EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Altered pulmonary blood volume distribution as a biomarker for predicting outcomes in COVID-19 disease

Michael F. Morris, Yash Pershad, Paul Kang, Lauren Ridenour, Ben Lavon, Maarten Lanclus, Rik Gordon, Jan De Backer, Marilyn K. Glassberg

Please cite this article as: Morris MF, Pershad Y, Kang P, *et al*. Altered pulmonary blood volume distribution as a biomarker for predicting outcomes in COVID-19 disease. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.04133-2020).

Title: Altered Pulmonary Blood Volume Distribution as a Biomarker for Predicting Outcomes in COVID-19 Disease

Authors: Michael F. Morris MD[1,2], Yash Pershad[3], Paul Kang MS[4], Lauren Ridenour DO[2], Ben Lavon MS[5], Maarten Lanclus PhD[5], Rik Gordon BSc[5], Jan De Backer PhD[5], Marilyn K. Glassberg MD[2,6]

[1]Department of Radiology, Banner University Medical Center Phoenix, Phoenix, Arizona
[2]Department of Medicine, Banner University Medical Center Phoenix, Phoenix, Arizona
[3]Department of Bioengineering, Stanford University, Palo Alto, California
[4]Department of Biostatistics, University of Arizona College of Public Health, Phoenix, Arizona
[5]FLUIDDA, New York City, New York
[6]Division of Pulmonary Medicine, Critical Care, and Sleep Medicine, University of Arizona College of Medicine – Phoenix, Phoenix, Arizona

Take Home Message: BV5% derived from chest CT may serve as an imaging biomarker for predicting adverse outcomes in patients with COVID-19 seeking acute medical care.

Abstract:

Background:

Evidence suggests that vascular inflammation and thrombosis may be important drivers of poor clinical outcomes in patients with COVID-19. We hypothesized that a significant decrease in the percentage of blood vessels with a cross-sectional area between 1.25-5 mm2 (BV5%) on chest computed tomography (CT) in COVID-19 patients is predictive of adverse clinical outcomes.

Methods:

Retrospective analysis of chest CT scans from 10 hospitals across two state in 313 COVID-19 positive and 195 COVID-19 negative patients seeking acute medical care.

Results:

BV5% was predictive of outcomes in COVID-19 patients in a multivariate model, with a BV5% threshold below 25% associated with an odds ratio (OR) 5.58 for death, OR 3.20 for intubation, and OR 2.54 for the composite of death or intubation. A model using age and BV5% had an area under the receiver operating characteristic curve 0.85 to predict the composite of intubation or death in COVID-19 patients. BV5% was not predictive of clinical outcomes in patients without COVID-19.

Conclusion:

This data suggests BV5% as a novel biomarker for predicting adverse outcomes in patients with COVID-19 seeking acute medical care.

Background:

The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) pandemic has placed substantial pressure on many aspects of the healthcare system (1), and patients presenting to the hospital with coronavirus disease 2019 (COVID-19) have significant risk for progression to respiratory failure or death (2,3). Increasing evidence suggests that vascular inflammation and thrombosis may be important drivers of poor clinical outcomes in patients with COVID-19 (4). Autopsy studies demonstrate that pulmonary endothelialitis and microangiopathy are significantly more common in COVID-19 compared to other viral respiratory illnesses (5).

Changes in the pulmonary vasculature on chest computed tomography (CT) may reflect the angiocentric injury caused by COVID-19 (6). Quantitative analysis of chest CT scans from patients with COVID-19 demonstrates a significant decrease in the percentage of blood vessels with a cross-sectional area between 1.25-5 mm^2 (BV5%) (7). Given the effects of COVID-19 on pulmonary microcirculation, we hypothesized that BV5% reduction on chest CT in COVID-19 patients is associated with adverse outcomes of respiratory failure requiring intubation or death.

Methods:

This was an institutional-review-board-approved retrospective study of patients seeking acute medical care within a large integrated healthcare network from 3/1/2020-6/30/2020. Patients presenting to the emergency department or directly admitted to the hospital and undergoing a chest CT within 24 hours of presentation and COVID-19 testing were eligible for participation (Figure 1). After identification of the COVID-19-positive cohort, a randomly selected group of COVID-19-negative patients were chosen in order to achieve a target study ratio of 60% COVID-19 positive and 40% COVID-19 negative cases for analysis.

Patient demographic information, treatment course, and outcome data was obtained from the clinical information system through a combination of custom coded data retrieval and manual abstraction. All COVID-19 testing was performed using nasopharyngeal swabs, with polymerase chain reaction (PCR) assays processed in a central laboratory. In patients with a negative COVID-19 PCR test, the medical record was checked for results of an additional COVID-19 test within 14 days. Initial blood laboratory values obtained within 24 hours of the CT scan were recorded.

Semi-quantitative CT analysis

A fellowship trained cardiothoracic radiologist visually scored CT scans for the severity of lung opacification, blinded to the patient's COVID status and clinical outcome. A semi-quantitative scoring method correlating with disease severity and short term outcomes in COVID-19 patients was utilized (8,9). Each lobe was scored as follows: 0: no opacification; 1: <

5% opacification; 2: 5–25% opacification; 3: 26–50% opacification; 4: 51–75% opacification; and 5: > 75% opacification. The severity score (SS) for each CT was calculated as the sum of the five lobar scores (range 0 to 25).

