Quantitative Burden of COVID-19 Pneumonia on Chest CT Predicts Adverse Outcomes: A Post-Hoc Analysis of a Prospective International Registry

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Summary Statement

Quantitative burden of consolidation or ground-glass opacities on chest CT predicts clinical deterioration or death in COVID-19 pneumonia.

Key Points
1. An increasing quantitative burden of consolidation or increasing attenuation of ground glass opacities on chest CT independently predict risk of clinical deterioration or death in COVID-19 pneumonia.
2. A burden of consolidation of greater than or equal to 1.8% or ground glass opacities of greater than or equal to 13.5% confers an approximately five-fold greater risk of adverse outcomes.
3. CT-derived quantitative lung measures have incremental prognostic value over and above other clinical parameters.

Abbreviations
COVID-19 = coronavirus disease 2019, GGO = ground glass opacities, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
ABSTRACT

Purpose: To examine the independent and incremental value of CT-derived quantitative burden and attenuation of COVID-19 pneumonia for the prediction of clinical deterioration or death.

Methods: This was a retrospective analysis of a prospective international registry of consecutive patients with laboratory-confirmed COVID-19 and chest CT imaging, admitted to four centers between January 10 and May 6, 2020. Total burden (expressed as a percentage) and mean attenuation of ground glass opacities (GGO) and consolidation were quantified from CT using semi-automated research software. The primary outcome was clinical deterioration (intensive care unit admission, invasive mechanical ventilation, or vasopressor therapy) or in-hospital death. Logistic regression was performed to assess the predictive value of clinical and CT parameters for the primary outcome.

Results: The final population comprised 120 patients (mean age 64 ± 16 years, 78 men), of whom 39 (32.5%) experienced clinical deterioration or death. In multivariable regression of clinical and CT parameters, consolidation burden (odds ratio [OR], 3.4; 95% confidence interval [CI]: 1.7, 6.9 per doubling; P = .001) and increasing GGO attenuation (OR, 3.2; 95% CI:
1.3, 8.3 per standard deviation, \( P = .02 \) were independent predictors of deterioration or death; as was C-reactive protein (OR, 2.1; 95% CI: 1.3, 3.4 per doubling; \( P = .004 \)), history of heart failure (OR 1.3; 95% CI: 1.1, 1.6, \( P = .01 \)), and chronic lung disease (OR, 1.3; 95% CI: 1.0, 1.6; \( P = .02 \)). Quantitative CT measures added incremental predictive value beyond a model with only clinical parameters (area under the curve, 0.93 vs 0.82, \( P = .006 \)). The optimal prognostic cutoffs for burden of COVID-19 pneumonia as determined by Youden’s index were consolidation of greater than or equal to 1.8% and GGO of greater than or equal to 13.5%.

**Conclusions:** Quantitative burden of consolidation or GGO on chest CT independently predict clinical deterioration or death in patients with COVID-19 pneumonia. CT-derived measures have incremental prognostic value over and above clinical parameters, and may be useful for risk stratifying patients with COVID-19.
INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an unprecedented global health crisis, with over 29.7 million confirmed cases worldwide as of September 17, 2020 (1). The most critical complication is acute respiratory failure requiring invasive mechanical ventilation, occurring in up to 17% of patients (2,3) which is associated with a high rate of in-hospital mortality (4,5). While the reverse transcription polymerase chain reaction (RT-PCR) assay is considered the reference standard for diagnosing COVID-19 infection (6), chest CT has greater sensitivity for early disease detection (7). This is particularly useful in patients in whom initial RT-PCR testing is negative and a high clinical suspicion remains (8). Furthermore, chest CT findings can indicate disease stage (9-11) and predict adverse outcomes (12,13) in COVID-19 pneumonia.

Characteristic CT abnormalities are bilateral patchy ground glass opacities (GGO) with or without consolidation in a peripheral, posterior, and diffuse or lower lung zone distribution (9-11). Increasing lung consolidation is typically observed later in the disease course (10,11) and is associated with critical illness (13,14). Studies have demonstrated that the extent of diseased lungs in COVID-19 pneumonia assessed by visual scoring correlates with clinical disease severity (15,16). Further, a reduction in well-aerated lung volume quantified using software has been shown to predict adverse outcomes (12). However, to the best of our knowledge, no international studies have examined the prognostic value of the quantitative burden of COVID-19 pneumonia by its lesion components. In this post-hoc analysis of a prospective, international, multicenter registry, we sought to examine the independent and incremental value of CT-derived quantitative burden and attenuation of diseased lung (GGO or consolidation) for the prediction of clinical deterioration or death in COVID-19 pneumonia.
MATERIALS AND METHODS

Study Design

This retrospective analysis was conducted with the approval of local institutional review boards (Cedars-Sinai Medical Center IRB# study 617) and written informed consent was waived for fully anonymized data analysis.

