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Portal hypertension-like pattern in coronavirus disease 2019 acute respiratory distress syndrome

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ABSTRACT

Objectives: Although respiratory failure is the most common feature in coronavirus disease 2019 (COVID-19), abdominal organ involvement is likewise frequently observed. To investigate visceral and thoracic circulation and abdominal organ damage in COVID-19 patients.
Materials and methods: A monocentric observational study was carried on. In COVID-19 patients affected by acute respiratory distress syndrome (ARDS) ($n = 31$) or mild pneumonia ($n = 60$) thoracoabdominal circulation was evaluated using Doppler-ultrasound and computed tomography. The study also included non-COVID-19 patients affected by ARDS ($n = 10$) or portal hypertension (n = 10) for comparison of the main circulatory changes.
Results: Patients affected by COVID-19 ARDS showed hyperdynamic visceral flow and increased portal velocity, hepatic artery resistance-index, and spleen diameter relative to those with mild-pneumonia ($p = 0.001$). Splanchnic circulatory parameters significantly correlated with the main respiratory indexes ($p < 0.001$) and pulmonary artery diameter ($p = 0.02$). The chest and abdominal vascular remodeling pattern of COVID-19 ARDS patients resembled the picture observed in the PH group, while differed from that of the non-COVID ARDS group. A more severe COVID-19 presentation was associated with worse liver dysfunction and enhanced inflammatory activation; these parameters both correlated with abdominal ($p = 0.04$) and chest imaging measures ($p = 0.03$).
Conclusion: In COVID-19 ARDS patients there are abdominal and lung vascular modifications that depict a portal hypertension-like pattern. The correlation between visceral vascular remodeling, pulmonary artery enlargement, and organ damage in these critically ill patients is consistent with a portal hyperlfow-like syndrome that could contribute to the peculiar characteristics of respiratory failure in these patients.

Abbreviations: ACE2, angiotensin converting enzyme 2; ALT, alanine-amino transferase; ARDS, acute respiratory distress syndrome; AST, aspartate-alanine transferase; BIL, bilirubin; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; FDR, false discovery rate; GGT, gamma-glutamine transferase; HARI, hepatic artery resistance index; ICU, intensive care unit; IL-6, interleukine-6; PAD, pulmonary artery diameter; PAD/AA, ascending aorta diameter ratio; PaO_2/FiO_2, ratio between the partial pressure of oxygen in arterial blood and the fraction of inspired oxygen; PH, portal hypertension; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; US, ultrasound examination.

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Clinical relevance statement: our data suggest that the severity of COVID-19 lung involvement is directly related to the development of a portal hyperflow-like syndrome. These observations should help in defining the need for a closer monitoring, but also to develop dedicated therapeutic strategies.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, named coronavirus disease 2019 (COVID-19), is characterized by a wide spectrum of respiratory symptoms from mild insufficiency to a critical picture of acute respiratory distress syndrome (ARDS) [1,2].

The increasing comprehension of the disease depicts COVID-19 as a multiorgan disorder, partly similar to other viral infections associated with systemic reactions [3,4]. However, COVID-19 shows distinctive features probably linked to endothelial dysfunction. Indeed, certain severe manifestations of COVID-19 appear to be related to endothelial activation and thrombosis [5,6]. Consistently, hypercoagulability, microthrombosis, and angiogenesis have been found in the lungs of COVID-19 patients and these abnormalities could contribute to the peculiar characteristics of the disease [7]. In addition, these features were related to enlarged pulmonary artery, high pulmonary pressure and right ventricular dilatation at echocardiogram, especially in more severe and non-survivor patients [8]. As a result, a role of right ventricular afterload dysfunction in outcome and disease severity definition became evident [9,10]. Moving from these observations, more recently, computed tomography (CT) have been used to determine median pulmonary artery diameter in COVID-19 patients and its impact on mortality. By using this well-known marker of pulmonary hypertension [11-13], the authors were able to stratify the risk of death of these patients [14].

It is clear that concurrent with lung disease, systemic COVID-19 can affect abdominal organs, making liver dysfunction the most frequent disorder [15]. Several studies that investigated the biochemical characteristics of COVID-19 found liver dysfunction in 7–53% of the global patient population [15], and the proportion raised to 62% in patients admitted to intensive care units (ICU) [16]. The origin of liver injury is still unclear and endothelial activation, virus-induced damage of hepatic parenchyma cells, inflammation, and drug-related damage have been proposed as potential pathogenetic mechanisms [17]. Therefore, the cause of the disorder requires further investigation.