Quantitative CT analysis

A recent publication provides a detailed description of the quantitative CT analysis technique utilized to calculate BV5% as well as the percentage of lung opacification (LO%) (10). Briefly, CT scans with slice thickness ≤ 2mm were used to generate 3D reconstructions of the lung tissue, airways, and pulmonary vasculature. An automated algorithm segmented the vasculature by identifying and enhancing cylindrical structures, and excluded airways via Hounsfield unit thresholds. Blood vessels were then clustered into three groups by cross-sectional area. BV5 denoted the volume of blood contained in vessels between 1.25-5 mm^2, BV5-10 the volume contained in vessels between 5-10 mm^2, and BV10 the volume contained in vessels above 10 mm^2. BV5% was calculated as the percentage of blood volume in vessels between 1.25 and 5 mm^2 relative to the total pulmonary blood volume, BV5-10% as the percentage of blood volume in vessels between 5-10 mm^2, and BV10% as the percentage of blood volume in vessels above 10 mm^2 (Figure 2).

Statistical analysis

Patient demographic and clinical characteristics were stratified by COVID-19 testing results, reported as means and standard deviations for continuous variables or frequencies and percentages for categorical variables. The Wilcoxon Rank Sum Test was used to assess differences in continuous variables, while the Fisher's Exact Test was used to compare categorical variables. For the outcomes of mortality, intubation, and its combination, multivariable logistic regression was implemented to ascertain the odds of the outcomes relative to BV5% as a continuous and categorical variable respectively. BV5% was categorized using the Lowess Smoother plot. If the relationship between BV5% and the log odds of the outcomes were not linear, the inflection point was used to create the threshold for categorization. Multivariable linear regression was also used to estimate the mean difference in

hospital length of stay and the number of intubation days relative to BV5%. Statistical models were adjusted for covariates that were prognostic for outcomes; thus, age, gender, race, BMI, tobacco use, diabetes, hyperlipidemia, hypertension, heart failure, chronic kidney disease, COPD/Emphysema, cerebrovascular disease, cancer, contrast enhanced CT scan, CT findings, anticoagulation treatment, steroid treatment, azithromycin treatment, remdesivir treatment, white blood cell count, lymphocyte count, hematocrit, platelet count, and estimated glomerular filtration rate were included in the models. Missing data were handled using multiple imputation with ten imputations. Two-sided p-values <0.05 were considered statistically significant. Data analyses were conducted using STATA version 15 (STATA Corp: College Station, TX).

A logistic regression model from scikit-learn (11) was trained on COVID-19 positive patients to predict the risk of mortality, intubation, and its combination. To prevent over-fitting, model performance was assessed in two ways: (1) accuracy of predictions in leave-one-out cross-validation, and (2) area under the receiver operating curve (AUC) and precision-recall curves after splitting data into training (80%) and testing (20%) sets (12). Differences in AUC were compared using a one-sample Z-test of proportions. With the coefficients and intercept determined from training, predictions of risk from the logistic regression model were used to simulate patients of varying age and BV5%.

Results:

A total of 508 patients from 10 hospitals across Arizona and Colorado were included in the analysis, including 313 COVID-19 positive patients and 195 COVID-19 negative patients (Table 1). 55% of patients were from Arizona (p=0.04). Compared to COVID-19-negative patients, COVID-19-positive patients were younger (54.9 +/-17 vs 58.8 +/- 18.5 yrs; p=0.02), from a racial/ethnic minority (p<0.01), had higher body mass index (33.5 +/- 12.3 vs 30.7 +/-8; p<0.01), and more likely to be diabetic (30.9% vs 21%; p=0.01). COVID-19 positive patients had a lower incidence of tobacco use (32% vs 53.3%; p<0.01), COPD/emphysema (4.8% vs 14.4%; p<0.01), heart failure (3.8% vs 11.8%; p<0.01), coronary artery disease (6.4% vs 12.3%; p=0.02), and cancer (4.2% vs 9.2%; p=0.02). Additional demographic data is reported in Table 1.

Radiology reports from chest CT scans stated findings of COVID-19 or atypical/viral pneumonia in 91.1% of COVID-19 positive patients and 32.3% of COVID-19 negative patients ($p<0.01$) (Table 2). A normal CT scan was reported in 3.2% of COVID-19 positive patients and 24.6% of COVID-19 negative patients ($p<0.01$). There was no significant difference in the frequency of pulmonary embolism ($p=0.45$). Patients with COVID-19 were significantly less likely to have findings of non COVID-19 pneumonia (2.9% vs 13.9%; $p <0.01$), pulmonary edema (1.3% vs 5.1%; $p=0.01$), emphysema (0.6% vs 9%; $p<0.01$), tumor (0.3% vs 5.6%; $p<0.01$), aspiration/bronchitis (0.3% vs 4.6%; $p<0.01$), pleural effusion (0.3% vs 6.7%), or pulmonary infarct (0% vs 2.1%; $p=0.02$).

On quantitative CT analysis (Table 2), patients with COVID-19 had significantly lower BV5% compared to COVID-19 negative patients (25.3% +/- 7.4 vs 30.1 % +/- 9.6; $p<0.01$). BV5% was also significantly lower for the subset of patients with COVID-19 and CT findings of COVID-19/atypical pneumonia (23.7% +/- 7.3 vs 27.2% +/- 27.2; $p=0.02$). Patients with COVID-19 had significantly higher SS compared to patients without COVID-19 (9.7 +/- 5.4 vs 6.9 +/-5.3; $p<0.01$). For patients with COVID-19, BV5% had a moderate correlation with SS (Spearman's rho -0.45, $p<0.0001$) (Figure 3). Differences in BV5% and Spearman's rho stratified by CT findings are reported in the supplement. There were no significant differences in total lung volume (3034 +/- 1203mL vs 2839 +/-1123mL; $p=0.06$) and total blood volume (210 +/- 72mL vs 215 +/- 72mL; $p=0.45$) in COVID-19 positive versus COVID-19 negative patients, respectively. CT scans from COVID-19 patients had a lower peak area (9.4% +/- 3.1 vs 11.4 +/-9.4; $p<0.01$) and weight mean (17.9% +/- 4 vs 19.4 +/-4.3; $p<0.01$), and higher area under the curve (272.8 +/- 32.9 vs 264.7 +/- 35.7; $p=0.02$).

