



CT-derived pulmonary vascular metrics and clinical outcome in COVID-19 patients

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Abstract: To assess pulmonary vascular metrics on chest CT of COVID-19 patients, and their correlation with pneumonia extent (PnE) and outcome, we analyzed COVID-19 patients with an available previous chest CT, excluding those performed for cardiovascular disease. From February 21 to March 21, 2020, of 672 suspected COVID-19 patients from two centers who underwent CT, 45 RT-PCR-positives (28 males, median age 75, IQR 66–81 years) with previous CTs performed a median 36 months before (IQR 12–72 months) were included. We assessed PnE, pulmonary artery (PA) diameter, ascending aorta (Ao) diameter, and PA/Ao ratio. Most common presentations were fever and dyspnea (15/45) and fever alone (13/45). Outcome was available for 41/45 patients, 15/41 dead and 26/41 discharged. Ground-glass opacities (GGOs) alone were found in 29/45 patients, GGOs with consolidations in 15/45, consolidations alone in 1/45. All but one patient had bilateral pneumonia, 9/45 minimal, 22/45 mild, 9/45 moderate, and 5/45 severe PnE. PA diameter (median 31 mm, IQR 28–33 mm) was larger than before (26 mm, IQR 25–29 mm) ($P<0.001$), PA/Ao ratio (median 0.83, IQR 0.76–0.92) was higher than before (0.76, IQR 0.72–0.82) ($P<0.001$). Patients with adverse outcome (death) had higher PA diameter ($P=0.001$), compared to discharged ones. Only weak correlations were found between Δ PA or Δ PA/Ao and PnE ($\rho\leq 0.453$, $P\leq 0.032$), with 4/45 cases with moderate-severe PnE and minimal increase in PA metrics. In conclusion, enlarged PA diameter was associated to death in COVID-19 patients, a finding deserving further investigation as a potential driver of therapy decision-making.

Keywords: Tomography, X-ray Computed; COVID-19; hypertension; pulmonary; pneumonia; viral; SARS-CoV-2; patient outcome assessment

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Introduction

Pathophysiological lung changes in patients affected by the novel Coronavirus Disease (COVID-19) are easily detectable with computed tomography (CT) and mirror the possible evolution from viral pneumonia to acute respiratory distress syndrome (ARDS) (1-7). Bilateral interstitial abnormalities are initially present as subpleural ground-glass opacities (GGOs), while progressive consolidations and reticular patterns can lately appear, reaching a large extent if cytokine dysregulation induces ARDS with diffuse alveolar and interstitial damage (1,3,5).

Extensive lung consolidation and ARDS can alter pulmonary vasculature features (8), engendering pulmonary hypertension (9,10), which in COVID-19 patients could also be caused by an overlap of these processes with increasingly-reported pulmonary arterial thrombosis (11-15). Early detection of pulmonary hypertension is therefore paramount to guide appropriate treatment (8) but remains a complex diagnostic challenge, also hampered by different and complementary shortcomings of available diagnostic techniques (10,16). While COVID-19 patients frequently undergo unenhanced CT, administration of iodinated contrast agents for CT pulmonary angiography, which would facilitate the diagnosis of pulmonary arterial thrombosis, may be contraindicated in COVID-19 patients. However, unenhanced CT measurements of the ratio between maximum diameters of the pulmonary artery (PA) and the ascending aorta (Ao)—PA/Ao ratio—were found to represent a helpful non-invasive option to detect pulmonary hypertension (9,10,16,17). A cut-off value of 29 mm for PA diameter is generally accepted as highly suggestive of pulmonary hypertension (16,18), while a PA/Ao ratio >0.9 has been found to be progressively correlated with pulmonary vascular impairment (9,10,17).

This retrospective study, performed in two hospitals near to the first area put in quarantine during the COVID-19 pandemic in Italy, aimed to evaluate intra-individual variations of pulmonary vascular metrics in COVID-19 patients, comparing unenhanced CT scans performed after emergency room (ER) admission and previous CTs performed for any reason except cardiovascular disease assessment, and to correlate vascular metrics to pneumonia extent (PnE) and clinical outcomes.

Methods

Study population

The local Ethics Committees approved this retrospective

study (Ethics Committee of Brescia; protocol code NP 4154; approved on May 13, 2020).