This prospective, international, multicenter registry included patients from: North America (Cedars Sinai Medical Center, Los Angeles, USA \(n = 41\)), Europe (Centro Cardiologico Monzino \(n = 56\), and Istituto Auxologico Italiano \(n = 17\) both Milan, Italy), and Australia (Monash Medical Centre, Victoria, Australia \(n = 6\)) enrolled consecutive patients who underwent chest CT and had a positive RT-PCR test result for SARS-CoV-2 during their index admission between January 10 and May 6, 2020 (Figure 1). For patients with serial chest CT imaging, we included only the results of their initial scan. A rapid (results in minutes to hours) RT-PCR test was not available at any of the four institutions during this period, and the two Italian centers had resource constraints necessitating urgent patient triage. Hence, the primary indication for initial chest CT in all centers was a high clinical suspicion for COVID-19 in the setting of a high pretest probability (a high community disease burden in Italy) or comorbidities associated with severe illness from COVID-19 (United States and Australian centers). The CT images from each patient and the clinical database were fully anonymized and transferred to Cedars-Sinai Medical Center for core lab analysis.

Scan Protocol and Image Reconstruction

Chest CT scans were performed with different multi-slice CT systems: Aquilion ONE (Toshiba Medical Systems, Otawara, Japan); GE Revolution, GE Discovery CT750 HD, or LightSpeed VCT (GE Healthcare, Milwaukee, WI, USA); and Brilliance iCT (Philips Healthcare, Cleveland, OH,
In press

USA). Parameters used for scans without intravenous contrast included a peak x-ray tube voltage of 120 kV, automatic tube current modulation (300-500 mAs), and slice thickness of 0.625 to 1.25 mm. The protocol for contrast-enhanced included a peak x-ray tube voltage of 120 kV, automatic tube current modulation (500-650 mAs), and slice thickness of 0.625 to 1.0 mm. A total of 80–100 ml iodinated contrast material (Iomeron 400, Bracco Imaging SpA, Milan, Italy; or Ominpaque 350, GE Healthcare, United States) was injected intravenously at a rate of 5 ml/s and followed by 20-30ml of saline chaser at flow are of 4-5 ml/s. Images were reconstructed using standard lung filters specific to each CT vendor. All scans were obtained in the supine position during inspiratory breath-hold.

**CT Image Analysis**

Images were analyzed at the Cedars-Sinai Medical Center core laboratory by two physicians (K.G. and A.L.) with 3 and 8 years of experience in chest CT, respectively, and who were blinded to clinical data. A standard lung window (width of 1500 Hounsfield units [HU] and level of −400 HU) was used. Lung abnormalities were quantified using semi-automated research software (FusionQuant Lung v1.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA). First, both lungs were segmented by a deep learning model based on U-Net architecture (17). The acquired pulmonary mask and a second deep learning model trained with the Lung Tissue Research Consortium dataset (18) were then used to compute lobe segmentations, with manual adjustments made by the reader as required. The right lung was divided into upper, middle, and lower lobes with respect to the horizontal and oblique fissures; while the left lung was separated into upper and lower lobes by the oblique fissure.

Lung abnormalities associated with COVID-19 pneumonia were then segmented using a semi-automated brush-like tool; the boundaries of which were delimited by a region-growing
algorithm. Adaptive thresholds were used, defined by a fixed window around the attenuation of the pixel clicked by the operator. Lesion segmentations were labeled according to their components: GGO, consolidation, or pleural effusion using the Fleischner Society lexicon (19) (Figure 2). Chronic lung abnormalities, such as emphysema or fibrosis, were excluded from segmentation, based on correlation with previous imaging and/or a consensus reading. GGOs were defined as hazy opacities that did not obscure the underlying bronchial structures or pulmonary vessels; consolidation as opacification obscuring the underlying bronchial structures or pulmonary vessels; and pleural effusion as a fluid collection in the pleural cavity. Volumes of lesion components and their respective burdens ([total lesion volume/total lung volume] x 100%) were automatically calculated by the software. The attenuation of lesion components was defined as the mean attenuation in HU of the total lesion volume. The average time taken for full lung and lesion segmentation ranged from 10-20 minutes depending on patient anatomy and extent of pneumonia. The axial distribution of lung abnormalities was visually classified as: peripheral (predominantly outer one-third of the lung), central (predominantly inner two-thirds of the lung), or diffuse (no clear distribution pattern) (12). The presence of any breathing artifact was also noted. Each scan was reviewed slice-by-slice by the expert readers to ensure accurate segmentation of COVID-19 pneumonia and exclude false positive opacities. Difficult cases of visual or quantitative analysis were resolved by consensus.

Outcomes and Definitions
The primary outcome was a composite of clinical deterioration (intensive care unit admission, invasive mechanical ventilation, or vasopressor therapy) or death. The time to first occurrence of any one of the components was documented. Chronic lung disease included asthma, chronic obstructive pulmonary disease, and/or obstructive sleep apnea. Chronic
kidney disease was defined as estimated glomerular filtration rate of less than 60 ml/min/1.73m². Immunodeficiency was defined as active cancer treated with chemotherapy or human immunodeficiency virus infection. Patient symptoms were self-reported upon hospital admission. Serum laboratory values were obtained at hospital admission.