There was no significant difference in BV5% obtained from contrast enhanced CT versus non-contrast CT ($p=0.23$). Average processing time for BV5% was 9 minutes and 22 seconds (+/- 6 minutes and 3 seconds), with processing time dependent on scan quality. No CT scans were unable to be analyzed.

Overall clinical outcomes for patients with COVID-19 were worse than for patients without COVID-19 (Table 3). COVID-19 patients were hospitalized for a longer duration (8.5 +/-

10.8 days vs 4.1 +/-5.7 days; p<0.01), more likely to be intubated (20.8% vs 6.2%; p<0.01), and trended towards higher in-hospital mortality (11.8% vs 7.2%; p=0.09).

In a multivariate regression analysis that did not include control for lung opacification, BV5% remained significantly associated with intubation and death in patients with COVID-19 (Table 4). Specifically, BV5% as a continuous variable had an odds ratio (OR) 0.87 for mortality (95% CI 0.79, 0.96; p<0.01), OR 0.89 for intubation (95% CI 0.84, 0.95; p<0.01), and OR 0.9 for the composite mortality or intubation (95%CI 0.84, 0.96; p<0.01). A BV5% threshold of 25% had an OR 5.58 for mortality (95% CI 1.54, 20.1; p<0.01), OR 3.20 for intubation (95% CI 1.55, 6.63; p<0.01), and OR 2.54 for the composite mortality or intubation (95%CI 1.15, 5.60; p=0.02). In patients without COVID-19 there was no significant association between BV5% and intubation or mortality.

BV5% was not predictive of length of hospitalization or duration of intubation in patients with COVID-19. Length of stay was associated with BV5% for COVID-19 negative patients, OR 0.97 (95%CI 0.96, 0.98; p<0.01).

After adding the visually assessed CT severity score to the multivariate regression analysis, a BV5% threshold of 25% remained significantly associated with mortality in patients with COVID-19, with an OR 4.27 for mortality (95% CI 1.02, 17.8; p=0.046). In the subset of patients without COVID-19 but with CT findings of pneumonia, BV5% as a continuous variable had an OR 1.24 for the composite mortality or intubation (95%CI 1.01, 1.52; p=0.039).

For COVID-19 positive patients, a logistic regression model using age and BV5% were chosen as features for the classifier because, after excluding treatments, they had the highest coefficients in the aforementioned multivariable linear regression for the primary outcomes. A model using age and SS was similarly created. Age and BV5% predicted the composite of death or intubation with an accuracy of 0.83 ($\pm$ 0.02) in iterative cross-validation. Age and SS predicted the composite of death or intubation with an accuracy of 0.82 (+/- 0.02) in iterative cross-validation. After training on 80% of the patients, the AUC 0.85 for age and BV5% and the AUC 0.87 for age and SS were not significantly different (p=0.18; Figure 4A). The model was also used to forecast risk for the composite of intubation or death using simulated data of patients between 50-80 years old and a BV5% ranging from 10%-60% (Figure 4B).

Conclusions

In this study of 508 patients presenting to the hospital, tested for COVID-19, and undergoing chest CT within 24 hours of presentation, BV5% from COVID-19 patients was significantly lower than BV5% from a heterogenous cohort of patients without COVID-19. This difference was driven mainly by patients with CT findings of COVID-19/atypical pneumonia. BV5% was predictive of outcomes in COVID-19 patients in a multivariate model that did not account for lung opacification, with a BV5% threshold < 25% associated with OR 5.58 for death, OR 3.2 for intubation, and OR 2.54 for the composite of death or intubation. After including the severity of lung opacification in the multivariate analysis, a BV5% threshold of 25% remained significantly associated with mortality, with an OR 4.27.

In healthy patients BV5% constitutes the majority of pulmonary blood volume distribution (13), and is closely correlated with histologic assessment of vascular cross sectional area (14). Alterations in BV5% are not exclusive to COVID-19, and can manifest in other diseases that diffusely affect pulmonary perfusion, such as COPD (15) and ARDS (7). In these cohorts, chronic vascular remodeling and small vessel loss are the underlying etiology for reduced BV5% (16). In COVID-19 the reduction in BV5% may reflect the acute sequela of microcirculatory disruption induced by SARS-CoV-2 (5), however the extent to which other processes such as ventilation/perfusion mismatch and shunting impact BV5% are unknown. The significant association between reduced BV5% and mortality in COVID-19 suggests that BV5% may offer insights into the underlying pathological processes involved in SARS-CoV2 infection, and potentially serve as a tool for quantifying the extent of these processes in an acute care setting.

Models using BV5% and SS had high AUCs for the composite of intubation or death in COVID-19 patients, supporting their role as imaging surrogates for disease severity. However, BV5% and SS are only moderately correlated, and the presence of a low BV5% in patients with a low SS may signify that changes in pulmonary vascular volume distribution represent either an early indicator of disease severity or a distinct (if low-frequency) phenotype. Since SS is a general measure of lung opacification in COVID-19, it can be influenced by alveolar disease (e.g. diffuse alveolar damage), interstitial changes (e.g. fibrosis), vascular impairment (e.g.

hemorrhage), or a combination of these processes (17–19), thus posing challenges in using SS to identify targeted treatments. On the other hand, because BV5% is closely correlated with histologic assessment of vascular cross sectional area (14), we speculate that BV5% may be able to inform possible treatment pathways for COVID-19, for example by identifying patients that would benefit from anticoagulation.

Based on a pilot study of 97 patients (not published), the association between BV5% and outcomes in COVID-19 patients was significant only for CT scans performed within 24 hours of presentation. Beyond this window an increasing number of variables likely obscure the prognostic impact of BV5%, especially given the absence of clear guidelines regarding hospitalization at the time the study data was collected during the initial phase of the pandemic. This may also explain why BV5% was not predictive of duration of hospitalization or duration of intubation in COVID-19 patients. Paradoxically, BV5% was associated with length of stay in patients without COVID-19. In addition, after including the severity of lung opacification in the multivariate analysis, BV5% was associated with the composite of mortality and intubation. These are subjects of current investigation.