Interestingly, portal hypertension and visceral hyperdynamic flow secondary to liver cirrhosis and systemic inflammatory reactions are frequently associated with an abnormal coagulation cascade and microcirculatory deregulation in both the chest and the abdomen [18,19]. Consequently, thoracoabdominal involvement with multiorgan damage is common in these pathological conditions. In this setting, ultrasound examination (US) and CT are currently used to monitor organ and circulatory modifications. Among other indications, US is used to asses abdominal hemodynamic status of cirrhotic patients, while CT was recently used to better assess the visceral artery remodeling secondary to splanchnic hyperdynamic circulation [20,21],

Despite systemic COVID-19 involvement is now manifest and the pathophysiological changes that occur in the thoracic district are progressively depicted, their etiopathogenetic mechanisms are usually studied separately from abdominal injury. The interplay between abdominal and thoracic damage has not been thoroughly explored as well as the possible implications of a portal hyperflow-like syndrome on lung injury. Therefore, moving from the observations on pulmonary vascular and cardiac remodeling, we decided to re-evaluate our collected data and, by describing the circulatory and vascular morphological changes in patients affected by COVID-19 of different severity, we aimed to investigate the potential relationship among respiratory function, chest and visceral circulation, and organ damage.

2. Methods

2.1. Study population and design

The study enrolled all consecutive COVID-19 patients (>18 years old) with a ratio between the partial pressure of oxygen in arterial blood and the fraction of inspired oxygen (PaO_2/FiO_2) lower than <300 mmHg at Emergency Department admission and hospitalized at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy) from March 11th to April 15th 2020. COVID-19 pneumonia was defined as interstitial pneumonia at CT or chest X-ray and positivity of SARS-CoV-2 real-time reverse-transcriptase–polymerase-chain-reaction assay of nasal and pharyngeal swabs [22]. Exclusion criteria were concomitant splenomegaly, primary liver disease diagnosis, lung and heart chronic disease history, vasoactive drug infusion at the time of abdominal ultrasound (US) examination.

Patients were divided into 2 groups according to respiratory failure treatment: ICU-COV group ($n = 31$), patients with severe SARS-CoV-2-induced ARDS admitted to ICU and requiring mechanical ventilation; MED-COV group ($n = 60$), patients with mild COVID-19 pneumonia admitted to Internal Medicine unit with spontaneous breathing. PaO_2/FiO_2 ratio was used to determine the severity of respiratory failure. Patients were followed until April 30th 2020 or occurrence of a censor event (discharge, death, or end of follow-up).

To test our hypothesis and to enable a more accurate evaluation of the main circulatory findings, the study included two additional groups of consecutive patients not infected with SARS-CoV-2 for whom CT evaluation was available: ARDS group ($n = 10$), patients suffering from ARDS and portal hypertension (PH) group (n = 10), patients affected by portal hypertension in liver cirrhosis awaiting liver transplantation (Child-Pugh score > C9) without portopulmonary hypertension. For these 2 study groups, data were retrospectively collected from existing datasets from previous studies [23].

An additional group of COVID-19 patients was included in the study to evaluate the relation between CT and hemodynamic parameters ($n = 20$). These patients were selected from those admitted to ICU during the second pandemic wave (ICU-COV2) and that received invasive hemodynamic monitoring thorough Swan-Ganz catheter. Patients with previous or ongoing cardiac disease and extracorporeal support were excluded.

All anthropometric and imaging measures, biochemical data, and vital parameters were collected according to clinical practice. The study was approved by and conducted according to Milano area 2 ethics committee requirements. There was no commercial support for this study.

2.2. Abdominal ultrasound technique

Abdominal ultrasound was performed by two experienced sonographers using a Philips EPIQ CVx. At the time of the US, the mean arterial blood had to be >60 mmHg and portal overload signs were ruled out. Patients from the ICU-COV group were subjected to US within 72 h after admission to ICU and before censor events, while in the MED-COV group, US evaluation was performed within the first 7 days after admission.