COVID-19 patients who underwent thoracic CT at ASST Crema - Ospedale Maggiore, Crema, Italy; Center 1 and Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy; Center 2 after ER admission from February 21 to March 21, 2020, were identified. At both institutions, during this timeframe, waiting times for reverse transcriptase-polymerase chain reaction (RT-PCR) results were too high to correctly triage the sheer number of suspected COVID-19 patients, CT being temporarily performed as a triaging test. We included in this study only patients who had subsequent confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by RT-PCR and had already performed another thoracic CT at the same institution for other clinical queries (except for cardiovascular disease): these previous CTs were considered as baseline examinations. Outcome data and arterial partial pressure of oxygen at admission (PaO₂-Adm) were retrieved from clinical records.

Image acquisition

At Center 1, all examinations during the COVID-19 pandemic were performed on one of the two currently-installed 64×2-slices CT scanners (Aquilion CXL, Toshiba/Canon Medical Systems, Ōtawara, Japan, or Revolution EVO, General Electric Healthcare, Chalfont St. Giles, UK), while all baseline examinations had been performed on the formerly-installed 16-slices CT scanner (Diamond Select Brilliance 16, Philips Healthcare, Best, The Netherlands). At Center 2, all current and baseline examinations were performed on a 16-slices CT scanner (LightSpeed RT 16, General Electric Healthcare, Chalfont St. Giles, UK). Patients' conditions were monitored during the procedure and all current scans were performed without the administration of iodinated contrast agents.

Image analysis

Two dedicated radiologists, with 7- and 20-year experience from each center, reviewed CTs from their own institution to assess pulmonary parenchyma, pulmonary vascular metrics, and Ao maximum diameter.

Lung parenchyma was assessed for the presence of the following features: GGOs and/or consolidation, crazy-paving pattern, pleural effusion, mediastinum lymphadenopathy. PnE was visually assessed according to the categories proposed by Bernheim *et al.* (2): 0% (absent); 1–25% (minimal); 26–50%

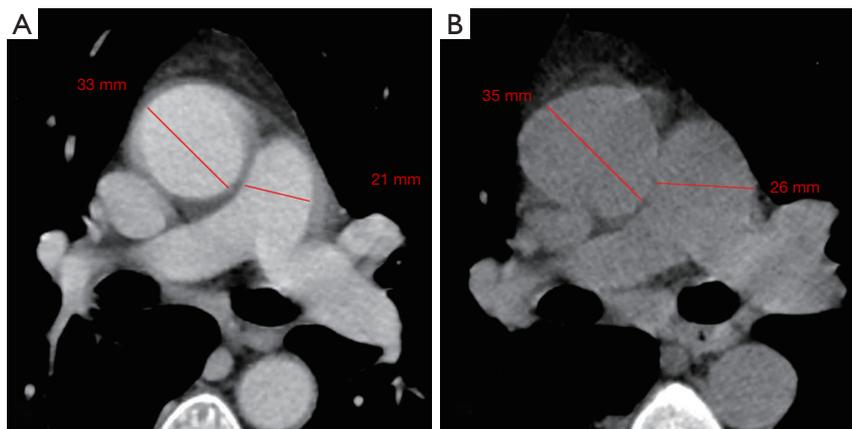


Figure 1 Pulmonary artery to ascending aorta (PA/Ao) ratio assessed on axial contrast-enhanced CT at baseline (A) and unenhanced at emergency room admission for suspected SARS-CoV-2 infection (B) in a 51-year-old woman with confirmed SARS-CoV-2 infection. Baseline CT was performed the previous year for oncologic follow-up. Soon after SARS-CoV-2 infection was confirmed, the patient began to show bilateral ground glass opacities and consolidation, with mild pneumonia extent.

(mild); 51–75% (moderate); over 75% (severe).

Perilesional vascular enlargement, defined as presence/absence of enlargement of pulmonary vessels next to lung parenchymal opacities, was qualitatively assessed (4).

Finally, as described by Wells *et al.* (9), the PA maximum diameter at the level of its bifurcation and the Ao maximum diameter were assessed in a single slice (Figure 1), and PA/Ao ratio then calculated.