There are several important limitations of this study. This was a retrospective study in which only a subset of patients with suspected COVID-19 underwent chest CT with the requisite ≤2mm slice thickness. However, the results should be generalizable due to the geographically and demographically diverse population. Only one fellowship trained cardiothoracic radiologist performed the semi-quantitative visual severity scoring of CT scans, and it is unknown if scoring from radiologists with different levels of expertise would have the same prediction for clinical outcomes. Although only patients presenting to a hospital for acute medical care were included, these are the patients at greatest risk for poor outcome with COVID-19 (20). It is possible that some patients with COVID-19 were miscategorized due to false negative PCR results (21), however we attempted to minimize this effect by checking for additional COVID-19 PCR testing within 14 days of the initial encounter. In addition, obtaining BV5% requires transporting the patient to a CT scanner. While limiting the movement of patients with COVID-19 throughout the hospital can mitigate exposure of the disease to healthcare personnel, the potential predictive benefit of BV5% may outweigh this risk.

As additional waves of the SARS-COV-2 pandemic are expected, there is urgent need for improved diagnostic, prognostic, and treatment tools. Although certain risk factors (22–24) and imaging findings (9) are associated with worse prognosis in COVID-19, accurately quantifying a patient's individual risk for progression to respiratory failure or death remains challenging. BV5% can be quickly derived from CT scans in patients with COVID-19 seeking acute medical care, without the need for contrast material. We hypothesize that BV5% is a unique imaging biomarker, in that it can potentially be used as a gatekeeper for identifying patients that may benefit for earlier or more aggressive therapy with anticoagulation, and we hope this study serves as a catalyst for prospective evaluation of this hypothesis.

Acknowledgements: The authors wish to thank Heather Pryzbyl RN and Corry Glade for assisting with the custom coding used for data retrieval. We thank Kathryn Olson MD for feedback on the manuscript**.**

Financial support: No funding was received for this research.

Disclosures:

Maarten Lanclus: Employee of FLUIDDA, a company that develops and markets part of the technology described in this paper.

Rik Gordon: Employee of FLUIDDA, a company that develops and markets part of the technology described in this paper.

Ben Lavon: Employee of FLUIDDA, a company that develops and markets part of the technology described in this paper.

Jan De Backer: Employee of FLUIDDA, a company that develops and markets part of the technology described in this paper.

Marilyn Glassberg: Serves on the advisory boards of Bellerophon Therapeutics, Genentech, Boehringer Ingelheim, and Bristol-Myers-Squibb.

References:

1. Cavallo JJ, Donoho DA, Forman HP. Hospital Capacity and Operations in the Coronavirus Disease 2019 (COVID-19) Pandemic—Planning for the Nth Patient. JAMA Heal Forum. 2020 Mar 17;1(3):e200345.
2. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. JAMA - J Am Med Assoc. 2020;323(20):2052–9.
3. Vahidy FS, Drews AL, Masud FN, Schwartz RL, Askary B "billy," Boom ML, et al. Characteristics and Outcomes of COVID-19 Patients during Initial Peak and Resurgence in the Houston Metropolitan Area. JAMA - J Am Med Assoc. 2020;324(10):998–1000.
4. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:148–50.
5. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120–8.
6. Lang M, Som A, Carey D, Reid N, Mendoza DP, Flores EJ, et al. Pulmonary Vascular Manifestations of COVID-19 Pneumonia. Radiol Cardiothorac Imaging. 2020 Jun 1;2(3):e200277.
7. Thillai M, Patvardhan C, Swietlik EM, McLellan T, De Backer J, Lanclus M, et al. Functional respiratory imaging identifies redistribution of pulmonary blood flow in patients with COVID-19. Thorax. 2020 Aug 28;
8. Pan F, Ye T, Sun P, Gui S, Liang B, Li L. Time Course of Lung Changes at Chest CT during Recovery. Radiology. 2020;295(3):715–21.
9. Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808–17.

10. Lins M, Vandevenne J, Thillai M, Lavon BR, Lanclus M, Bonte S, et al. Assessment of Small Pulmonary Blood Vessels in COVID-19 Patients Using HRCT. Acad Radiol. 2020;27(10):1449–55.
11. Pedregosa F, Michel V, Grisel O, Blondel M, Prettenhofer P, Weiss R, et al. Scikit-learn: Machine Learning in Python. Vol. 12, Journal of Machine Learning Research. 2011.
12. Pershad Y, Guo M, Altman RB. Pathway and network embedding methods for prioritizing psychiatric drugs. In: Biocomputing 2020. WORLD SCIENTIFIC; 2019. p. 671–82.
13. Estépar RSJ, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, et al. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. Am J Respir Crit Care Med. 2013 Jul 15;188(2):231–9.
14. Rahaghi FN, Argemí G, Nardelli P, Domínguez-Fandos D, Arguis P, Peinado VI, et al. Pulmonary vascular density: comparison of findings on computed tomography imaging with histology. Eur Respir J. 2019;54(2).
15. Washko GR, Nardelli P, Ash SY, Vegas Sanchez-Ferrero G, Rahaghi FN, Come CE, et al. Arterial Vascular Pruning, Right Ventricular Size, and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. A Longitudinal Observational Study. Am J Respir Crit Care Med. 2019;200(4):454–61.
16. Synn AJ, Li W, San José Estépar R, Washko GR, O'Connor GT, Tsao CW, et al. Pulmonary Vascular Pruning on Computed Tomography and Risk of Death in the Framingham Heart Study. Am J Respir Crit Care Med. 2020 Sep 14;rccm.202005-1671LE.
17. Peys E, Stevens D, Weygaerde Y Vande, Malfait T, Hermie L, Rogiers P, et al. Haemoptysis as the first presentation of COVID-19: a case report. BMC Pulm Med. 2020 Dec 22;20(1):275.
18. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol. 2020 Nov 22;33(11):2128–38.
19. Zhang H, Zhou P, Wei Y, Yue H, Wang Y, Hu M, et al. Histopathologic Changes and SARS-CoV-2 Immunostaining in the Lung of a Patient With COVID-19. Ann Intern Med. 2020 May 5;172(9):629–32.