The following parameters were analyzed by means of the US technique: the presence of liver steatosis, mean velocity of the portal vein and hepatic artery resistance index (HARI), hepatic vein waveform (measured on middle hepatic vein, triphasic, biphasic, monophasic) according to Zhang and colleagues [24], and spleen cranio-caudal

diameter.

2.3. Computed tomography

CT was performed according to clinical practice requests within the first week after ICU or MED admission. We obtained 36 CT scans: 9 MED-COV, 12 ICU-COV, and 15 ICU-COV2. In ARDS group, CT evaluation was performed before any invasive procedure, while in PH group, it was executed before liver transplantation. CT images were used to assess by three independent investigators pulmonary artery, pulmonary artery diameter (PAD), and ascending aorta diameter ratio (PAD/AA), according to Peretti et al. to investigate whether splanchnic and thoracic circulation were related [12]. Splanchnic and hepatic artery diameters were measured according to Patrono et al. [20] to evaluate visceral vascular remodeling secondary to splanchnic and liver hypervascularization.

2.4. Hemodynamic measures

Swan-Ganz catheter, central venous catheter, and arterial catheter were placed, and measures were collected according to the standard practice. Systemic and pulmonary vascular resistance were calculated following standard equations, following the measurement of cardiac output using the thermodilution technique. All data were registered in a prospective database.

2.5. Laboratory testing in COVID-19 groups

Laboratory parameter evaluation was performed according to clinical practice. Inflammatory biomarkers consisted of leucocytes, ferritin, C-reactive protein (CRP), interleukine-6 (IL-6). Liver dysfunction was defined based on increased concentrations of alanine-amino transferase (ALT), aspartate-alanine transferase (AST), bilirubin (BIL), gamma-glutamine transferase (GGT). Creatinine, urea, microalbuminuria, and proteinuria are used to determine kidney function.

2.6. Statistical analyses

Comparisons between ICU-COV and MED-COV groups were conducted using Student's *t*-tests. Differences across ICU-COV, MED-COV, ARDS, and PH groups were investigated using Fisher-Snedecor test of one-way ANOVA. In both analyses, *p*-values were adjusted with the Benjamini-Hochberg method to control the false discovery rate (FDR). The effect of individual-specific confounding factors (e.g., age, gender) was further investigated through multiple linear regression models, showing that their presence did not affect the results. Dependencies between variables were investigated with Pearson's Product Moments correlation tests, using FDR-adjusted *p*-values. All statistical analysis was performed using R (version 3.6.2, R Core Team, 2019).

3. Results

3.1. Patients

Characteristics of the ICU-COV group and the MED-COV group are reported in Table 1, while features of non-COVID-19 patients are presented in Appendix table 1.

ICU-COV patients were younger than subjects from the MED-COV ($p = 0.001$) and had a shorter time from symptoms onset to hospitalization ($p = 0.05$). Metabolic comorbidities were diagnosed in 20/31 (65%) of patients of the ICU-COV and in 25/60 (42%) of the MED-COV ($p = 0.038$). Antiviral therapy was administered to 10/31 patients (39%) of ICU-COV and 2/60 (3%) of the MED-COV group ($p = 0.001$).

ICU-COV patients had a worse respiratory impairment (PaO_2/FiO_2) compared to MED-COV (99 [80–129] mmHg vs 286 [246–313] mmHg, $p < 0.001$) (Fig. 1A). The ARDS group had a lower PaO_2/FiO_2 ratio than ICU-COV ($p = 0.003$) and higher PEEP ($p < 0.001$) (Appendix table 1).

After 11 days [7–16], 25/31 (81%), ICU-COV patients recovered spontaneous breathing (Appendix table 2) whereas 4/31 (12%) patients still needed mechanical ventilation. There were 2/31 (6%) fatal events.

Transaminases and inflammatory biomarkers progressively normalized during ICU stay (Appendix table 2). The prevalence of liver dysfunction was significantly higher in ICU-COV than in MED-COV (86% vs 32%, $p < 0.001$). Similarly, inflammatory parameters were significantly higher in ICU-COV than in MED-COV (ferritin, $p = 0.012$;

Table 1
Main patient characteristics, laboratory testing and imaging measures in the two study groups ICU-COV and MED-COV.