**Statistical Analysis**

Data were tested for normality using the Shapiro–Wilk test. Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as absolute numbers (percentage). Continuous variables were compared using the Student’s t-test or nonparametric Mann-Whitney U-test, as appropriate. Categorical variables were compared using a Chi-square test. Univariable logistic regression analysis was performed to evaluate the association of individual clinical factors and CT measures with the primary outcome. Based on these results and prognostic variables established by prior studies (3,20,21), the following clinical predictors were entered into backward stepwise multivariable logistic regression analysis: age, sex, diabetes mellitus, hypertension, smoking history, chronic lung disease, history of heart failure, history of coronary artery disease, chronic kidney disease, and serum C-reactive protein level (Model 1). To this, we added the following CT parameters based on univariable analysis and their clinical applicability: burden (%) and mean attenuation (HU) of GGO and consolidation (Model 2). Lesion burden and C-reactive protein were not normally distributed and hence normalized with logarithmic adjustment; base-2 log transformation was used as this represented doubling of the variable. The performance of the two models was assessed using receiver operating characteristic analysis, and the area under the curve values were compared using the DeLong test. We selected the optimal cutoff values for quantitative burden of GGO and consolidation by identifying the receiver operating characteristic values that maximized
Youden’s J statistic (sensitivity + specificity - 1). A two-sided P-value < .05 was considered statistically significant. All analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA).
RESULTS

Patient Characteristics

The final study population comprised 120 patients (mean age 64 ± 16 years, 78 men) with laboratory-confirmed COVID-19 who underwent chest CT during their admission. The primary outcome occurred in 39 (32.5%) patients: 30 (25.0%) were admitted to an intensive care unit, 15 (12.5%) required mechanical ventilation, 17 (14.2%) received vasopressors, and 15 (12.5%) died. The median time from self-reported onset of symptoms to chest CT was 6 days (IQR, 4-8 days), and the median time from chest CT to the occurrence of the primary outcome was 3 days (IQR, 1-12 days). The remaining patients (n = 81; 67.5%) did not require critical care or had been discharged alive at the time of data collection.

Patients who experienced deterioration or death were older and had a greater number of comorbidities compared to those who did not experience deterioration or death (72 ± 13 vs 60 ± 16 years, P < .001) (Table 1). Presenting symptoms were similar between the two groups. Serum inflammatory markers were increased in patients with versus those without the primary outcome (Table 1).

Chest CT Findings

The median time from chest CT to positive RT-PCR testing was 0 (IQR, 0-3) days. A total of 93 (77.5%) patients underwent noncontrast chest CT, while the remaining 27 (22.5%) underwent CT angiography for exclusion of pulmonary embolism. Breathing artifacts were observed in 25 (20.8%) patients. The prevalence of lung abnormalities was comparable between the two groups, apart from pleural effusion being more common in patients with versus without deterioration or death (33.3% vs 8.6%, P = .001) (Table 2). The extent of COVID-19 pneumonia was predominantly bilateral and involving at least three lung lobes in both groups. Patients...
that underwent deterioration or death more frequently had a diffuse axial distribution of lung abnormalities (71.1% vs 50.0%, \( P = .03 \)) compared to those without deterioration or death.

Quantitative lung features on CT are summarized in Table 3 and Figure 3. Patients with deterioration or death had a higher total burden of COVID-19 pneumonia compared to patients that did not experience deterioration or death (25.9% [IQR, 11.9–49.7%] vs 6.5% [IQR, 1.5–11.9%]; \( P < .001 \)). With respect to lesion components, patients who deteriorated or died had a near three-fold greater GGO burden (14.2% [IQR, 4.3–35.6%] vs 5.8% [IQR, 1.1–11.0%]) and 15-fold greater consolidation burden (2.8% [IQR, 0.3–11.9%] vs 0.2% [IQR, 0.0–1.1%]; both \( P < .001 \)) compared to patients who did not require critical care or were discharged alive. The mean attenuation of GGO was higher in patients that experienced deterioration or death than those that did not (-437.7 ± 120.2 HU vs -510.3 ± 126.9 HU, \( P = .004 \)). Figures 4 and 5 show representative cases of CT findings in each of the outcome groups.