20. Karagiannidis C, Mostert C, Hentschker C, Voshaar T, Malzahn J, Schillinger G, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med. 2020 Sep 1;8(9):853–62.
21. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19). JAMA. 2020 Aug 25;324(8):782.
22. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug 20;584(7821):430–6.
23. Homayounieh F, Ebrahimian S, Babaei R, Karimi Mobin H, Zhang E, Bizzo BC, et al. CT Radiomics, Radiologists and Clinical Information in Predicting Outcome of Patients with COVID-19 Pneumonia. Radiol Cardiothorac Imaging. 2020 Aug 1;2(4):e200322.
24. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res. 2020;8(1).

		COVID-19 Positive N=313	COVID-19 Negative N=195	p-value
Demographics	Age, years	54.9 (17.0)	58.8 (18.5)	0.02
	Male gender	162 (51.8)	89 (45.6)	0.18
	Race			<0.01
	Caucasian	11 (35.5)	119 (61.0)	
	Hispanic	160 (51.1)	55 (28.2)	
	African American	17 (5.43)	18 (9.23)	
	Native American/Pacific Islander/Asian American	25 (7.99)	3 (1.54)	
	State (Arizona)	162 (51.8)	119 (61.0)	0.04
	Body mass index	33.5 (12.3)	30.7 (7.97)	0.04
	Any tobacco Use	101 (32.3)	104 (53.3)	<0.01
	Diabetes	97 (30.9)	41 (21.0)	0.01
	Hyperlipidemia	72 (23.0)	38 (19.5)	0.35
	Hypertension	125 (39.9)	82 (42.1)	0.64
	Heart failure	12 (3.83)	23 (11.8)	<0.01
	Chronic kidney disease	10 (3.19)	6 (3.08)	0.94
	Asthma	32 (10.2)	25 (12.8)	0.37
	COPD/Emphysema	15 (4.79)	28 (14.4)	<0.01
	Cerebral vascular disease	12 (3.83)	7 (3.59)	0.88
	Transplant	0 (0.0)	2 (1.03)	0.15
	Cancer	13 (4.15)	18 (9.23)	0.02
	Autoimmune disease	8 (2.56)	11 (5.64)	0.08
	Coronary artery disease	20 (6.39)	24 (12.3)	0.02
	Hepatitis C	4 (1.28)	9 (4.62)	0.02
	Pulmonary hypertension	2 (0.64)	5 (2.56)	0.11
	Cirrhosis	0 (0.0)	2 (1.03)	0.15
Lab values	White blood cell count	8.80 (15.1)	13.2 (25.9)	<0.01
	Lymphocyte count	2.40 (14.5)	1.71 (1.21)	<0.01
	Hemoglobin	13.8 (1.89)	12.9 (2.38)	<0.01
	Hematocrit	41.5 (5.15)	39.7 (6.71)	<0.01
	Platelet	220.4 (87.5)	262 (105.0)	<0.01
	Creatinine	1.13 (0.85)	1.27 (1.70)	0.26
	eGFR	78.5 (29.8)	77.1 (30.7)	0.65
	BNP	1247.2 (3663.3)	5582.7 (15837.4)	<0.01
Medical therapy	Anti-coagulation			<0.01
	None	49 (15.7)	62 (31.8)	
	Full Dose	49 (15.7)	30 (15.4)	
	Prophylaxis	215 (68.7)	103 (52.8)	
	Steroids	171 (54.6)	59 (30.3)	<0.01
	Azithromycin	252 (80.5)	99 (50.8)	<0.01
	Remdesivir	23 (7.35)	1 (0.51)	<0.01

Table 1: Baseline demographic, laboratory, and treatment parameters in patients with and without COVID-19. Findings reported as mean (standard deviation) or frequency (percentage). Chronic obstructive pulmonary disease (COPD). Estimated glomerular filtration rate (eGFR). NT-proB-type Natriuretic Peptide (BNP).

		COVID-19 Positive N=313	COVID-19 Negative N=195	p-value
Type of CT scan	Contrast enhanced CT	197 (62.9)	147 (75.3)	<0.01
Radiologist interpretation	COVID-19/atypical pneumonia	285 (91.1)	63 (32.3)	<0.01
	Pulmonary embolism	8 (4.15)	9 (6.34)	0.45
	Normal	10 (3.19)	48 (24.6)	<0.01
	Non COVID-19 pneumonia	9 (2.88)	27 (13.9)	<0.01
	Pulmonary edema	4 (1.28)	10 (5.13)	0.01
	Emphysema	2 (0.64)	9 (4.62)	<0.01
	Tumor	1 (0.32)	11 (5.64)	<0.01
	Aspiration/Bronchitis	1 (0.32)	9 (4.62)	<0.01
	Pleural effusion	1 (0.32)	13 (6.67)	<0.01
	Pulmonary infarct	0 (0.0)	4 (2.05)	0.02
	Interstitial lung disease	0 (0.0)	1 (0.51)	0.38
Visual CT Analysis	CT severity score	9.7 (5.4)	6.9 (5.3)*	<0.01
Quantitative CT Analysis	BV5%	25.3 (7.4)	30.1 (9.6)	<0.01
	BV5-10%	22.6 (3.7)	25.0 (3.5)	<0.01
	BV10%	52.0 (9.7)	45.2 (10.9)	<0.01
	Total blood volume (mL)	210 (72)	215 (72)	0.45
	Total lung volume (mL)	3034 (1203)	2839 (1123)	0.06
	Peak Area	9.42 (3.06)	11.4 (3.75)	<0.01
	Peak Volume	24.4 (3.71)	24.1 (3.43)	0.40
	AUC	272.8 (32.9)	264.7 (35.7)	0.02
	Weight Mean	17.9 (4.04)	19.4 (4.32)	<0.01
	Kurtosis	-0.74 (0.43)	-0.77 (0.38)	0.64
	Skewness	0.79 (0.21)	0.78 (0.21)	0.56