	ICU-COV (n = 31)	MED-COV (n = 60)	p
Time from symptoms to hospital admission, days	7 (5–8)	10 (5–15)	0.05
Time from hospital to ICU/ward admission, days	4 (1.5–5)	2 (0–6)	0.25
Age, yr	60 (52–65)	74 (64–83)	0.001
Male sex, n (%)	24 (77)	34 (57)	0.06
Body mass index, kg/mq	28 (26–30)	25 (23–28)	0.02
Coexisting metabolic comorbidities, n (%)			
No comorbidities	11 (35)	35 (58)	0.04
Hypertension	10 (32)	24 (40)	0.16
Diabetes	4 (13)	17 (29)	0.10
Hyperlipidemia	5 (16)	21 (35)	0.06
Antiviral therapy, n (%)	10 (39)	2 (6)	0.001
Median respiratory parameters (IQR)			
PaO2/FiO2 ratio, mmHg	99 (80–129)	286 (246–313)	<0.001
Partial blood oxygen pressurre, mmHg	76 (67–87)	82 (66–90)	0.19
Partial blood carbon dyoxid pressurre, mmHg	46 (42–52)	36 (33–40)	<0.001
Inspired oxygen fraction, %	60 (50–82)	25 (21–35)	0.001
Positive end-expiratory pressure, cmH20	13 (12–14)	–	
Median ultrosound parameters (IQR)			
Mean portal vein velocity, ml/min	29.8 (29.2–31.7)	25.9 (24.2–27.6)	0.001
Hepatic artery resistance index	0.89 (0.83–0.91)	0.69 (0.65–0.75)	0.001
Spleen diameter, cm	12.6 (11.3–13.0)	10.1 (8.6–11.5)	0.001
Mild steatosis, n (%)	4 (13)	18 (30)	
Moderate steatosis, n (%)	15 (48)	34 (56)	0.02
Severe steatosis, n (%)	12 (39)	9 (14)	
Median computed tomography parameters (IQR)			
Pulmunary artery diameter (PAD), mm	29 (28–31)	26 (25–28)	0.001
PAD/ascending aorta diameter	1.14 (1.04–1.27)	0.95 (0.88–0.96)	0.001
Hepatic artery diameter, mm	5.1 (4.5–5.4)	3.5 (3.2–4.1)	0.01
Left gastric artery diameter, mm	3.8 (3.6–4.4)	2.7 (2.5–2.9)	0.001
Gatsroepiploic arcade diameter, mm	3.1 (2.7–3.5)	2.4 (2.0–2.6)	0.008
Median laboratory values (IQR)			
Aspartate alanino-transferase, IU/l	144 (66–157)	38 (33–58)	0.001
Alanino-transferase, IU/l	114 (68–206)	49 (19–68)	0.001
Gamma-glutammil-transferase, IU/l	235 (150–391)	32 (19–56)	0.005
Bilirubin, mg/dl	0.7 (0.4–1.7)	0.4 (0.3–0.9)	0.52
Creatinine, mg/dl	1.4 (0.9–1.9)	0.9 (0.7–1.2)	0.03
Microalbuminuria, n (%)	22 (72)	–	
Ferritin, ng/ml	1537 (1038–2950)	465 (273–899)	0.02
C-reactive protein, mg/dl	17.7 (7.8–20.3)	2.2 (0.6–6.15)	0.001
Interleukine-6, ng/ml	115.5 (65.5–269.2)	12.8 (5.3–30)	0.03
Death, n (%)	2 (6)	2 (3)	0.47

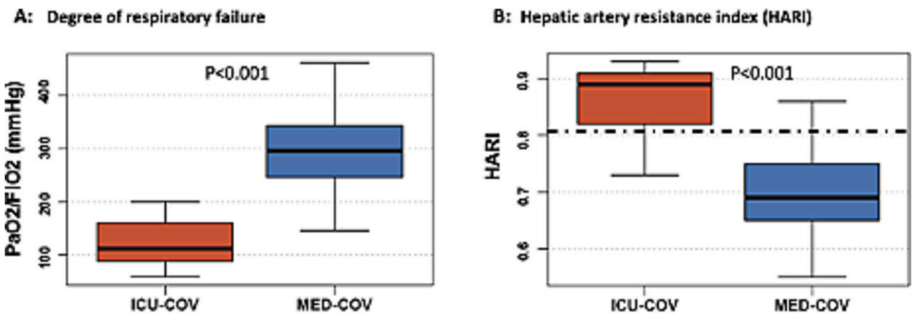

Fig. 1. Hepatic artery resistance index (HARI) (A) and COVID-19 respiratory involvement expressed as PaO_2/FiO_2 ratio (B) in the two study groups. The boxes reflect the interquartile range, and the whiskers indicate the rage (up to 1.5 times the interquartile range).