**Predictors of Clinical Deterioration or Death**

The results of the univariable logistic regression analysis are summarized in Table E1 (supplement). In multivariable analysis of clinical parameters, serum C-reactive protein was the only independent predictor of deterioration or death (OR, 2.1; 95% CI: 1.3, 3.4, \( P = .001 \); Table 4, Model 1). In multivariable analysis of clinical and quantitative CT parameters, burden of consolidation (OR, 3.4; 95% CI: 1.7, 6.9; \( P = .001 \)) and attenuation of GGO (OR, 3.2; 95% CI: 1.3, 8.3 per one standard deviation increase; \( P = .02 \) were independent predictors of deterioration and death, as was C-reactive protein, history of heart failure, and chronic lung disease (Table 4, Model 2). Quantitative CT measures added incremental value in risk prediction over and above the model with clinical parameters (area under the curve 0.93 vs 0.82, \( P = .006 \); Figure 6). The optimal cutoff values for COVID-19 pneumonia burden as
determined by Youden’s index were GGO of greater than or equal to 13.5% and consolidation of greater than or equal to 1.8%, above which there was a steep increase in the risk of deterioration and death with OR of 5.1 (95% CI: 1.5, 3.6; \( P = .008 \)) and an OR of 4.8 (95% CI: 1.5, 10.2, \( P = .007 \)) respectively, adjusted for clinical parameters.
DISCUSSION

COVID-19 pneumonia is associated with substantial morbidity and mortality (1,2) and has overwhelmed healthcare systems worldwide (22,23). The daily number of new COVID-19 cases globally reached a record high on June 7 2020 (1) and there is also the looming threat of recurrent post-pandemic outbreaks (24). Early risk stratification would assist medical staff in triaging infected patients and allocating limited healthcare resources. In this international multicenter study of patients with COVID-19, we found (a) an increasing quantitative burden of consolidation or increasing attenuation of GGO on chest CT independently predicts risk of clinical deterioration or death; (b) burden of consolidation of greater than or equal to 1.8% or GGO of greater than or equal to 13.5% confers an approximately five-fold greater risk of adverse outcomes; (c) CT-derived quantitative lung measures have incremental prognostic value over and above clinical parameters.

The major histopathological finding in COVID-19 pneumonia is diffuse alveolar damage, characterized by inflammatory infiltrates and intra-alveolar edema and exudates(25,26). GGO on CT are thought to represent an early exudative phase of this disease, progressing to consolidation with intra-alveolar organization, fibroblastic proliferation, and alveolar collapse (25). Accordingly, chest CT within the first five days of symptom onset typically demonstrates a GGO-predominant pattern, followed by increasing consolidative changes for up to 14 days (9-11,27). Hence, consolidation represents the peak stage of COVID-19 pneumonia, and its presence corresponds to the phase of infection when patients are most critically ill (3). As demonstrated by the present analysis and prior investigators (13,14), consolidation is more common in patients who experience respiratory failure, intensive care unit admission, or death compared to those with an uncomplicated hospital course. Further, we showed an
increasing burden of consolidation to independently predict adverse outcomes; the same association was not observed for burden of GGO. An increasing attenuation of GGO to less negative attenuation values in the lung parenchyma had prognostic importance; this likely reflects the underlying pathophysiology of progressive alveolar filling and loss of lung volume in the evolution of the pneumonia to consolidation.

Semi-quantitative scoring of the extent of COVID-19 pneumonia has been shown to associate with duration of infection (9-11) and clinical disease severity (15,16). However, these metrics are based on visual assessment and do not characterize specific lung abnormalities associated with COVID-19. More recently, Colombi et al (12) demonstrated that software-based quantification of well-aerated lung volume using HU thresholds can be used to predict the risk of intensive care unit admission or in-hospital mortality. In a Chinese multicenter study, Yu et al (13) quantified the lesion volume percentage in each lung lobe using a deep learning algorithm. They reported larger consolidation lesions, but not larger GGO lesions, to associate with increased risk of adverse outcomes. However, their lesion measurements did not exclude underlying lung abnormalities such as emphysema or fibrosis, and their prediction models were not adjusted for clinical variables. By contrast, the semi-automated method used in this analysis specifically quantified lung disease burden due to COVID-19 pneumonia, and we demonstrated the predictive value of consolidation burden to be independent of clinical risk factors. Ours was an international multicenter study, inclusive of institutions in two countries worst afflicted by COVID-19: the United States, with the most cases worldwide; and Italy, which was devastated by rapid contagion early in the global outbreak (1).

It is established that the presence and number of comorbidities predict clinical outcomes in patients with COVID-19 (20). Specifically, older age, chronic cardiac or pulmonary disease,
hypertension, diabetes, and chronic kidney disease all confer an increased risk of in-hospital mortality (3,20,21). Elevated serum C-reactive protein levels on admission have also been shown to associate with a greater risk of worse clinical course (28,29). While chest CT is not routinely used as a first-line investigation to diagnose COVID-19, it has an auxiliary role to RT-PCR testing and can also aid in subsequent management of infected patients (30,31). A systematic review of 16 COVID-19 risk prediction models showed age and CT features to be the most frequently reported predictors of adverse in-hospital outcomes (20). However, few studies have combined clinical variables with chest CT for prognostication in COVID-19 pneumonia (12,32). Here, we demonstrate that a model integrating clinical parameters and CT-derived quantitative measures outperforms a model with clinical parameters alone in predicting clinical deterioration or death. Further, consolidation burden and GGO attenuation on CT were the strongest predictors of risk when adjusted for age, comorbidities, and C-reactive protein.