Statistical analysis

Data were reported as mean and standard deviation (SD) or as median and IQR according to their normal or non-normal distribution, assessed with the Shapiro-Wilk test. The Wilcoxon test was used to assess significant differences among PA/Ao ratio and PA maximum diameter before and after SARS-CoV-2 infection, Spearman's ρ being used to assess correlations between vascular metrics, PnE, admission PaO₂, and hospitalization length. The Mann-Whitney *U* test and the χ^2 test were used to compare vascular metrics and PnE between groups with different outcomes.

Statistical analysis was performed using SPSS v.22.0 (IBM SPSS Inc., Chicago, IL, USA), and P values <0.05 were considered statistically significant.

Results

Population characteristics

In the study timeframe, 374 patients underwent triage

chest CT for suspected SARS-CoV-2 infection at Center 1, 298 patients at Center 2. A previous CT examination was available for 45 of subsequently confirmed COVID-19 patients (median age 75.2 years, IQR 66.0–81.0 years), twenty-eight of them (62%) being males. At ER admission, fifteen patients (33%) had both fever and dyspnea, nine (20%) patients had both fever and cough, thirteen (29%) only fever, four (9%) only dyspnea, one (2%) only cough, and three (7%) respiratory insufficiency. PaO₂-Adm was available for 37 patients, with a median 70 mmHg (IQR 55–94 mmHg). Outcome data were available for 41/45 patients, 15/41 (37%) died after progression to severe ARDS and 26/41 (63%) discharged after a median 10 days hospitalization (IQR 0–20 days).

The previous CT scans used as baseline examinations were performed a median 36 months before ER admission (IQR 12–72 months).

Pulmonary parenchymal CT features

All but one patient had bilateral pneumonia, GGOs without consolidation being found in 29 (65%) patients, both GGOs and consolidation in 15 (33%), consolidations alone in one patient only (2%). Only one patient had associated crazy-paving. PnE was categorized as minimal in nine patients (20%), mild in 22 (49%), moderate in 9 (20%), and severe in 5 (11%). Pulmonary perilesional vascular enlargement was found in 10 patients (22%), 6 of them with bilateral consolidations. Five patients had bilateral pleural effusion

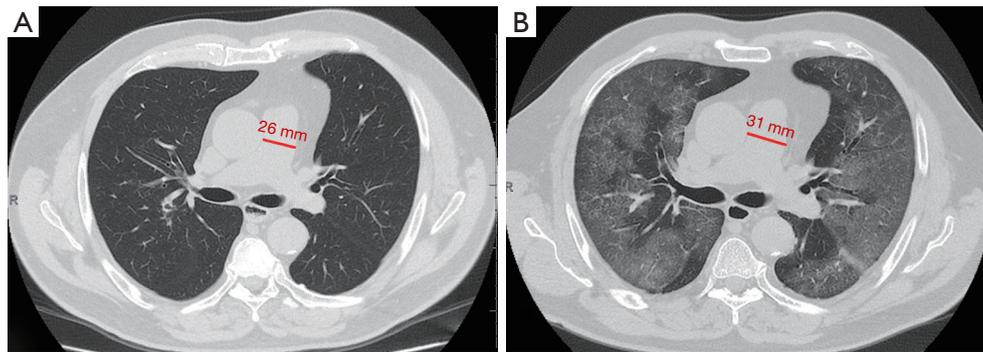


Figure 2 Axial unenhanced CT images at baseline (A) and at emergency room admission for suspected SARS-CoV-2 infection (B) in a 66-year-old man with confirmed COVID-19. Baseline CT was performed the previous year for oncologic follow-up. In (B), the patient had bilateral ground glass opacities with severe pneumonia extent and enlarged pulmonary artery.