Table 2: Computed tomography (CT) findings in patients with and without COVID-19. Findings reported as mean (standard deviation) or frequency (percentage). Percentage of blood volume in vessels between 1.25 and 5 mm^2 relative to the total pulmonary blood volume (BV5%), in vessels between 5-10 mm^2 (BV5-10%), and in vessels above 10 mm^2 (BV10%). Area under the receiver operating characteristic curve (AUC). *Limited to the 90 patients with findings of COVID-19/atypical pneumonia or non COVID-19 pneumonia on CT.

	COVID-19 Positive N=313	COVID-19 Negative N=195	p-value
Death	37 (11.8)	14 (7.18)	0.09
Intubation	65 (20.8)	12 (6.15)	<0.01
Intubation or Death	78 (24.9)	22 (11.3)	<0.01
Days from admission to intubation	2.5 (3.9)	0.4 (0.9)	<0.01
Days intubated	10.7 (10.8)	3.8 (4.6)	<0.01
Length of stay, days	8.5 (10.8)	4.1 (5.7)	<0.01
Length of stay >1 day	267 (85.3)	146 (74.9)	<0.01

Table 3: Outcomes in patients with and without COVID-19. Findings reported as mean (standard deviation) or frequency (percentage).

	COVID-19 Positive		**COVID-19 Negative**	
Mortality	OR (95% CI)	p-value	OR (95% CI)	p-value
BV5% continuous	0.87 (0.79, 0.96)	<0.01	1.02 (0.94, 1.10)	0.61
BV5% categorical < 25%	5.58 (1.54, 20.1)	<0.01	0.50 (0.08, 3.24)	0.46
Intubation	OR (95% CI)	p-value	OR (95% CI)	p-value
BV5% continuous	0.89 (0.84, 0.95)	<0.01	1.00 (0.91, 1.10)	0.96
BV5% categorical < 25%	3.20 (1.55, 6.63)	<0.01	3.31 (0.59, 18.5)	0.17
Mortality or intubation	OR (95% CI)	p-value	OR (95% CI)	p-value
BV5% continuous	0.90 (0.84, 0.96)	<0.01	0.99 (0.93, 1.05)	0.69
BV5% categorical < 25%	2.54 (1.15, 5.60)	<0.01	2.05 (0.62, 6.73)	0.24
Length of Stay	exp (Beta (95% CI)	p-value	exp (Beta (95% CI)	p-value
BV5% continuous	0.98 (0.96, 1.00)	0.075	0.97 (0.96, 0.98)	<0.01
Intubation Days	exp (Beta (95% CI)	p-value	exp (Beta (95% CI)	p-value
BV5% continuous	0.99 (0.93, 1.06)	0.83	1.02 (0.95, 1.09)	0.51

Table 4: Multivariate regression analysis of outcomes relative to BV5% as a continuous and categorical variable in patients with and without COVID-19. Percentage of blood volume in vessels between 1.25 and 5 mm^2 relative to the total pulmonary blood volume (BV5%).

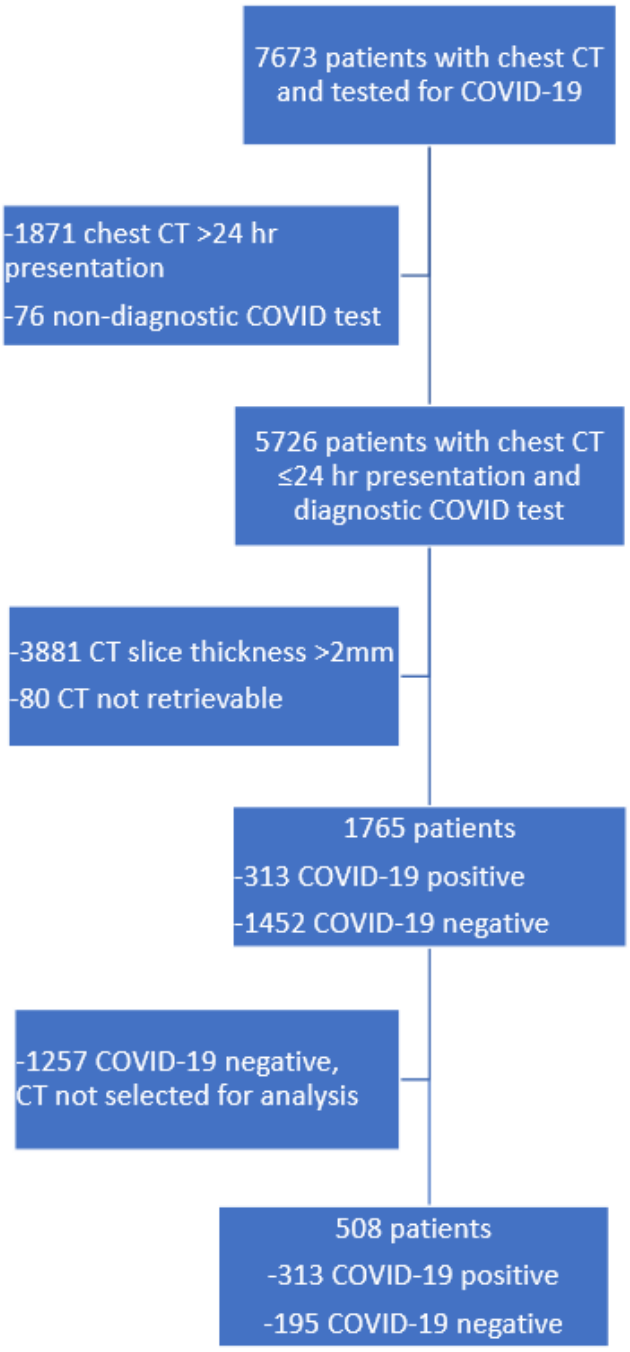

Figure 1. Flow chart of eligible patients. Computed tomography (CT)

