The caliber of segmental and subsegmental vessels in COVID-19 pneumonia is enlarged: a distinctive feature in comparison with other forms of inflammatory and thromboembolic disease

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Abstract

Objective: to compare COVID-19 patients' vessel caliber with that of normal lungs and lungs interested by other inflammatory and thromboembolic processes.

Methods: between March and April 2020, 42 patients affected by COVID-19 pneumonia [COV-P] underwent a CT scan of the lung at Verona University Hospital for clinical indications. Lung images were compared to 4 different groups of patients (normal lung [NL], distal thromboembolism [DTE], bacterial and fungal pneumonia [Bact-P, Fung-P]) by a 4-year-experienced radiologist.

Results: COV-P patients' segmental and subsegmental vessels, as evaluated as the ratio with the corresponding bronchial branch (V/B ratio) were larger with respect to NL, DTE in the apparently healthy parenchyma, a result confirmed in the zones of opacification with respect to Bact-P and Fung-P.

Conclusions: This is the first study to comparatively showing that segmental and subsegmental COVID-19 patients' vessel caliber is significantly enlarged. This is a distinctive feature of COVID-19 pneumonia suggesting distinct pathophysiology as compared to other inflammatory and thromboembolic diseases and alerting radiologists to consider it when evaluating CT scan of suspected patients.

Introduction

Since the outbreak of the SARS-CoV–2 infection from the Hubei province in China in late December 2019 [1] it has been evident that a prevalent target of Coronavirus disease–19 (COVID–19) was the lungs with a broad spectrum of clinical respiratory syndromes [2]. Clinical features ranged from either an asymptomatic presentation or mild upper airways symptoms to progressive life-threatening respiratory distress [3]. A recent study has suggested that microvascular thrombotic processes together with ARDS may play a role in respiratory failure in COVID–19 patients [4]. Like clinical manifestations, a wide range of radiologic patterns have been described, from ground-glass opacities (GGO) only to consolidative pulmonary opacities, often with a bilateral and peripheral lung distribution [5]. Therefore, the presence of GGO, mainly in patients with mild forms of COVID–19, such as the interlobular septal thickening, parenchymal consolidation with air bronchogram, pleural effusion and pulmonary fibrosis, more prevalent in the severe clinical form, have characterized chest CT features of COVID–19 pneumonia [6]. Changes in pulmonary vascularization such as segmental or subsegmental vascular enlargement have been also described as a specific feature of COVID–19 disease [7]. To date, however, the cause of the vessel enlargement has not been clarified. Some hypotheses have been made, not mutually exclusive [8]. In particular, microvascular pulmonary thrombi and emboli were often associated with COVID–19 pneumonia being related also to the severe hypoxaemia that characterizes the disease [9]. Another possibility involved the profound inflammation and the vasodilatory effects of cytokines released in abundance in response to pulmonary parenchymal damage itself and also correlated to the so-called "cytokine storm" [10]. A final hypothesis was related to the induction of endothelitis and angiogenesis, mediated by SARS-CoV–2 infection [11].

To our best knowledge, there are no published studies focusing on the caliber of segmental and subsegmental branches of pulmonary arteries in patients with COVID–19 pneumonia. In order to clarify if the enlargement of the vessels caliber is a COVID–19 specific phenomenon or can be present in other primary thromboembolic or inflammatory conditions we selected different control groups: (i) patients without evidence of lung disease (normal lung [NL]; (ii) patients with microvessels embolisms (distal thromboembolism [DTE]), and patients with distinct forms of pneumonia of respectively bacterial (Bact-P) and fungal origin (Fung-P).

Methods

Study population

All consecutive patients admitted at the emergency department or COVID units of our Hospital from March the 1st to April the 25th 2020, who had respiratory symptoms, positivity to SARS-COV2 confirmed by reverse-transcription polymerase chain reaction (RT-PCR) and who underwent chest CT were enrolled in this retrospective study. Exclusion criteria were the presence of severe respiratory artifacts on chest CT.

We also collected CT images from four control groups: patients who underwent chest CT before January 2020 or after March 2020 without evidence of lung disease or COVID–19 positivity (NL), patients with pulmonary embolism involving only distal branches of pulmonary arteries (DTE) and patients with confirmed bacterial (Bact-P) or fungal (Fung-P) pneumonia, with pathogen isolated at blood culture or bronchiolar alveolar lavage (BAL) or, for fungal infection, serum positivity of beta-glucan. Groups DTE, Bact-P and Fung-P included only patients examined before December 2019.