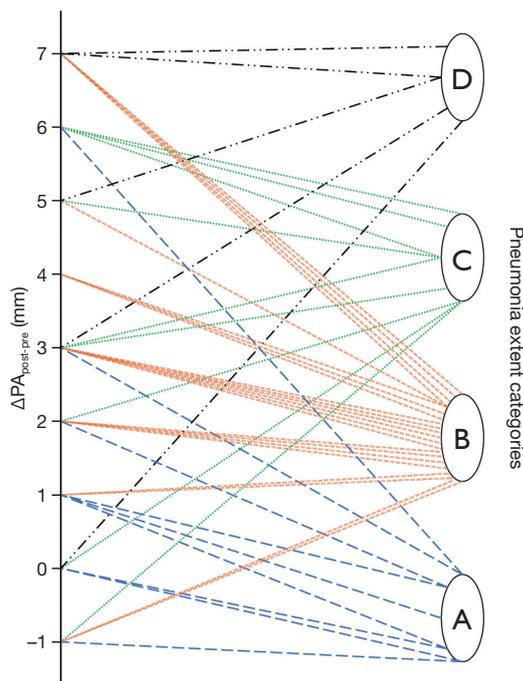


Figure 3 $\Delta PA_{\text{post-pre}}$ values and their relations with the four categories of pneumonia extent. A, minimal pneumonia extent; B, mild pneumonia extent; C, moderate pneumonia extent; D, severe pneumonia extent.

and three others showed mediastinum lymphadenopathies.

Vascular metrics

Median PA_{pre} diameter was 26 mm (IQR 25–29 mm), median PA_{post} diameter was 31 mm (IQR 28–33 mm) ($P < 0.001$, *Figures*

1,2), and median overall $\Delta PA_{\text{post-pre}}$ was 3 mm (IQR 1–5 mm). Median Ao_{pre} diameter was 35 mm (33–39 mm), while median Ao_{post} diameter was 36 mm (IQR 33–39 mm) ($P = 0.005$).

Median PA/Ao ratio at ER admission (0.83, IQR 0.76–0.92) was significantly higher ($P < 0.001$) than at baseline (0.76, IQR 0.72–0.82), the median overall value of $\Delta PA/Ao_{\text{post-pre}}$ being 0.07 (IQR 0.02–0.11).

Correlation between clinical data, radiological data, and outcome

In patients with unfavorable outcome (i.e., death), we found lower $PaO_2\text{-Adm}$ values ($U = 77$, $P = 0.023$) and worse PnE ($P = 0.024$) than in discharged patients. Among vascular metrics, only the PA_{post} diameter was significantly higher ($U = 74$, $P = 0.001$) in patients with unfavorable outcome.

As noticeable in *Figure 3*, $\Delta PA_{\text{post-pre}}$ values showed a significant but weak correlation with PnE ($\rho = 0.321$, $P = 0.032$). $\Delta PA/Ao_{\text{post-pre}}$ values (*Figure 4*) showed a higher correlation with PnE ($\rho = 0.453$, $P = 0.002$), and a relatively higher correlation was also found between PA/Ao ratio at ER admission and PnE ($\rho = 0.631$, $P < 0.001$) (*Figure 5*). $PaO_2\text{-Adm}$ values likewise showed a significant but intermediate correlation with PnE ($\rho = -0.459$, $P = 0.004$) and a significant but weak correlation with PA/Ao ratio at ER admission ($\rho = -0.356$, $P = 0.030$). No other correlation was found among vascular metrics and the duration of hospitalization before discharge or death.