IL-6, $p = 0.02$; CRP, $p < 0.001$). Among ICU-COV, 22/31 (72%) had microalbuminuria and 10/31 (31%) macroproteinuria associated with acute kidney injury stage 2–3, according to KIDGO, while 2/31 (6%) patients were subjected to continuous-venous-venous hemofiltration.

3.2. Abdominal ultrasound findings

The ICU-COV patients showed increased portal velocity (ICU-COV vs. MED-COV: 29.8 [29.2–30.4] cm/s vs. 25.9 [24.2–27.6] cm/s, $p = 0.001$) and spleen diameter (12.5 [12.3–12.7] cm vs. 9.7 [9.2–10.22] cm, $p < 0.001$), and HARI (0.87 [0.85–0.89] vs. 0.69 [0.66–0.71], $p < 0.001$, Fig. 1B) relative to subjects from the MED-COV group (Table 1).

Within the group of recovered ICU-COV patients, HARI and mean portal vein velocity tended to normalize, while splenomegaly remained manifest (Appendix Table 2). Compared to MED-COV patients, the recovered ICU-COV showed significantly higher HARI (0.772 ± 0.063 vs. 0.690 ± 0.069, $p < 0.001$) and spleen diameter (12.1 ± 0.6 cm vs. 9.7 ± 1.8 cm, $p < 0.001$), while mean portal vein velocity ($27.1 \pm 1.7 \pm 25.9 \pm 5.9$, $p = 0.30$) was similar (Appendix Table 2).

Among ICU-COV recovered patients, 9/25 (36%) subjects underwent a US follow-up after at least three weeks after ICU discharge (Appendix Table 3). Over this period, one death was registered due to gastrointestinal bleeding, and could not receive a US examination. Splenomegaly did not change over time ($p = 0.29$), while HARI and mean portal vein velocity significantly decreased during follow-up ($p = 0.03$ and $p = 0.03$, respectively). These parameters were similar to those of patients from the MED-COV group, except for spleen diameter that remained persistently increased in ICU-COV (12.1 cm vs 9.8 cm, $p = 0.002$).

3.3. Computed tomography findings

Pulmonary artery diameters were significantly higher in ICU-COV compared to MED-COV (PAD: ICU-COV 30 [28–31] mm vs. 27 [24–29], $p = 0.049$) and PAD/AA (ICU-COV 1.17 [1.06–1.28] vs. MED-COV 0.93 [0.85–1.01], $p < 0.001$) (Table 1 and Appendix Fig. 1). ICU-COV patients likewise showed increased visceral artery diameter relative to MED-COV (left gastric artery, $p < 0.001$; gastroepiploic arcade, $p = 0.008$; proper hepatic artery, $p = 0.004$) (Table 1). As shown in Fig. 2, PAD and PAD/AA were higher in ICU-COV than in both MED-COV and ARDS (both $p < 0.001$), while they were comparable to the values measured in patients from the PH group ($p = 0.697$ and $p = 0.38$, respectively). Consistently, CT-measured abdominal artery diameters