The prospective and retrospective study was approved by our local institutional review board (IRB; 2695CESC) and written informed consent was obtained from all study participants. COVID–19 patients were prospectively enrolled in a registry (COVID–19 2577CESC), and gave oral informed consent, allowing the use of their data for research.

Image acquisition

All chest scans were performed on a 64 or 6-row multiple detector computed tomography scanner (Brilliance 64 or 6, Philips, the Netherlands) with the patients in supine position with the arms extended above the head during end-inspiration.

For patients in group Bact-P, Fung-P and COV-P without suspicion of pulmonary embolism, the acquisition was made without contrast administration.

For the other Patients the acquisition was obtained after weight-based amount (1,4 ml/Kg) of high-concentration contrast agent (370 mgI/ml, Ultravist 370, BayerScheringPharma) at a rate of 3–4 ml/sec, followed by a 50 mL saline bolus administered by means of a dual-head injector (Medrad Stellant,

Indianola, US) through an antecubital vein. Scan timing was determined using a bolus-tracking technique, with the monitoring region of interest in the thoracic aorta for group NL or performing a computerized tomography pulmonary angiography (CTPA) in the pulmonary trunk for patients with suspicion of pulmonary embolism. Scan delay after trigger was 15 seconds for NL patients and the minimum for CTPA.

All scans were reconstructed with sharp lung filter at a slice thickness of 1.25 mm.

Image analysis

One radiologist with 4 years of experience on chest imaging analyzed the cases using a PACS workstation on axial images with a parenchymal window.

In all patients, the radiologist measured the caliber of one segmental branch of both right and left pulmonary arteries and their corresponding bronchial branch and one subsegmental branch of right and left pulmonary arteries and their corresponding bronchial branch.

For patients in groups COV-P, Bact-P and Fung-P the radiologist measured also the caliber of one segmental and one subsegmental branch of the pulmonary artery together with their corresponding bronchial branches in the main area of lung opacification.

The ratio between the caliber of each vessel and its corresponding bronchus (V/B RATIO) was calculated for each measurement site.

Statistics

The caliber of segmental and subsegmental pulmonary arteries branches, of their corresponding bronchial branches and the V/B ratio were compared across groups using a Kruskal-Wallis test and a post hoc Mann-Whitney U test implemented in the “Statistical Package for Social Sciences” software (SPSS/PC for Mac version 26.0, IBM Corporation, Chicago, Illinois, USA): Graphs were performed using GraphPad Prism software (version 7.00, GraphPad Software, La Jolla, CA, USA, www.graphpad.com). P values < 0.05 were considered statistically significant.

Results

Between the 1st of March and the 25th of April 2020, 56 patients with respiratory symptoms and positivity to SARS-COV2 confirmed with RT-PCR underwent CT at our Institute. Fourteen patients underwent CTPA in the suspicion of pulmonary embolism and the other 42 patients underwent non enhanced chest CT. Fourteen patients were excluded due to severe motion artifacts at CT, with the other 42 Patients formed group COV-P (12 Females, 30 Males, mean age 64.5±13.5 years). Most of them had moderate to critical COVID–19 pneumonia, as demonstrated also by their average PaO2/FiO2 ratio 241±117 (available in 35

patients at admission). Only 12 over 42 patients had blood oxygen saturation >94% while breathing ambient air.

Group NL (17 Females, 24 Males, mean±SD age 65.3±14.5 years) included 42 patients without respiratory symptoms who underwent MDCT at our Institute for follow-up for pathologies not involving the lungs; 30 patients underwent the exam before December 2019, and 12 patients between the 4th and the 7th of May.

Group DTE (18 females, 23 males, mean age 66.0±17.1 years) included 42 patients who underwent CTPA in the suspicion of pulmonary embolism with evidence of endoluminal defects not involving the main pulmonary arteries but only their distal branches.

Group Bact-P (14 females, 28 males, mean age 59.8±13.7 years) included 42 Patients who underwent MDCT of the chest for pulmonary infection, and in whom a bacterium was isolated at blood cultures or BAL.

Group Fung-P (9 females, 33 males, mean age 57.0±14.7 years) included 42 patients who underwent MDCT of the chest in the suspicion of pulmonary infection and in whom a fungus was isolated at blood cultures or BAL or beta-glucan positivity was demonstrated.

Age but not sex was slightly different between the groups ($p<0.05$ for Fung-P vs. DTE and NT, for Bat-P vs DTE and NT, for COV-P vs Fung-P).

