological opacities segmentation-Lung opacities volume (LOV) [30]: It indicates the extension of the hyperattenuating findings within the lung parenchyma related to the affection by COVID-19. Finding included zones of crazy paving, ground-glass opacity, and consolidation [22], (defined as increased attenuation or pathological opacities), among others [31].

The selected attenuation threshold ranged between -500 HU and 20 HU. The structures not related to pathological opacities were excluded with the semi-automatic option. Then, the segmentation of the lesion was approved by an expert radiologist (Figure 3).

Finally, a chest imaging expert performed a final review of lung segmentation. Inexact segmentation that may cause over or underestimation of lesion boundaries were corrected manually using ROI-based segmentation methods. After lung segmentation was completed, we performed a 3D reconstruction of the lung parenchyma for volumetric analysis. Volume calculations from each side were added to determine total NLV and LOV (Figure 4).

2.4. Laboratory results

Routine blood tests were performed at the baseline, including complete blood count (CBC), D-dimer, thrombin time, prothrombin time, aspartate aminotransferase (AST), alanine amino-transferase (ALT), glucose, creatinine, uric acid, ferritin, and interleukin-6 (IL-6).

2.5. Study outcomes

The primary endpoint of the study was the occurrence of critical illness, as defined as, admission to an intensive care unit (ICU) and/or the need of mechanical ventilation. Secondary endpoints included mortality of patients with critical illness.

2.6. Statistical analysis

Counts and percentages were used to report categorical variables. Continuous variables were reported using means with ± SD or median with interquartile range (IQR). Furthermore, all continuous variables were tested for normal distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. For variables with non-normal distribution, logarithmic transformation techniques were applied. However, lung segmentation results persisted with non-normal distribution after logarithmic transformation. Therefore, univariate analysis was performed using non-parametric analysis using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square/Fisher test.
Variables with univariate significant associations with the primary endpoint were included in a logistic regression model. To predict critical illness, odds ratios and 95% confidence intervals (95% CI) were calculated.

The diagnostic performance of our model was tested using the receiver operating characteristic curve method. We calculated the area under the curve index (ROC) to determine the optimal cutoff point predictive of critical illness including sensitivity and specificity.

SAS 9.4 software (SAS Institute, Cary, NC) was used for statistical analysis.

3. Results

A total of 162 patients were reviewed over a 30-day period. Only 24 patients (14.8%) failed inclusion and exclusion criteria assessment. Therefore, 138 patients (84 men [61%] and 54 women [39%]) with...
COVID-19 were included in the study. The mean age of our cohort was 47.3 years [± 14.3 years]. Among them, hypertension was present in 38 patients (28%), obesity in 33 (25%), diabetes in 33 (25%), and smoking history in 27 (20%).

After hospital admission, the median length of stay was 8 days (IQR, 5–11 days) with 51 patients (37%) requiring ICU admission/mechanical ventilation. In total, 29 of our patients (21%) died at a median time of 7 days (IQR, 4–11 days). Baseline serum inflammatory markers results showed a median IL6 level of 36.10 pg/ml (IQR 11.10–83.20 pg/ml), median ferritin of 677 ng/ml (IQR, 224–1302.5 ng/ml), procalcitonin of 0.175 (IQR 0.050–0.550) ng/ml, D-dimer of 0.90 (IQR 0.60–2.20) ng/ml, leukocytes of 7700 (IQR 6675–9970) cells/μl, and median neutrophil count of 63.9 % (IQR 5.98–80.7%).

### Values laboratory

| Variable                        | Overall (N = 138) | Critically Ill With Covid-19 (N = 51) | Not Critically Ill With Covid-19 (N = 87) | P value |
|---------------------------------|-------------------|---------------------------------------|-----------------------------------------|---------|
| IL6 (pg/ml)                     | 36.10 (IQR 11.10–83.20) | 60.9 (IQR 31.1–116) | 23.45 (IQR 6.29–53) | <0.01   |
| Ferritin (ng/ml)                | 677.0 (IQR 224.0–1302.5) | 1050 (IQR 444.5–1550) | 544 (IQR 191.5–1020) | 0.01    |
| Procalcitonin (ng/ml)           | 0.175 (IQR 0.050–0.550) | 0.49 (IQR 0.17–1.23) | 0.08 (IQR 0.05–0.23) | <0.01   |
| D-Dimer (mg/ml)                 | 0.90 (IQR 0.60–2.20) | 2.3 (IQR 0.9–14.6) | 0.70 (IQR 0.50–1.1) | <0.01   |
| Leukocytes (%)                  | 7700 (IQR 5625–9970) | 8.8 (IQR 6.7–12.4) | 7.1 (IQR 5.3–9.5) | 0.02    |
| Lymphocytes (%)                 | 8 % (IQR 15.20–18.30%) | 6.6 % (IQR 1.4–11.8) | 11.2 % (IQR 1.6–21.7) | 0.01    |
| Neutrophils (%)                 | 63.9 % (IQR 5.98–80.7%) | 73.7 % (IQR 7.5–85.3) | 61.3 % (IQR 5.4–74.3) | 0.02    |