We determined optimal cutoffs for percentage of consolidation or GGO above which there was a steep increase in the risk of clinical deterioration or death. These thresholds have the potential to aid rapid risk stratification of patients with COVID-19 who undergo chest CT. Studies have shown good agreement between visual and software-based quantification of percentage lung involvement on CT in COVID-19 pneumonia (12,33). Further, excellent inter-rater agreement among radiologists for visually-estimated extent of consolidation or GGO has been demonstrated in studies of patients with chronic lung disease (34,35). These reported agreement values suggest that a burden of GGO of greater than or equal to 13.5% or consolidation of greater than or equal to 1.8% on CT could be reliably estimated by clinicians’ visual assessment in real time. Moreover, these CT parameters could be used as candidate
predictors for new clinical risk prediction scores which are rapidly entering the literature(20). Combining such imaging features with clinical variables may in the future identify patients at high risk who would benefit from more aggressive treatment and closer monitoring. It should be noted that most patients in our study had a mixed pattern of COVID-19 pneumonia with both GGO and consolidation, and further studies are needed to determine prognostic cutoff values for burden of GGO and consolidation at different stages of COVID-19 pneumonia.

Our study has several limitations. Different patient profiles and treatment protocols between countries may have resulted in heterogeneity in COVID-19 pneumonia severity or in-hospital outcomes. Furthermore, chest CT indications and acquisition protocols were not standardized across centers. Data on patients’ respiratory status at the time of intensive care unit admission was not uniformly available, however, we included intubation and invasive ventilation as a hard endpoint. We did not evaluate follow-up CT findings since they were not available for all patients. The effect of treatment on outcomes was not examined; however, supportive care remains the mainstay of therapy in COVID-19 and few patients in our study received targeted interventions. Finally, serum levels of D-dimer, interleukin-6, lactate dehydrogenase, and troponin were not uniformly available and thus not included in our risk prediction models.

Quantitative burden of consolidation or ground glass opacities on chest CT independently predicts clinical deterioration or death in COVID-19 pneumonia. CT-derived quantitative lung measures have incremental prognostic value beyond clinical parameters, and may be useful for clinical risk stratification in patients with COVID-19.
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Table 1. Clinical and Laboratory Characteristics of Patients on Admission

| Clinical characteristics                      | Yes (n = 39) | No (n = 81) | P value |
|-----------------------------------------------|--------------|-------------|---------|
| Age, years                                    | 72 ± 13      | 60 ± 16     | < .001  |
| Male sex                                      | 27 (69.2)    | 51 (63.0)   | 0.5     |
| Body mass index, kg/m²                         | 27.2 ± 4.8, 25 | 26.6 ± 3.7, 31 | .64     |
| Hypertension                                  | 27 (69.2)    | 36 (44.4)   | .01     |
| Diabetes mellitus                             | 17 (43.6)    | 14 (17.3)   | .002    |
| Hyperlipidemia                                | 19 (48.7)    | 22 (27.2)   | .02     |
| Smoking status                                |              |             |         |
| Former smoker                                 | 9 (23.1)     | 10 (12.4)   | .21     |
| Current smoker                                | 0 (0.0)      | 2 (2.5)     |         |
| History of lung disease                       | 9 (23.1)     | 8 (9.9)     | .05     |
| History of heart failure                      | 11 (28.2)    | 5 (6.2)     | .001    |
| History of coronary artery disease            | 25 (64.1)    | 14 (17.3)   | .009    |
| Chronic kidney disease                        | 9 (23.1)     | 7 (8.6)     | .03     |
| Immunodeficiency                              | 4 (10.3)     | 1 (1.2)     | .02     |
| Symptoms                                      |              |             |         |
| Fever                                         | 24 (61.5)    | 65 (80.2)   | .03     |
| Chills                                        | 3 (7.7)      | 9 (11.1)    | .56     |
| Fatigue                                       | 24 (61.5)    | 51 (63.0)   | .88     |
| Dyspnea                                       | 25 (64.1)    | 42 (51.9)   | .21     |
| Dry cough                                     | 23 (59.0)    | 36 (44.4)   | .14     |
| Sputum production                             | 3 (7.7)      | 5 (6.2)     | .76     |
| Hemoptysis                                    | 0 (0.0)      | 2 (2.5)     | .32     |
| Sore throat                                   | 2 (5.1)      | 3 (3.7)     | .72     |
| Loss of smell                                 | 0 (0.0)      | 4 (4.9)     | .16     |
| Loss of taste                                 | 1 (2.6)      | 5 (6.2)     | .4      |
| Muscle and/or joint pain                      | 14 (35.9)    | 31 (38.3)   | .8      |
| Headache                                      | 7 (17.9)     | 13 (16.0)   | .79     |
| Nasal congestion                              | 6 (15.4)     | 7 (8.6)     | .27     |
| Nausea or vomiting                            | 6 (15.4)     | 5 (6.2)     | .1      |
| Diarrhea                                      | 6 (15.4)     | 9 (11.1)    | .51     |
| Blood laboratory results*                     |              |             |         |
| Lymphocytes, % (n = 14, 66)                   | 22.7 (18.2 – 26.3) | 17.8 (12.4 – 22.6) | .03     |
| Lactate dehydrogenase, U/L, (n = 11, 57)      | 465 ± 248    | 271 ± 103.8 | < .001  |
| C-reactive protein, mg/L (n = 36, 70)         | 104.8 (52.7 – 201.3), 36 | 17.1 (5.2 – 54.0), 70 | < .001  |
| Ferritin, ng/mL (n = 29, 30)                  | 863 (537 – 1364) | 540 (427 – 709) | .02     |
| Prothrombin time, s (n = 9, 43)               | 13.6 (12.4 – 14.5) | 12.4 (1.3 – 13.6) | .35     |
|                          | Yes (95, 100) | No (50, 67) | p     |
|--------------------------|---------------|-------------|-------|
| D-dimer, μg/mL (n = 26, 37) | 2.1 (0.8 – 3.6) | 0.7 (0.4 – 1.2) | < .001 |
| Troponin, ng/mL (n = 30, 41) | 0.28 (0.1 – 0.50) | 0.01 (0.01 – 0.05) | < .001 |
| Creatine phosphokinase, U/L (n = 8, 56) | 57 (24 – 122) | 63 (34 – 83) | .99   |
| Interleukin-6, pg/mL (n = 19, 6) | 8.1 (3.9 – 12.7) | 3.8 (2.1 – 7.0) | .08   |