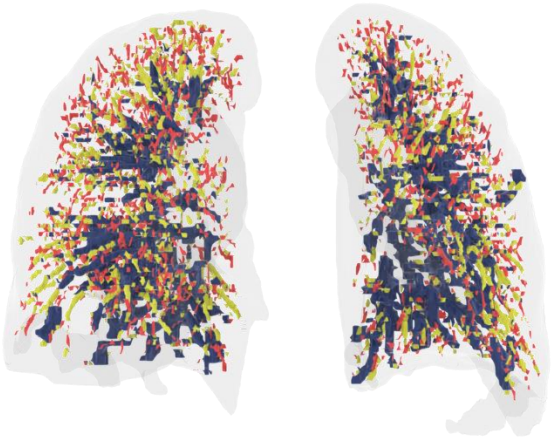

Figure 2A

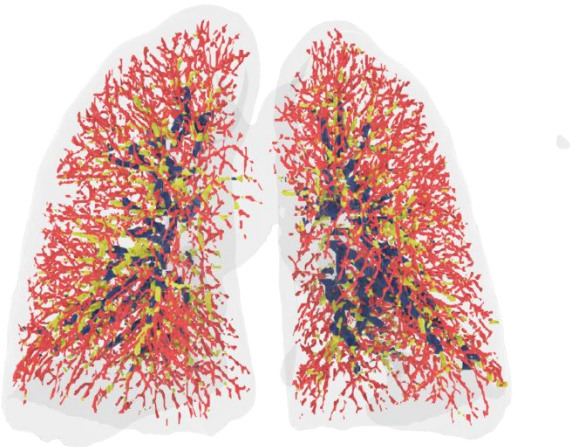

Figure 2B

Figure 2: Volume rendered images of chest CT scans from two different patients with COVID-19, with color coded segmentation of the pulmonary vascular cross sectional area. (a) Patient with BV5% of 21%; (b) Patient with BV5% of 55%. Red color denotes blood volume in vessels between 1.25-5 mm^2, yellow color is vessels between 5-10 mm^2, and blue color is vessels >10 mm^2.