Discussion

Known disruption of pulmonary hemodynamics following

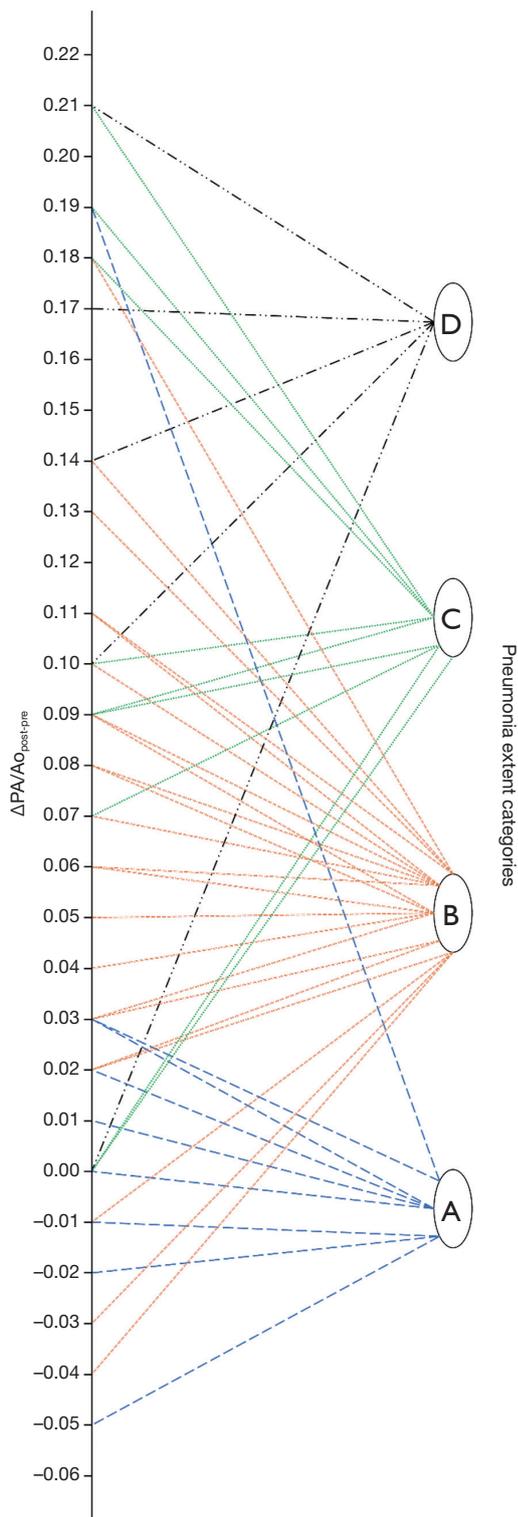


Figure 4 $\Delta PA/Ao_{post-pre}$ values and their relations with the four categories of pneumonia extent. A, minimal pneumonia extent; B, mild pneumonia extent; C, moderate pneumonia extent; D, severe pneumonia extent.

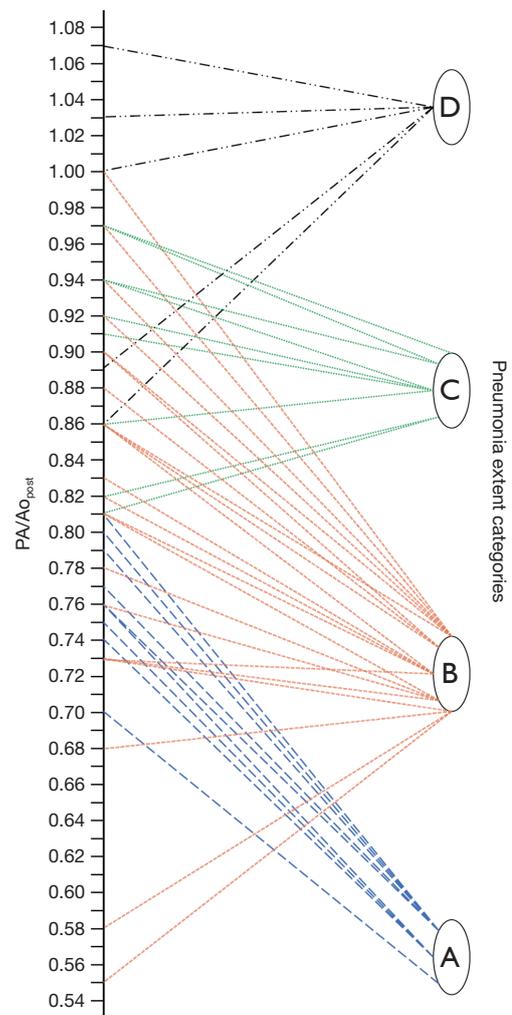


Figure 5 PA/Ao_{post} values and their relations with the four categories of pneumonia extent. A, minimal pneumonia extent; B, mild pneumonia extent; C, moderate pneumonia extent; D, severe pneumonia extent.

large scale consolidation with inflammatory and vascular changes, expressed as vascular enlargement (4), could also be a concern in COVID-19 patients, which already present a frail intravascular equilibrium with high thromboembolic risk (15,19-25). Diagnosis of pulmonary hypertension is fraught with complications (8-10,16,17), but CT measurements of PA diameter and PA/Ao ratio constitute a helpful non-invasive option for the detection of pulmonary hypertension even in unenhanced CT, as demonstrated on large populations (9,17). While such metrics are easily attainable in COVID-19 patients which already perform unenhanced CT scans and could represent a potential