### Severity scores

| Score        | Overall (N = 138) | Critically Ill With Covid-19 (N = 51) | Not Critically Ill With Covid-19 (N = 87) | P value |
|--------------|-------------------|---------------------------------------|-----------------------------------------|---------|
| News2        | 6 (IQR 4–8)       | 8 (IQR 6–10)                           | 5 (IQR 3–7)                             | <0.01   |
| qSofa        | 1 (IQR 0–1)       | 1 (IQR 1–2)                            | 1 (IQR 0–1)                             | <0.01   |
| SatO2 (%)    | 90% (IQR 80–93%)  | 79% (IQR 70.5–89.5)                    | 92% (IQR 88–94)                         | <0.01   |

** Statistical significance, p-value < 0.05.

### 3.3. Correlation analysis: lung segmentation and inflammatory response

Correlation analysis demonstrated a significant correlation between lung opacities volume and procalcitonin (r = 0.47, p < 0.01), D-Dimer (r = 0.52, p < 0.01), and IL6 (r = 0.48 p < 0.01). However, weak correlations between LOV and ferritin (r = 0.25, p = 0.01) and Neutrophils (r = 0.22, p = 0.01) were found (Figure 6).

### 3.4. Correlation analysis: lung segmentation and clinical severity scores

Significant correlations between lung opacities volume and clinical variables, such as: age (r = 0.39, p < 0.01), News-2 (r = 0.49, p < 0.01), and O₂ saturation (SpO₂) (r = -0.67, p<<0.01) were found. A weak correlation between LOV and qSofa score (r = 0.24 p<<0.01) was observed (Figure 7).

### Table 1. Demographics and baseline characteristics of patients with COVID-19 by critical illness.

| Variables                        | Overall (N = 138) | Critically Ill With Covid-19 (N = 51) | Not Critically Ill With Covid-19 (N = 87) | P value |
|----------------------------------|-------------------|---------------------------------------|-----------------------------------------|---------|
| Age (year)                       | 47.3 ± 14.3       | 52.7 ± 14.5                           | 44.1 ± 13.4                             | <0.01   |
| Gender (male)                    | 86 (61)           | 34 (67)                               | 50 (57)                                 | 0.28    |

### Table 2. CT-based lung segmentation volumes by critical illness.

| Lung Segmentation | Critically Ill With Covid-19 (N = 51) | Not Critically Ill With Covid-19 (N = 87) | P value |
|-------------------|---------------------------------------|-----------------------------------------|---------|
| Total Lung Volume (cc) | 2033 (IQR 1580–2389) | 2391 (IQR 1749–3190) | 0.002 |
| Lung Opacities Volume (%) | 50 (IQR 34–65) | 12.1 (IQR 1.5–31) | <0.01 |
| Lung Opacities Volume (cc) | 918 (IQR 680–1390) | 294 (IQR 40–604) | <0.01 |
| Normal Lung Volume (cc) | 982 (IQR 676–1523) | 2047 (IQR 1193–3046) | <0.01 |

** Statistical significance, p-value < 0.05.
3.5. Multivariate analysis

Following recommendation to build multivariate models, up to 5 independent variables were included in logistic regression models to adjust models to the total number of endpoint events. Different logistic regression models were analyzed including inflammatory response biomarkers, clinical parameters, and chest CT findings (Table 3). In the first model, inflammatory laboratories were analyzed. The model demonstrated that IL6 and D-dimer were independent predictors of critical illness (IL6: OR, 1.00 [95% CI, 1.00–1.02]; and D-dimer: OR, 1.41 [95% CI, 1.03–1.92]). Subsequently, IL6, D-dimer, and lymphocyte count were incorporated in a further analysis including clinical parameters. Neither qSOFAnor NEWS2 scores demonstrated statistical significance on multivariate analysis. Similarly, IL6 was not found to be an independent predictor of critical illness (OR, 1 [95% CI, 1–1.02]). In a final model, D-dimer, Lymphocytes, SpO2 and lung opacities volume were

Figure 5. Box and whiskers graphs illustrate differences on normal lung volume (cc) (A) lung opacities volume (cc) (B) and lung opacities volume (%) (C) between patients critically ill and not critically ill. Patients critically ill demonstrated larger pathological lung opacities volumes.