The V/B RATIO of the segmental branches of healthy lung parenchyma in group COV-P was significantly higher than the one of all the other groups ($p<0.0001$; table 1, graph1, Fig.1). The V/B RATIO of the subsegmental branches of healthy lung parenchyma in group COV-P was the highest between the groups and significantly superior to that of groups NL, DTE, and Fung-P ($p\leq0.0001$; table 1, graph 2).

When analyzing the measure of the segmental V/B RATIO in patients of groups COV-P, Bact-P and Fung-P in the area of lung opacification, the values in group COV-P were always the highest than the corresponding ones in the two other groups (table 2, graphs 3, Fig.1).

V/B RATIO values of the subsegmental branches in the area of lung opacification in group COV-P were the highest between the groups and significantly superior to that of Fung-P ($p = 0.0003$; table 2, graph 4).

Among the groups of patients with pulmonary infections (COV-P, Bact-P and Fung-P), considering the caliber of the segmental and subsegmental branches of pulmonary arteries in the area of lung opacification, the calibers in group COV-P were significantly higher than those in groups Bact-P and Fung-P. No significantly difference was found in segmental bronchi calibers, while the caliber of subsegmental bronchi was significatively higher in group COV-P than in groups Bact-P, and Fung-P ($p<0.0001$).

Discussion

Severe COVID–19 disease manifests as a devastating pneumonia characterized by diffuse ground-glass and consolidative pulmonary opacities, often with a bilateral and peripheral lung distribution leading to respiratory failure. The low blood oxygenation is not only driven by the extensive involvement of the lung or the development of the acute respiratory distress syndrome (ARDS), but also by microvascular thrombotic processes, contributing to the high mortality [12].

In the present study, we focused our attention on the caliber of segmental and subsegmental branches of pulmonary arteries on healthy lung parenchyma and in correspondence of lung opacities. Not surprisingly, the caliber of the COVID–19 patients' segmental and subsegmental vessels was on average significantly higher respect to the one of patients suffering from other forms of infectious or thromboembolic diseases. These enlargements are present both in sites of radiologically active disease (opacifications) and in apparently healthy parenchyma. Thus, our study proves this is a feature that belongs especially to COVID–19 pneumonia and is more pronounced than in other inflammatory or thromboembolic disease.

Also other studies already reported the same finding but without any comparison group: i.e. Caruso et al. described enlarged subsegmental pulmonary vessels in 52 over 58 COVID–19 patients (89%), as defining vessel enlargement as a vascular caliber >3 mm. Vessel enlargement was described in proximity to areas with GGO, and the authors postulated that this could be compatible with thrombo-inflammatory processes [7]. Even Parry et Al observed segmental and subsegmental pulmonary vascular enlargement on chest CT [8]. At variance with these studies, in order to normalize the caliber measured in the vessels, which could be influenced by physical features of the single patients, we decided to measure the corresponding bronchial branches and to calculate the ratio between each arterial and bronchial branch. The ratio between segmental branch of pulmonary artery and corresponding bronchus was already proposed, together with other imaging features, to identify at CT presence of pulmonary hypertension non peripheral pulmonary vascular disorders [13].

Moreover, not only we compared the calibers with subjects without evidence of lung disease, but also with patients with pulmonary embolism of segmental or subsegmental branches of pulmonary arteries and with other infections. In particular, with respect to patients with bacterial and fungal pneumonia the V/B segmental RATIO on lung opacifications was significantly higher for COVID–19 patients and, since the caliber of the correspondent bronchial branches among the groups was not significatively different, this was due to the dilatation of the segmental vessels on COVID–19 patients compared to the other groups (table 2). At the same time the V/B subsegmental RATIO on lung opacifications was higher on COVID–19 patients but not significatively because, together with the dilatation of the subsegmental vessels also a dilatation of the correspondent bronchial occurred with a consequently lower increase in the V/B ratio (table 2). The dilatation of distal bronchial branches on lung opacifications, such as the presence of bronchiectasis, has already been described on COVID–19 patients and could be related to an evolution to a fibrosing lung patter ("Rapid onset of bronchiectasis in COVID–19 Pneumonia: a series of two patients studied with CT" by Ambrosetti MC et Al., submitted in April 2020, BJR case report).