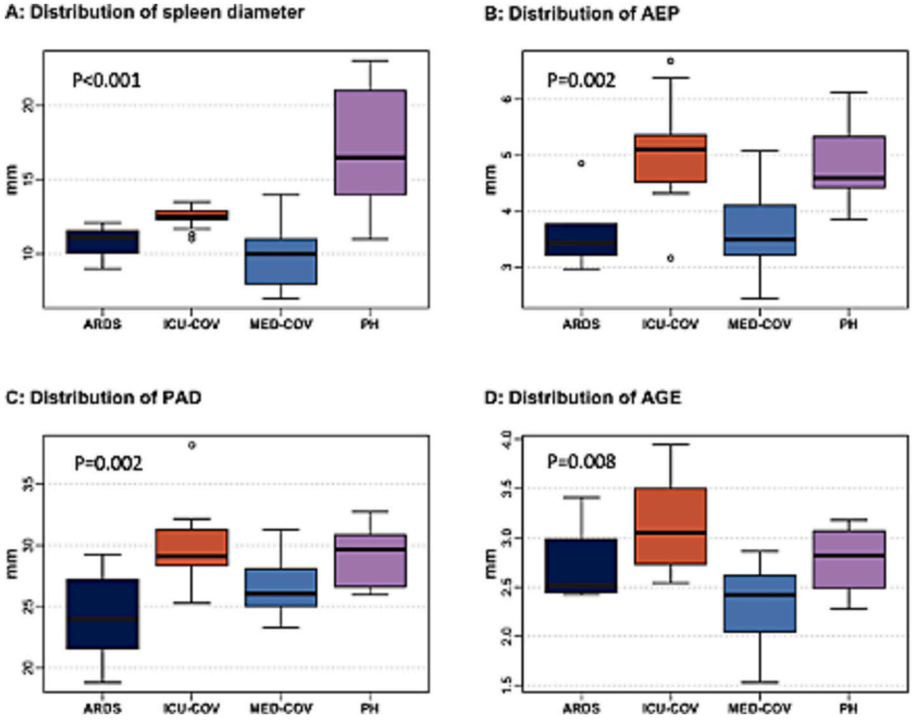

Fig. 2. Main differences between the COVID-19 groups (ICU-COV and MED-COV) and non-COVID ARDS (ARDS) and portal hypertension (PH) group. The boxes reflect the interquartile range, and the whiskers indicate the rage (up to 1.5 times the interquartile range). PEA, proper hepatic artery; GEA, gastro-epiploic arcade.

were increased in ICU-COV and PH patients. Only the left gastric artery diameter was greater in ICU-COV compared to PH group ($p = 0.001$) (Fig. 2) (Appendix Table 1).

3.4. Correlation analysis

3.4.1. Respiratory function

PAD/AA showed an inverse linear correlation with PaO_2/FiO_2 ($p = 0.03$; R = -0.552) (Fig. 3A) and a positive correlation with $PaCO_2$ ($p = 0.008$; $R = 0.603$) (Appendix Table 4).

Consistently, PaO_2/FiO_2 had an inverse linear correlation with the hepatic Doppler US (HARI, Fig. 3B) and vascular remodeling measures, while $PaCO_2$ showed a positive linear correlation with the US parameters and left gastric artery (Appendix Table 4).

Among the ICU-COV group, mechanical ventilation parameters (PEEP; FiO_2) increased together with mean portal vein velocity ($p = 0.009$, $R = 0.480$; $p = 0.01$, $R = 0.449$), HARI ($p = 0.001$, $R = 0.585$; $p = 0.046$, $R = 0.470$) and spleen diameter (p = 0.01, $R = 0.479$; $p = 0.010$, R = 0.470).

3.4.2. Imaging findings

HARI had a positive linear correlation with PAD ($p = 0.03$, $R = 0.486$), PAD/AA ($p = 0.005$, $R = 0.608$) (Fig. 3C), and left gastric artery ($p = 0.02$; $R = 0.507$).

An upregulated inflammation led to higher HARI and increased splenomegaly ($p < 0.007$; $R > 0.329$.

Left gastric artery had a positive linear correlation with spleen diameter ($p = 0.05$; $R = 0.503$) and pulmonary artery diameter (p = 0.001, $R = 0.456$) (Appendix Table 4).

ALT (Fig. 3D) and GGT showed an inverse linear correlation with PaO_2/FiO_2, and a positive correlation with IL-6 (p = 0.05, $R = 0.257$ and p = 0.03, $R = 0.525$) and HARI (ALT: p = 0.03, $R = 0.297$ and GGT: $p = 0.04$, $R = 0.380$, Fig. 3E). PaO_2/FiO_2 showed an inverse linear correlation with clinical inflammatory parameters (Fig. 3F) (Appendix Table 4), while $PaCO_2$ had a positive linear correlation with PCR and ferritin ($p = 0.01$, $R = 0.457$; p = 0.01, $R = 0.475$, respectively).