Note.—Data are expressed as n (%), median (IQR), or mean ± standard deviation.

*Not all patients had blood laboratory results available. The first n value is for the “Yes” group while the second n value is for the “No” group. These indicate the number of patients that had blood samples collected for these metrics.
Table 2. Classification and Distribution of Lung abnormalities on Chest CT

| Lung abnormality                                      | Clinical deterioration or death |       |       | P value |
|-------------------------------------------------------|---------------------------------|-------|-------|---------|
|                                                       |                                 | Yes   | No    |         |
|                                                       |                                 | (n = 39) | (n = 81) |         |
| Only ground-glass opacities                           |                                 | 4 (10.3) | 11 (13.6) | .61     |
| Only consolidation                                    |                                 | 0 (0.0) | 1 (1.2) | .049    |
| Ground-glass opacities and consolidation              |                                 | 34 (87.2) | 62 (76.5) | .17     |
| Pleural effusion                                      |                                 | 13 (33.3) | 7 (8.6) | .001    |
| Emphysema                                             |                                 | 4 (10.3) | 6 (7.4) | .60     |
| Fibrosis                                              |                                 | 3 (7.7) | 3 (3.7) | .35     |
| None                                                  |                                 | 1 (2.6) | 7 (8.6) | .21     |
| Laterality*                                           |                                 |       |       |         |
| Unilateral                                            |                                 | 2 (5.3) | 7 (9.5) |         |
| Right                                                 |                                 | 2 (5.3) | 3 (4.1) | .44     |
| Left                                                  |                                 | 0 (0.0) | 4 (5.4) |         |
| Bilateral                                             |                                 | 36 (94.7) | 67 (90.5) |         |
| Lobar distribution*                                   |                                 |       |       |         |
| Right upper lobe                                       |                                 | 36 (94.7) | 62 (83.8) | .10     |
| Right medial lobe                                      |                                 | 34 (89.5) | 62 (83.8) | .42     |
| Right lower lobe                                       |                                 | 37 (97.4) | 66 (89.2) | .13     |
| Left upper lobe                                        |                                 | 35 (92.1) | 67 (90.5) | .78     |
| Left lower lobe                                        |                                 | 36 (94.7) | 69 (93.2) | .76     |
| Lobar involvement*                                     |                                 |       |       |         |
| 1 lobe                                                 |                                 | 0 (0.0) | 2 (2.7) |         |
| 2 lobes                                                |                                 | 2 (5.3) | 5 (6.8) | .59     |
| 3 lobes                                                |                                 | 1 (2.6) | 6 (8.1) |         |
| 4 lobes                                                |                                 | 4 (10.5) | 9 (12.2) |         |
| 5 lobes                                                |                                 | 31 (81.6) | 52 (70.3) |         |
| Axial distribution*                                    |                                 |       |       |         |
| Central                                               |                                 | 0 (0.0) | 0 (0.0) | .03     |
| Peripheral                                             |                                 | 11 (28.9) | 37 (50.0) |         |
| Diffuse                                                |                                 | 27 (71.1) | 37 (50.0) |         |

Note.—Data are expressed as n (%).