The pathophysiology of such an enlargement of the lung small vessels is poorly understood but can derive from the complex interplay of all the mechanisms that were previously proposed: thromboembolism, inflammation, endothelial impairment [7]. Indeed, it could reflect the presence of micro-thrombi in small pulmonary vessels. McGonagle et al. suggested that hypoxaemia might determine endothelial dysfunction and activate the coagulation cascade, and it might also play a role in adjacent small pulmonary vascular thrombosis; other factors, including mechanical ventilation might contribute [14]. Anyhow, it is worth underlying that none of the COVID–19 patients included in the present study was intubated at the time of the CT-scan.

Several studies observed high plasma levels of proinflammatory cytokines in COVID–19 patients admitted to intensive care units, the so-called “cytokine storm”: these pro-inflammatory cytokines might trigger the coagulation system [10]. Other authors, have suggested that vascular enlargement may be due to pro-inflammatory factors that determine vascular hyperemia [15]. In a recent autopsy study Ackermann et al. examined 7 lungs obtained from patients who died from COVID–19 and compared them with 7 lungs obtained from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1) infection and 10 age-matched, uninfected control lungs. The lungs from patients with COVID–19 showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels in patients with Covid–19 showed widespread thrombosis with microangiopathy. Furthermore, vascular angiogenesis distinguished the pulmonary pathobiology of COVID–19 [16]. As the V/B ratio of segmental and subsegmental branches is higher in all the groups of patients with pulmonary infection, as compared with those with pulmonary embolism, we can suggest that the role of inflammation could be predominant on the small-vessel enlargement. To add to the inflammatory hypothesis, when comparing the level of C-reactive protein measured at the emergency department in 31 COVID–19 patients divided according to the median value of segmental vessel V/B ratio (1.23), we noticed higher values in patients with the V/B ratio above the median as compared to below the median (124±93 vs 62±49 mg/L; $p<0.05$).

Limitations of the study are the fact that its design is retrospective and only patients with clinical indication to the CT were evaluated, ages between group is slightly different, only one radiologist who was not blinded to the lung pathologies analyzed the images, either CT or CTPA were evaluated, interstitial forms of pneumonia are missing as well as clinical and laboratory data in many patients so that a completely trustable comparison between groups and subgroups is not feasible. Anyhow, as far as we know, this is the first study focusing on a quantitative evaluation of vessel enlargement on COVID–19 patients and comparing this group of patients with different control groups adding important information about the specific lung involvement in the disease.

In conclusion, we have proven that the caliber of segmental and subsegmental vessels in COVID–19 pneumonia is significantly higher than in normal lungs and in other forms of TE and infectious disease, at least in sites of parenchymal opacification. The process leading to vessel enlargement could be the sum of the profound inflammation and distal thromboembolic processes that altogether contribute to the

pathophysiology of this devastating disease. Radiologists should pay attention to this characteristic when analysing CT-scan of patients with suspected COVID–19 pneumonia.

Abbreviations

CT: computed tomography

PACS: picture archiving and communication system

ARDS: acute respiratory distress syndrome

GGO: ground glass opacities

RT-PCR: reverse-transcription polymerase chain reaction

CTPA: computerized tomography pulmonary angiography

Declarations

Competing interests: The authors declare no competing interests.

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Tables

Due to technical limitations, Tables 1-2 are provided in the Supplementary Files section.