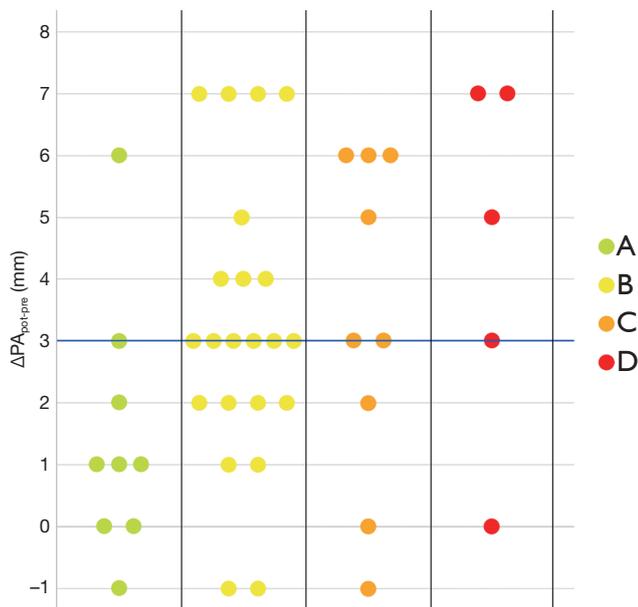


Figure 6 Category-divided scatter plot of per-patient $\Delta PA_{\text{post-pre}}$ values. A, minimal pneumonia extent; B, mild pneumonia extent; C, moderate pneumonia extent; D, severe pneumonia extent. The blue horizontal line represents the overall median $\Delta PA_{\text{post-pre}}$ value.

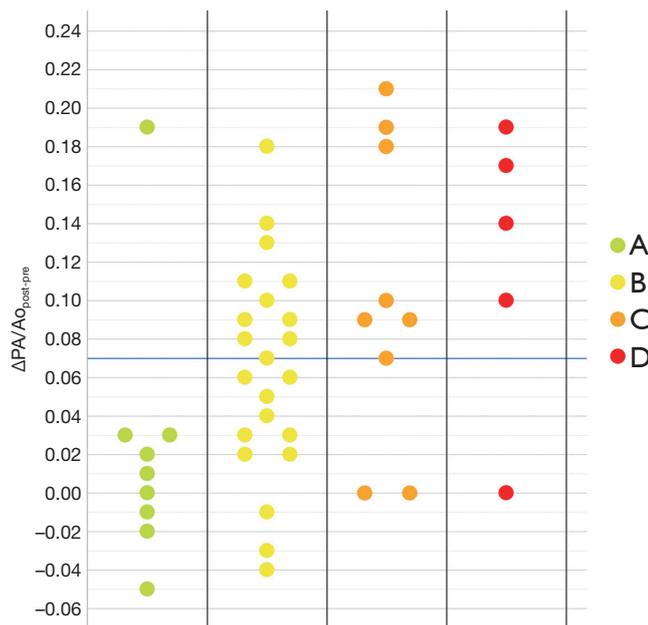


Figure 7 Category-divided scatter plot of per-patient $\Delta PA/Ao_{\text{post-pre}}$ values. A, minimal pneumonia extent; B, mild pneumonia extent; C, moderate pneumonia extent; D, severe pneumonia extent. The blue horizontal line represents the overall median $\Delta PA/Ao_{\text{post-pre}}$ value.

prognostic index, to date no study to evaluate possible pulmonary hypertension has been conducted on these patients. We therefore performed this retrospective study considering two of the first clusters of patients in the Italian COVID-19 epidemic, aiming to compare intra-patient vascular metrics on chest CT performed before and during SARS-CoV-2 infection and their correlation with baseline PaO_2 and patient outcome. Including only patients with a previous CT, our data comes from fragile patients, with a median age of 75 years and main reason to perform previous examinations of oncological nature.

When measuring PA diameter after SARS-CoV-2 infection we found a median value of 31 mm (IQR 28–33 mm), above the 27 mm and 29 mm reference values established for women and men, respectively, in the Framingham Heart Study (18). The large majority (37/45, 82%) of COVID-19 patients from our cohort presented an increased PA caliber compared to their baseline measurements. We also found an increase both in the median PA/Ao ratio and in the PA diameter absolute median value, that rose from 26 to 31 mm after SARS-CoV-2 infection. Of note, all ten patients without an increased PA/Ao ratio showed already high baseline values for both components of this parameter, suggesting that an increase in pulmonary vascular pressure may be related to the inflammatory status triggered by SARS-CoV-2 infection.