*Calculated for patients with presence of COVID-19 pneumonia (n = 112).
Table 3. Quantitative Measures of Lung Lesions on Chest CT in COVID-19 Pneumonia

|                              | Clinical deterioration or death |   |   |   |
|------------------------------|---------------------------------|---|---|---|
|                              | Yes                              | No |   |
|                              | *(n = 39)*                       | *(n = 81)* |
| Lung lesion volume (mL)      |                                 |   |   |   |
| Total                        | 868.7 (403.0 – 1412.2)          | 273.5 (84.5 – 523.6) |
| Ground-glass opacities       | 498.4 (126.8 – 968.9)           | 222.2 (62.6 – 440.2) |
| Consolidation                | 92.4 (11.0 – 380.5)             | 10.4 (0.3 – 45.9) |
| Pleural effusion             | 0.0 (0.0 – 58.7)                | 0.0 (0.0 – 0.0) |
| Lungs lesion burden (%)      |                                 |   |   |   |
| Total                        | 25.9 (11.9 – 49.7)              | 6.5 (1.5 – 11.9) |
| Ground-glass opacities       | 14.2 (4.3 – 35.6)               | 5.8 (1.1 – 11.0) |
| Consolidation                | 2.8 (0.3 – 11.9)                | 0.2 (0.0 – 1.1) |
| Pleural effusion             | 0.0 (0.0 – 1.5)                 | 0.0 (0.0 – 0.0) |
| Lungs lesion mean attenuation (HU) |                                |   |   |   |
| Total                        | -306.5 ± 184.7                  | -446.3 ± 172.1 |
| Ground-glass opacities       | -437.7 ± 120.2                  | -510.3 ± 126.9 |
| Consolidation                | -84.1 ± 162.2                   | -107.8 ± 89.7 |
| Pleural effusion             | -11.1 ± 76.3                    | 1.2 ± 38.1 |

Note.—Data are expressed as median (interquartile range) or mean ± standard deviation.
Table 4. Association of Clinical and CT Parameters with Risk of Clinical Deterioration or Death in Multivariable Logistic Regression Analysis

|                              | Model 1: Clinical parameters | Model 2: Clinical + CT parameters |
|------------------------------|------------------------------|-----------------------------------|
|                              | OR (95% CI) | P value | OR (95% CI) | P value |
| Age                          | 1.0 (1.0,1.1) | .08     | 1.1 (1.0, 1.1) | .05     |
| Male sex                     | -            | -       | -            | -       |
| Diabetes mellitus            | -            | -       | -            | -       |
| Hypertension                 | -            | -       | -            | -       |
| Smoking history              | -            | -       | 5.2 (0.9, 31.2) | .07     |
| Chronic lung disease         | 1.1 (1.0, 1.3) | .09     | 1.3 (1.1, 1.6) | .02     |
| History of heart failure     | 1.1 (1.0, 1.3) | .07     | 1.3 (1.1, 1.6) | .02     |
| History of coronary artery disease | -          | -       | -            | -       |
| Chronic kidney disease       | -            | -       | -            | -       |
| C-reactive protein*          | 1.7 (1.2, 2.3) | 0.001   | 2.1 (1.3, 3.4) | .004    |
| Ground glass opacities burden (%) | -        | -       | -            | -       |
| Consolidation burden (%)†   | -            | -       | 3.4 (1.7, 6.9) | .001    |
| Ground glass opacities attenuation (HU)† | - | - | 3.2 (1.3, 8.3) | .02 |
| Consolidation attenuation (HU) | -          | -       | 0.4 (0.2, 1.0) | .05     |

Note.—Final models based on backward stepwise selection of variables at a Wald $P$-value of 0.1. CI = confidence interval, HU = Hounsfield units, OR = odds ratio

*Odds ratios are per two-fold increase (doubling) of the variable.
†Odds ratios are per standard deviation increase.
**Supplementary Table E1.** Association of clinical and CT parameters with risk of clinical deterioration or death in univariable logistic regression analysis

| Clinical characteristics                              | OR   | 95% CI      | P value |
|--------------------------------------------------------|------|-------------|---------|
| Age (yrs)                                              | 1.1  | 1.0 – 1.1   | < .001  |
| Male                                                   | 1.3  | 0.6 – 3.0   | .501    |
| Body mass index (kg/m²)                                | 1.0  | 0.9 – 1.2   | .636    |
| Hypertension                                           | 2.8  | 1.3 – 6.3   | .012    |
| Diabetes mellitus                                      | 3.7  | 1.6 – 8.7   | .003    |
| Hyperlipidemia                                         | 2.6  | 1.2 – 5.7   | .021    |
| Smoking status                                         | 1.3  | 0.6 – 3.1   | .533    |
| Chronic lung disease                                   | 2.7  | 1.0 – 7.8   | .058    |
| History of heart failure                               | 6.0  | 1.9 – 18.7  | .002    |
| History of coronary artery disease                     | 3.2  | 1.3 – 7.9   | .011    |
| Chronic kidney disease                                 | 3.2  | 1.1 – 9.3   | .035    |
| Immunodeficiency                                       | 9.0  | 1.0 – 83.7  | .053    |