Figures

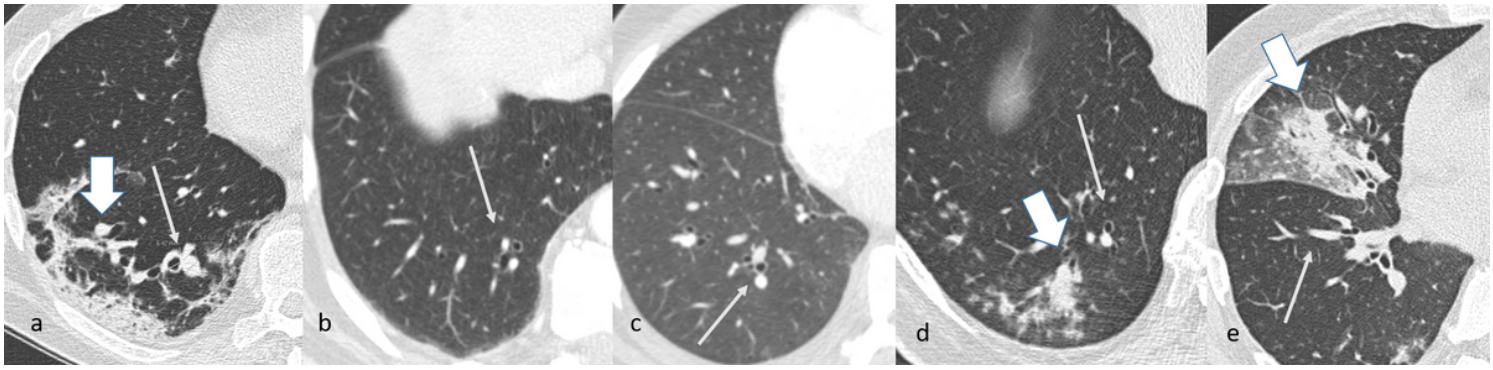


Figure 1

Chest CT of patients of respectively group COV-P (a), NL (b), DTE (c), Bact-P (d) and Fung-P (e). Note segmental branches of pulmonary artery and corresponding bronchus on healthy parenchyma (thin arrows; a-e) and on lung opacification (wide arrows; a,d,e).