While an intermediate correlation was found between PaO_2 -Adm and PnE, we found a weak correlation both between PaO_2 -Adm and PA/Ao_{post} and between vascular metrics and PnE, as depicted in *Figures 6,7*. Considering the two categories with lowest PnE, we observed 9 patients with $\Delta PA_{\text{post-pre}}$ values higher than the overall median value (*Figure 6*), and 11 patients with $\Delta PA/Ao_{\text{post-pre}}$ higher than the overall median value (*Figure 7*). Conversely, considering the two categories with highest PnE, we observed 4 patients with $\Delta PA_{\text{post-pre}}$ values lower than the overall median value and 3 patients with $\Delta PA/Ao_{\text{post-pre}}$ lower than the overall median $\Delta PA/Ao_{\text{post-pre}}$. This could be explained considering that only one of our patients had already progressed to the late phase of mostly consolidative pulmonary damage, during which—as already demonstrated in various types of acute and chronic pulmonary interstitial disease (8–10, 16,17)—pulmonary hypertension severity reaches its peak. However, a relatively better correlation with PnE was found for $\Delta PA/Ao_{\text{post-pre}}$ than for $\Delta PA_{\text{post-pre}}$. Indeed, $\Delta PA/Ao_{\text{post-pre}}$ is known to be a more robust parameter for the evaluation of

pulmonary hypertension (10,17).

The overall weakness of these correlations, and especially the fact that only the PA_{post} diameter was higher in patients who subsequently died than in discharged patients, suggest that pulmonary vascular metrics of COVID-19 patients and their relation with outcome are also influenced by factors other than PnE. Hypotheses to explain such findings could involve both a viral-induced autoimmune endothelial damage, already associated to other coronaviruses such as SARS-CoV-1 in the early 2000s (26), and a large spectrum of procoagulant abnormalities, increasingly observed in COVID-19 patients. These abnormalities include high levels of D-dimer and fibrin degradation products, presence of antiphospholipid antibodies, longer prothrombin time and activated partial thromboplastin time (15,19-25), resulting in pulmonary arterial thrombosis (13,14). Patients with a low increase in pulmonary metrics could be less affected by endothelial damage and thrombosis, already reported in COVID-19 patients with poor prognosis (12,19-25,27,28).

The observation that—among vascular metrics—only PA diameter was significantly higher in patients with unfavorable outcome than in discharged patients, could be related to a precocious manifestation of pulmonary arterial thrombosis. Thus, pulmonary vascular metrics on unenhanced CT scans could be useful to understand patients' conditions, possibly working as a gate-keeper to contrast-enhanced CT, especially in patients with a mismatch between PnE and oximeter saturation data. Early detection of pulmonary hypertension at admission could also guide treatment of COVID-19 patients, triggering modifications of anticoagulation therapies from prophylactic to therapeutic dosage (21,27,29).

This study has limitations, the main one being the limited number of patients. We included all confirmed COVID-19 patients with a previous chest CT, performed for any reason (except cardiovascular diseases) at any time, even those with old previous CTs: this could bias the value of comparing previous pulmonary vascular metrics with those during infection. Moreover, tachypnoea and dyspnea are common in COVID-19 patients and motion artifacts during CT examinations could have influenced the measurements. Another limitation of our study is the manual measurement of great vessels diameters on axial scans, which is only a rough approximation for real vessels' size. A more accurate approach would be to measure vessel areas on reformatted oblique reconstructions considering

vessels' axes, also considering the potential role of automatic recognition and measurement, already demonstrated for Ao on MRI (30). In addition, three-dimensional vascular metrics and flow parameters obtained by MRI or contrast-enhanced CT could also be considered in future studies.

In conclusion, COVID-19 patients showed higher median PA maximum diameter and median PA/Ao ratio compared to values measured on previous chest CTs performed for any reason except cardiovascular diseases. In this limited cluster of fragile patients, PA maximum diameter showed significant difference between patients with favorable and unfavorable outcome, a finding deserving further investigation as a potential driver of therapy decision-making.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-546>). SS declares to be member of speakers' bureau for General Electric and to have received travel support from Bracco. FS declares to have received grants from or to be member of speakers' bureau/advisory board for Bayer, Bracco and General Electric. The other authors have no conflicts of interest to declare.

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