Figure 6. Correlation analysis between lung opacities volume and immune response. A) interleukin-6, B) Ferritin, C) Procalcitonin, D) D-dimer.
included in the analysis. Only, D-dimer and lung opacities volume were found to be independent predictors of critical illness (Figure 8).

### 3.6. Performance of lung opacities volume in critically illness

The ROC curve was used to assess the diagnostic performance of LOV on critically illness. The area under ROC curve was 0.85. A lung opacities volume (LOV) equal or greater than 60% demonstrated a sensitivity of 82.1% and a specificity of 70.2% to predict critical illness (adjusted OR = 19.4; 95% CI, 4.2–88.9) (Table 4 and Figure 9).

| Predictor             | OR (95%CI) | P Value |
|-----------------------|-----------|---------|
| Model 1               |           |         |
| IL6 (pg/ml)           | 0.98 (0.97-0.99) | <0.01   |
| Neutrophils           | 0.99 (0.97-1.01) | 0.36    |
| Procalcitonin         | 0.90 (0.79-1.03) | 0.13    |
| D-Dimer (mg/ml)       | 0.70 (0.51-0.96) | 0.03    |
| Ferritine (mg/ml)     | 0.99 (0.99-1.0) | 0.13    |
| Model 2               |           |         |
| IL6 (pg/ml)           | 0.98 (0.97-0.99) | <0.01   |
| D-Dimer (mg/ml)       | 0.67 (0.50-0.91) | 0.01    |
| Leucocytes            | 0.98 (0.83-1.17) | 0.89    |
| Lymphocytes (%)       | 1.05 (1.0-1.1)  | 0.02    |
| Model 3               |           |         |
| IL6 (pg/ml)           | 0.98 (0.97-0.99) | 0.01    |
| D-Dimer (mg/ml)       | 0.69 (0.51-0.94) | 0.02    |
| News2                 | 0.81 (0.58-1.1)  | 0.22    |
| Lymphocytes (%)       | 1.06 (1.01-1.1)  | 0.01    |
| qSofa                 | 0.84 (0.26-2.68) | 0.77    |
| Model 4               |           |         |
| D-Dimer (mg/ml)       | 0.66 (0.49-0.95) | 0.02    |
| Lymphocytes (%)       | 1.03 (0.98-1.08) | 0.14    |
| Lung Opacities Volume (cc) | 0.99 (0.99-0.99) | <0.01   |
| Model 5               |           |         |
| D-Dimer (mg/ml)       | 0.67 (0.47-0.95) | 0.02    |
| Lymphocytes (%)       | 1.03 (0.98-1.08) | 0.18    |
| Lung Opacities Volume (%) | 0.95 (0.92-0.97) | <0.01   |
| Model6               |           |         |
| D-Dimer (mg/ml)       | 0.70 (0.50-0.99) | 0.04    |
| Lymphocytes (%)       | 1.03 (0.98-1.08) | 0.23    |
| Lung Opacities Volume (%) | 0.95 (0.92-0.99) | 0.01    |
| SatO2 (%)             | 1.04 (0.95-1.13) | 0.37    |

*Statistical significance, p-value <0.05.

### 3.7. Survival analysis

Median freedom from critical illness time was 6 days (IQR, 2–9.5 days). Freedom from critical illness for patients with a LOV equal or greater than 60% was 31%, 20.5% and 20.5% at 5, 10 and 15 days, respectively; compared to patients with lower LOVs with a freedom from critical illness of 77%, 69% and 64% at 5, 10, and 15 days, respectively (p < 0.01) (Log-Rank = 13.99) (see Figure 10).

### 3.8. Mortality among patients critically ill

In the univariate analysis assessing mortality among patients critically ill, diabetes mellitus (p = 0.03), neutrophils (p = 0.01) and qSofa (p = 0.04) were found to be associated with death. Interestingly, patients that died were found to have lower D-dimer levels than patients that survived (p = 0.05) (Table 5).