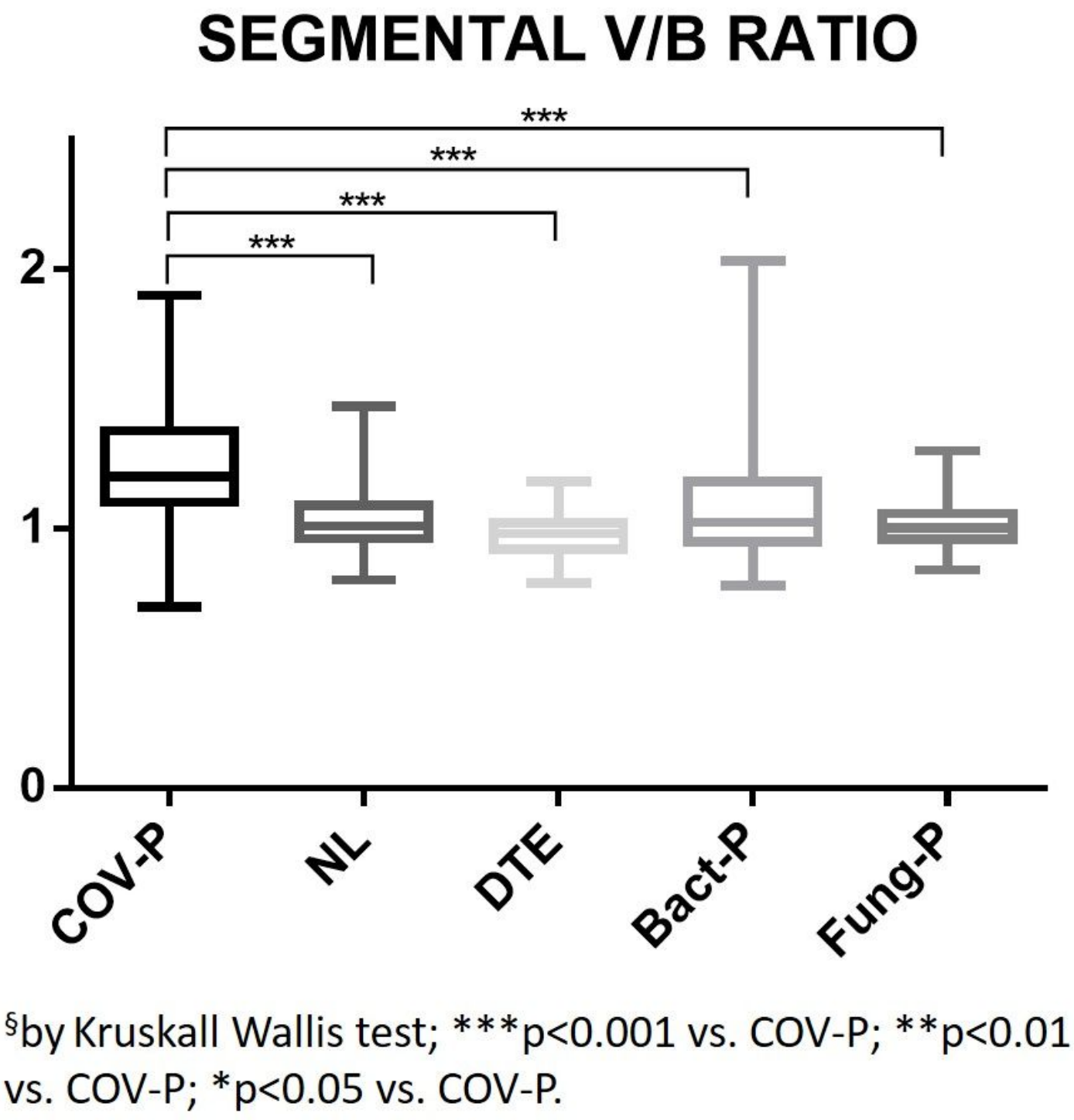
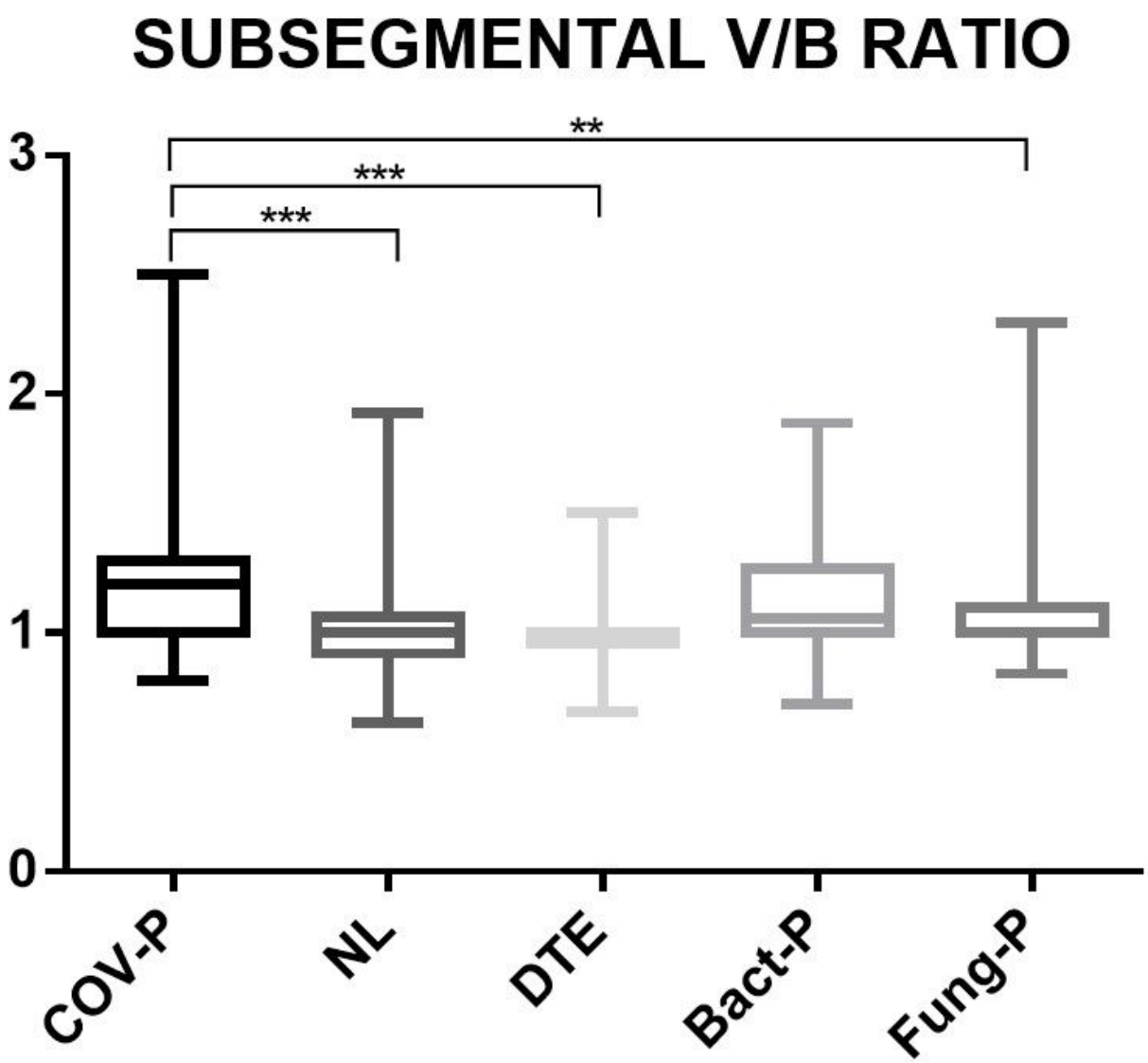


Figure 2

Graph1: ratio between caliber of segmental branches of pulmonary arteries and their corresponding bronchial branches measured on healthy lung parenchyma. COV-P, COVID-19 pneumonia; NL, normal

lung; DTE, distal thromboembolism; Bact-P, bacterial pneumonia, Fung-P, fungal pneumonia.