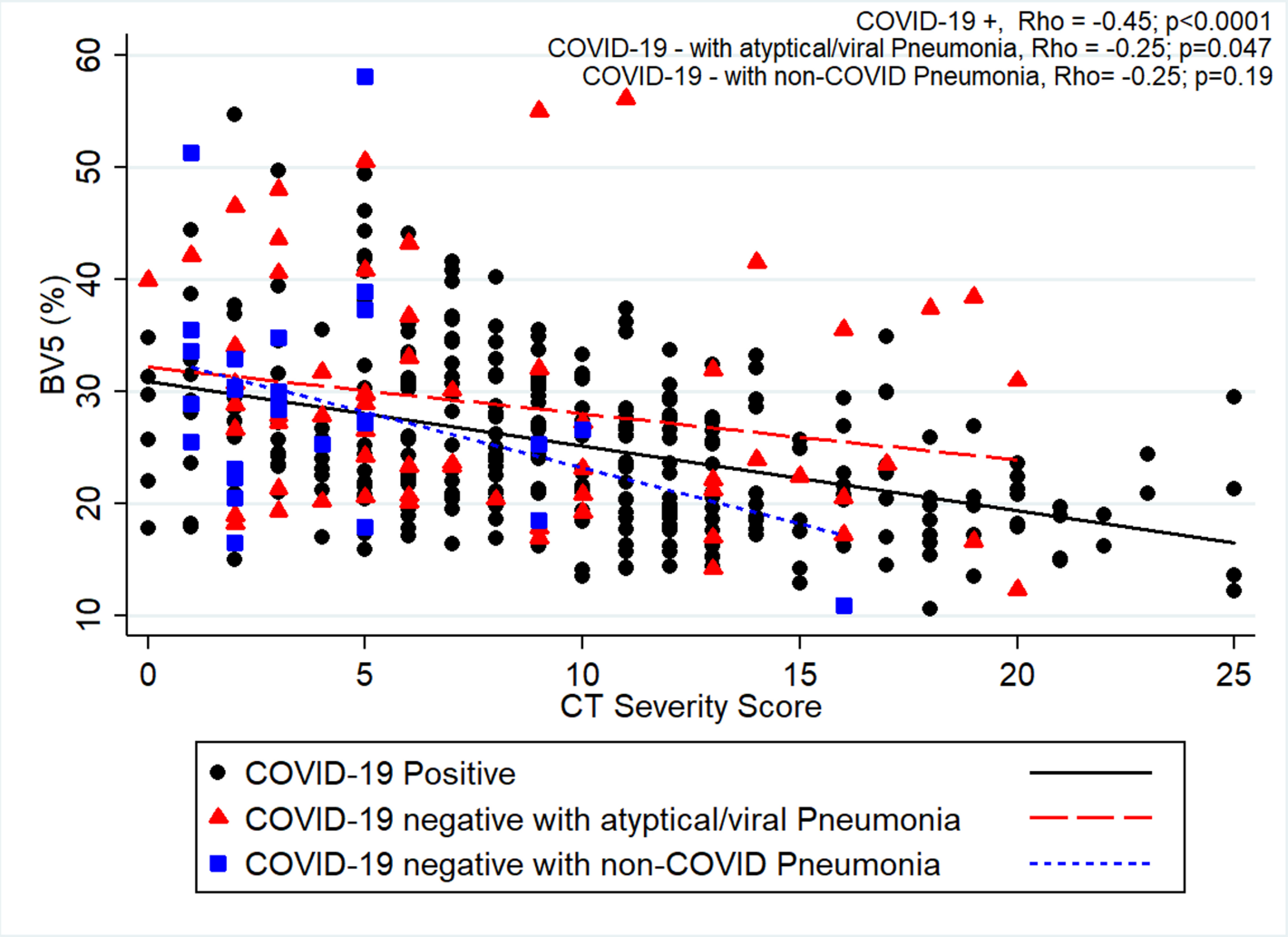

Figure 3. Spearman's rank correlation between BV5% and the visually assessed CT severity score, stratified by COVID-19 status and CT findings. Percentage of blood volume in vessels between 1.25 and 5 mm^2 relative to the total pulmonary blood volume (BV5%).

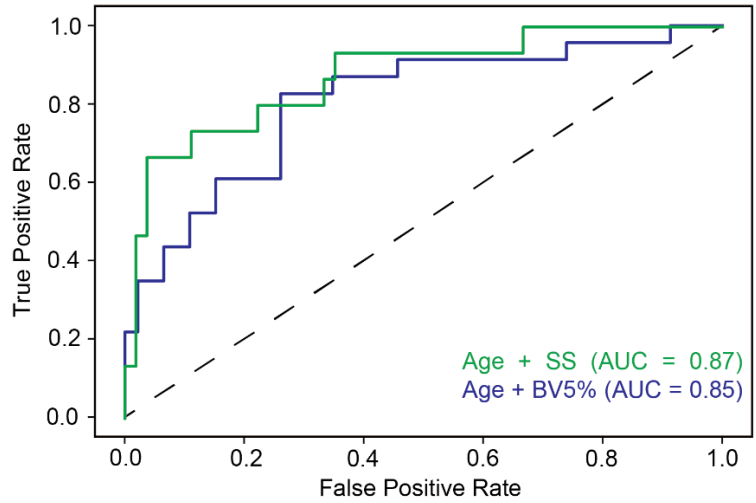

Figure 4A

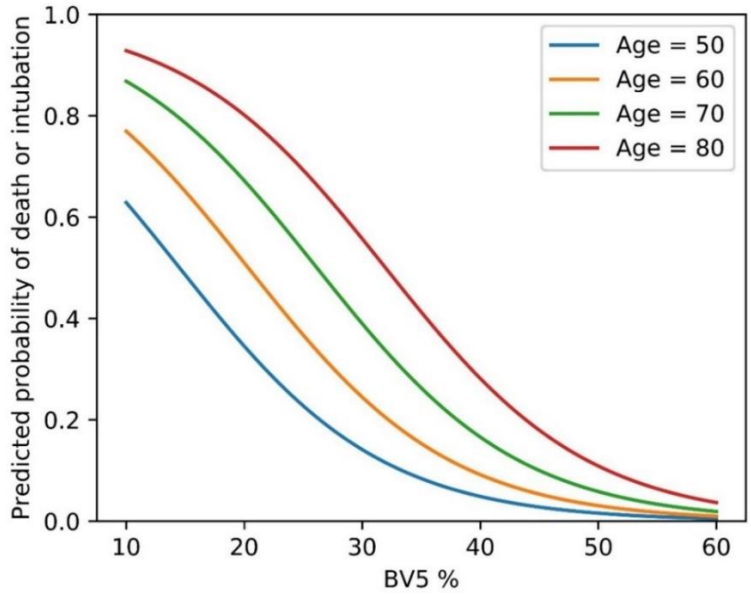

Figure 4B

Figure 4. (A) Receiver operating characteristic curve from the testing set of the logistic regression model. Patient age and BV5% have AUC 0.85 to predict the composite of intubation or death in patients with COVID-19, not significantly different than AUC 0.87 for age and SS (p=0.18). (B) Probability of the composite death or intubation for simulated COVID-19 patients ages 50, 60, 70, and 80 with BV5% ranging from 10% to 60%. Percentage of blood volume in vessels between 1.25 and 5 mm^2 relative to the total pulmonary blood volume (BV5%). Visually assessed CT severity score (SS).

CT Findings	COVID-19 Positive	COVID-19 Negative	p-value
COVID-19/atypical pneumonia	23.7 (7.3)	27.2 (10.3)	0.02
Non COVID-19 pneumonia	26.2 (5.1)	28.4 (9.9)	0.32
Pulmonary edema	26.8 (4.3)	25.7 (4.7)	0.88
Pulmonary embolism	25.1 (7.5)	30.8 (11.5)	0.35
Emphysema	26.8 (6.8)	28.7 (8.4)	0.35
Tumor	37.7 (N/A)	26.7 (5.3)	0.19
Interstitial lung disease	N/A	33.2 (N/A)	N/A
Aspiration/Bronchitis	54.7 (N/A)	27.1 (8.7)	0.12
Pleural effusion	21.9 (N/A)	29.2 (9.5)	0.17
Pulmonary infarct	N/A	39.9 (13.1)	N/A
Normal	28.6 (5.2)	30.5 (9.9)	0.21

Table S1. BV5% stratified by COVID status and CT findings. Findings reported as mean (standard deviation)

The equation for the model computing probability of death or intubation of COVID-19 positive patients as a function of age and BV5% was:

$$P = \frac{1}{1+e^{-(0.03\times A-0.06\times B-1.70)}}$$

A = age (years) and B = BV5% (percent)