### 4. Discussion

In our series, 37% of the patients with COVID-19 required mechanical ventilation and/or ICU admission with an overall mortality rate of 21%. Among patients critically ill, larger volumes of abnormal pathological opacities were found with higher levels of inflammatory response biomarkers. Furthermore, a strong correlation between CT-based lung opacities volumes and inflammatory response parameters were found. However, in multivariate analysis models only D-dimer and LOV were found to be significant predictors of critical illness. In fact, patients with a LOV equal or greater than 60% were found to have a 19.4-fold increased risk of critical illness.

Previous studies have reported that cytokine storm has been associated with severe COVID-19. In these patients, characteristic elevated serum levels of IL6 were found. Gao et al, analyzed different inflammatory response parameters in patients with severe COVID-19. They found that IL6 (OR, 17.304 [95% CI: 2.416, 123.933]; P = 0.005) and D-dimer (OR, 12.319 [95% CI: 1.716, 85.862]; P = .012) were significant predictors of sever COVID-19 [20]. Similarly, Herold et al. found that higher serum levels of IL6 and CRP were predictors of mechanical ventilation [21]. In our series, we found that IL6, Ferritin, D-dimer were associated with critical illness. However, in the multivariate analysis, D-dimer (OR, 1.41; 95% CI, 1.01–1.97) was the only significant predictor of mechanical ventilation and/or ICU admission.

Similarly, clinical scales have been studied to assess the severity of COVID-19 symptoms. Jang et al. studied symptoms severity of 110 hospitalized patients using the NEWS2, qSOFa and SIRS scales. Patients with critical illness were found to have higher scores of NEWS2, qSOFa and SIRS scores, with a significant superiority of the NEWS2 score system [22]. In a different study, Gidari et al reported that the NEWS2 score was a significant predictor of ICU admission [23]. In our results, patients with critical illness were found to have a higher NEWS 2 score at hospital
admission with a significant lower SpO2. Multivariate analysis, however, failed to demonstrate significant association between severity scores and the need of mechanical ventilation and/or ICU admission.

To assess the severity of patients with COVID-19, chest CT has been used to evaluate pulmonary injury and extension of pathological opacities [24]. Furthermore, imaging-based severity scores including quantification of the lung findings have been proposed. Li et al proposed a chest...
CT-based score including the quantification of the affected lung segments as percentages. They found that a higher percentage of lung injury was associated with a severe form of COVID-19 [25]. In a different study, a significant association between lung opacities extension and disease severity was found. In the same study, a significant correlation between affected lung volume with IL6 levels was found [26]. In our study, similar results were found. We found a significant correlation between LOV and IL6, D-dimer, procalcitonin and ferritin levels. Similarly, LOV demonstrated a significant correlation with NEWS-2 score and an inverse correlation with SpO2. In multivariate models, however, only LOV was found to be an independent predictor of adverse course of patients with COVID-19 requiring mechanical ventilation and/or ICU admission.

According to our results, the quantification of pathological lung opacities, using lung segmentation methods, was an important instrument to assess immune response severity and to evaluate the risk of adverse outcomes of patients with COVID-19. Furthermore, patients with pathological lung opacities extension equal or greater than 60% was associated with a 19-fold increase on the risk of critical illness. In fact, patients with a pathological lung opacities volume greater than 60% had significantly decreased freedom from critical illness period; certainly, only 20% of the patients reached 15 days. Additionally, patients that required mechanical ventilation at the time of hospital admission had almost twice the volume of pathological lung opacities than patients that were admitted without the need of mechanical ventilation.

Recently, many severity prognostic models have been proposed for COVID-19. However, in a recent systematic review Wynants et al [32, 33] reported that most studies that used imaging findings to determine outcomes of COVID-19, were at high risk of bias due to the use subjective and unclear scores. Therefore, reproducible, and objective imaging analysis methods should be used to complement clinical findings assessing outcomes of COVID-19 [32,33]. In our study, we suggest that CT-based lung segmentation analysis should be added to the assessment COVID-19 severity and prognosis.