*§by Kruskall Wallis test; ***p<0.001 vs. COV-P; **p<0.01 vs. COV-P; *p<0.05 vs. COV-P.*

Figure 3

Graph2: ratio between caliber of subsegmental branches of pulmonary arteries and their corresponding bronchial branches measured on healthy lung parenchyma. COV-P, COVID-19 pneumonia; NL, normal lung; DTE, distal thromboembolism; Bact-P, bacterial pneumonia, Fung-P, fungal pneumonia.

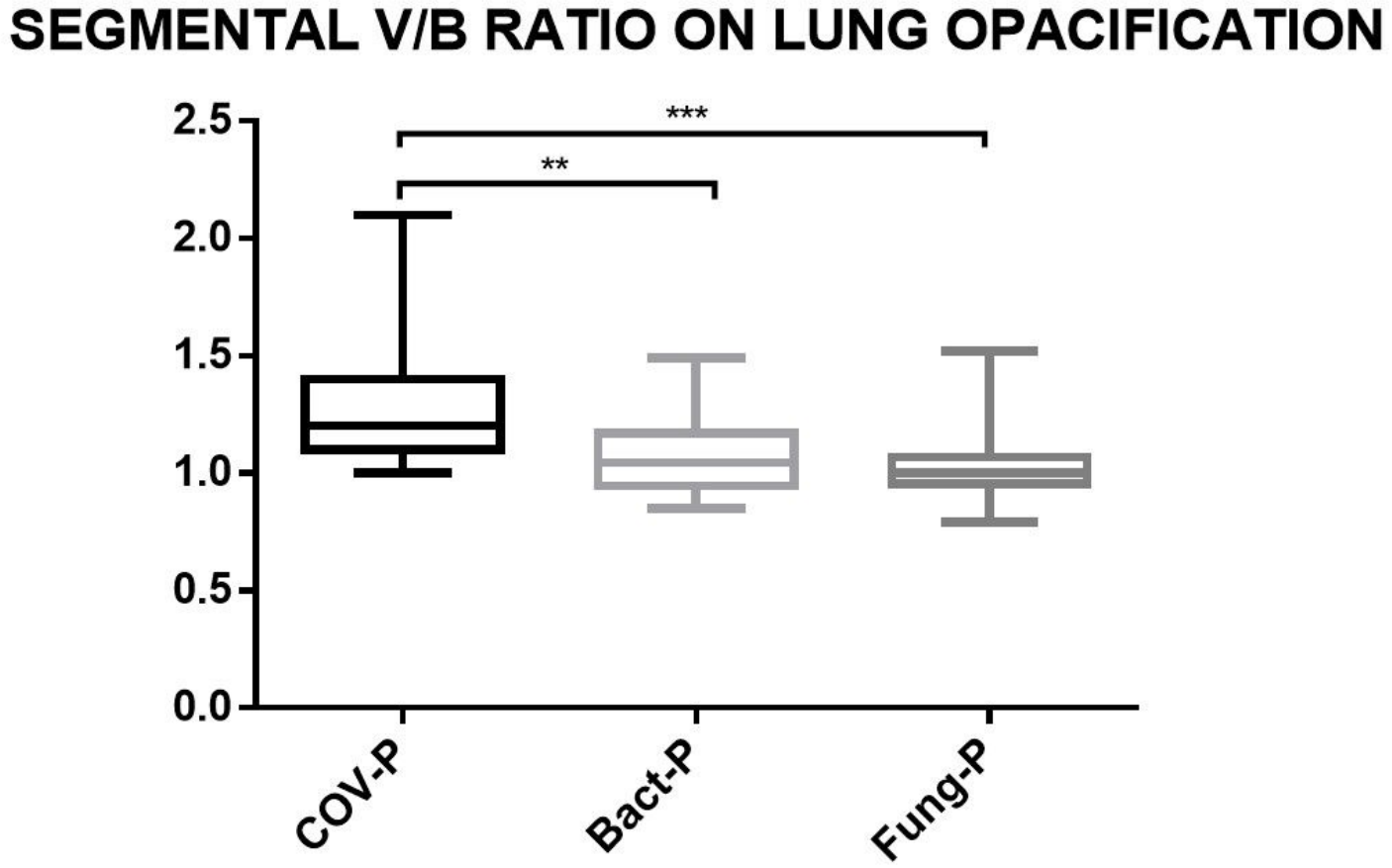


Figure 4

Graph3: ratio between caliber of segmental branches of pulmonary arteries and their corresponding bronchial branches measured on lung opacification. COV-P, COVID-19 pneumonia; Bact-P, bacterial pneumonia; Fung-P, fungal pneumonia.