| Blood laboratory results (per 1 SD increase)           | OR   | 95% CI      | P value |
|--------------------------------------------------------|------|-------------|---------|
| Lymphocyte (per 6.6% increase)                         | 1.9  | 1.0 – 3.5   | .048    |
| Lactate dehydrogenase (per 153 U/L increase)           | 3.0  | 1.4 – 6.0   | .003    |
| C-reactive protein (per 72.8 mg/L increase)            | 4.4  | 2.4 – 8.1   | < .001  |
| Ferritin (per 845 ng/mL increase)                      | 1.9  | 0.9 – 3.7   | .076    |
| Prothrombin time (per 5.2 s increase)                  | 0.9  | 0.4 – 2.1   | .857    |
| D-dimer (per 2.2 μg/mL increase)                       | 4.5  | 1.6 – 12.5  | .004    |
| Troponin (per 0.2 ng/mL increase)                      | 9.0  | 2.5 – 31.9  | < .001  |
| Creatine phosphokinase (per 37 U/L increase)           | 1.2  | 0.6 – 2.4   | .703    |
| Interleukine-6 (per 5.3 pg/mL increase)                | 2.9  | 0.7 – 12.5  | .145    |

| Lungs abnormality volume (per 1 SD increase)           | OR   | 95% CI      | P value |
|--------------------------------------------------------|------|-------------|---------|
| Total (per 683.1 mL increase)                           | 3.6  | 2.0 – 6.5   | < .001  |
| Ground-glass opacities (per 510.4 mL increase)         | 2.8  | 1.6 – 4.9   | < .001  |
| Consolidations (per 199.5 mL increase)                 | 3.9  | 2.0 – 7.6   | < .001  |
| Pleural effusion (per 265.8 mL increase)               | 1.3  | 0.8 – 1.8   | .280    |

| Lungs abnormality burden (per 1 SD increase)            | OR   | 95% CI      | P value |
|--------------------------------------------------------|------|-------------|---------|
| Total (per 18.1% increase)                              | 3.7  | 2.1 – 6.4   | < .001  |
| Ground-glass opacities (per 13.4% increase)             | 2.8  | 1.7 – 4.7   | < .001  |
| Consolidations (per 5.8% increase)                      | 3.8  | 2.1 – 7.2   | < .001  |
| Pleural effusion (per 6.0% increase)                    | 1.4  | 0.9 – 2.1   | .107    |

| Lungs abnormality mean attenuation (per 1 SD increase)  | OR   | 95% CI      | P value |
|--------------------------------------------------------|------|-------------|---------|
| Total (per 187.7 HU increase)                           | 2.2  | 1.4 – 3.5   | < .001  |
| Ground-glass opacities (per 128.8 HU increase)          | 1.8  | 1.2 – 2.9   | .008    |
| Consolidations (per 120.4 HU increase)                  | 1.2  | 0.8 – 2.0   | .353    |
| Pleural effusion (per 64.6 HU increase)                 | 0.8  | 0.3 – 2.4   | .682    |
FIGURES

Figure 1. Study flowchart of included patients.
**Figure 2.** (a) Workflow for the quantification of COVID-19 pneumonia on chest CT in a patient with typical ground-glass opacities. (b-c) First, both lungs and (d-e) their respective lobes were automatically segmented by a deep-learning algorithm. Second, semi-automated segmentation of lesions was performed using (f) axial slices and shown with (g) three-dimensional rendering.
Figure 3. Burden of lung abnormalities on CT in patients with versus without clinical deterioration or death. Box plots demonstrate the median, interquartile range 25th-75th, and minimum and maximum values.
Figure 4. (a) Chest CT of a 48-year-old man with COVID-19 pneumonia who was discharged following an uncomplicated 6-day hospital admission. (b) Axial slice demonstrates bilateral peripheral ground glass opacities (GGO, blue) with patchy consolidation (yellow). Lesion quantification revealed a GGO burden of 5.1% and consolidation burden of 0.7%. Three-dimensional lung renderings depict the distribution of disease in (c) coronal and (d) axial planes.
Figure 5. (a) Chest CT of an 87-year-old man with COVID-19 pneumonia who died 10 days later. (b) Axial slice shows bilateral diffuse ground glass opacities (GGO, blue) and consolidation (yellow). Lesion quantification revealed a GGO burden of 44.0% and consolidation burden of 8.0%. Three-dimensional renderings depict the distribution of disease in (c) coronal and (d) axial planes.
Figure 6. Performance of clinical and CT parameters for the prediction of clinical deterioration or death. Quantitative CT measures added incremental predictive value beyond a model containing only clinical parameters (area under the curve, 0.93 vs 0.82, \( P = .006 \)).