Our results corroborated previous reports indicating an association between the inflammatory response and severity of respiratory insufficiency in patients with COVID-19, according to different clinical scales used in respiratory emergency rooms. Additionally, lung volumes measured using CT-based segmentation, were found to be significantly associated with clinical severity of respiratory insufficiency and biomarkers of inflammatory response. These findings may support the hypothesis proposed by different authors trying to describe the pathophysiology of severe COVID-19, where a disproportionate release of cytokines cause extensive lung damage and multi organ failure. Frisonni et al in a recent study performed in patients that died due to COVID-19 reported an association between pro-inflammatory cytokines (IL-1β, IL-6, IL-15, and TNF-α) and SARS-CoV-2 infection [29].

Limitations of our study include: 1. Retrospective design including only patients with COVID-19 that required hospital admission. However, a systematic and standardized protocol was used to enroll patients in our

| Table 5. Univariate analysis assessing mortality of COVID-19 patients critically ill. |
|----------------------|----------------------|----------------------|----------------------|
| **Variables**        | **Patient Critically Ill That Died (N = 28)** | **Patient Critically Ill That Survived (N = 23)** | **P value** |
|----------------------|----------------------|----------------------|----------------------|
| Age (year)           | 57(IQR 46–63.5)      | 55(IQR 38–62)        | 0.27                 |
| Gender (male)        | 17 (61)              | 17 (61)              | 0.31                 |
| Comorbidities        |                       |                      |                      |
| Hypertension         | 13 (46)              | 6 (27)               | 0.16                 |
| Diabetes             | 13 (46)              | 4 (18)               | 0.03                 |
| COPD*                | 2 (7)                | 1 (4)                | 1                    |
| Cardiovascular       | 2 (7)                | 4 (18)               | 0.38                 |
| Obesity              | 8 (32)               | 10 (45)              | 0.34                 |
| Laboratory/Severity score |                     |                      |                      |
| Neutrophils (%)      | 83.4(IQR 61–89)      | 16(IQR 6.81)         | 0.01                 |
| qSofa                | 1Q(1–2)              | 1Q(0–1)              | 0.04                 |
| D-Dimer (mg/ml)      | 5.05(IQR 2.3–16.4)   | 1.30(IQR 0.6–11.5)   | 0.05                 |
| Lung Segmentation    |                       |                      |                      |
| Lung Opacities Volume (%) | 47(IQR 31–63) | 52(IQR 36–66)        | 0.78                 |

*COPD: Chronic obstructive Pulmonary Disease.

**Statistical significance, p-value <0.05.

Figure 10. Freedom from critical illness according to Kaplan-Meier Curve of patients by LOV ≥ 60% and < 60%.
study. To determine hospital admission eligibility, all our patients were evaluated in the emergency department using NEWS 2 and qSOFA scales.

2. Lung segmentation was performed using a commercially available software that required final verification by a radiologist (semi-automated methods). 3. Extension of abnormal lung opacities on CT were used as a surrogate of COVID-19 injury. However, histologic confirmation of CT findings was not performed. 4. Patients with severe dyspnea were not able to tolerate prolonged full inspiration. Therefore, lower total lung volumes were observed in patients with severe disease. To prevent bias, we decided to use the ratio between total lung volume and affected lung (expressed in percentage) to determine extension of lung affection (LOV).

We believe that further studies are needed to evaluate and replicate our results assessing the impact of LOV cutoff points on predicting the occurrence of critical disease. Further studies are needed to replicate and validate our results, specifically the impact of LOV cutoff points assessing the probability of critical illness.

5. Conclusions

In conclusion, critical illness may occur in up to 37% of the patients with COVID-19 with an overall mortality rate of 21%. Among patients with critical illness, higher serum concentrations of inflammatory response biomarkers with larger pathological lung opacities volumes were observed. Furthermore, after multivariate analysis LOV was determined as an independent predictor of critical illness. In fact, a lung opacities volume equal or greater than 60% was associated with a 19.4-fold increased risk of critical illness. Among them, the mortality rate was 55%.

Declaration

Author contribution statement

Christian Alexander Torres-Ramirez; David E Timaran-Montenegro: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Edgar Tapia-Rangel; Rafael Punzo; Leonardo Morales-Jaramillo; Yohana Mateo-Camacho: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Pedro Saenz; Lina Parrar; Daniel Obando; Valeria Morales; Katherine Jacome; Ana Hernandez; Jovana Govea Palma; Daniela Fuentes; Gustavo Feria; Manuel Falla; Giovanni Contla; Joshua Chavez & Santiago Carrillo: Contributed reagents, materials, analysis tools or data.

Julita Orozco-Vazquez & Dulce Bonifacio: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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