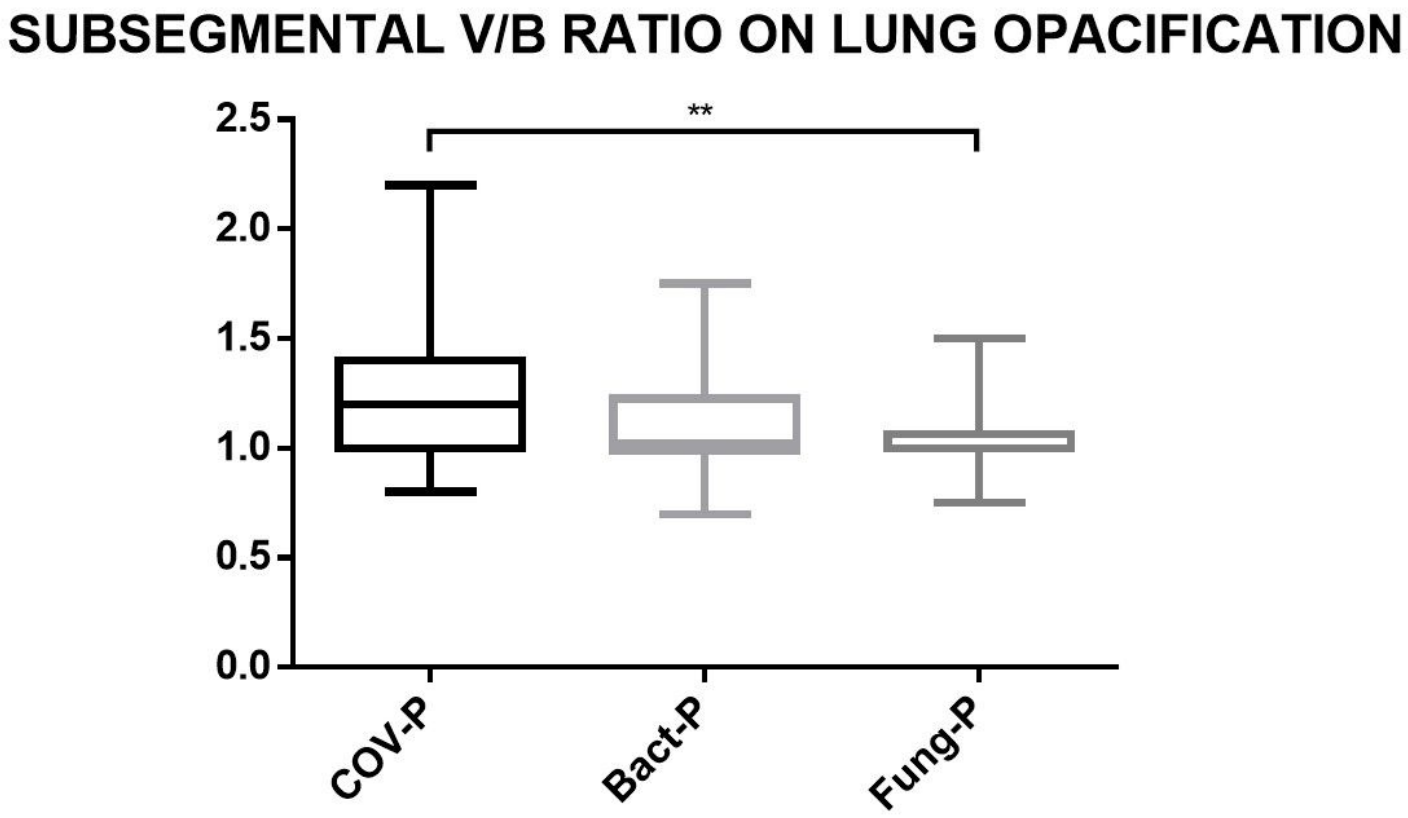


Figure 5

Graph4: ratio between caliber of subsegmental branches of pulmonary arteries and their corresponding bronchial branches measured on lung opacification. COV-P, COVID-19 pneumonia; Bact-P, bacterial pneumonia; Fung-P, fungal pneumonia.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tabella1.jpg
- Tabella2.jpg