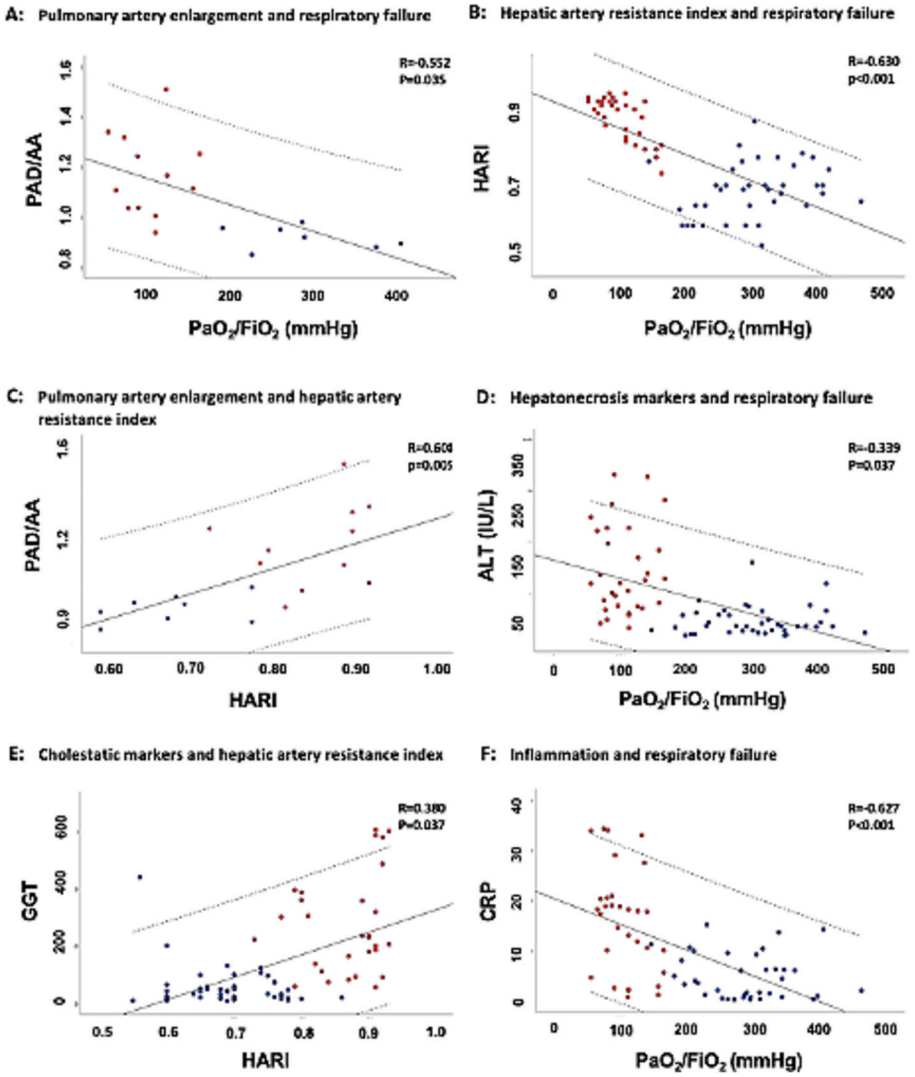

Fig. 3. Panels A and B show that the degree of respiratory failure (P/F, PaO_2/FiO_2 ratio) had an inverse linear correlation with pulmonary artery ratio (PAD/AA) (A) and hepatic artery resistance index (HARI), respectively. In panels C, the positive linear correlation between HARI and PAD/AA was displayed. Panel D shows a negative correlation between PaO_2/FiO_2 and the degree of hepatonecrosis markers (alanine-transferase, ALT), while in panel E a positive correlation between cholestasis biomarkers (gamma-glutammil transferase, GGT) and HARI was described. Ultimately, panel F reports the correlation between C-reactive protein (CRP) and PaO_2/FiO_2. For a visual inspection of linear correlations (continuous line), the area encompassed between the two interrupted lines represent 95% prediction interval. Red dots ICU-COV; blue dots MED-COV. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.5. Hemodynamic parameters

To offer a hemodynamic interpretation of the morphological changes, we investigated hemodynamic and morphological parameters in ICU-COV2 patients. There were no clinical and CT parameter differences between ICU-COV and ICU-COV2 patients (Supplementary Table 8). Mean pulmonary artery pressure was 32 [25–35] mmHg with a mean occlusion pressure (mPHOP) of 14 [11–16] mmHg, a central venous pressure (CVP) of 10 [8–13] mmHg, and a cardiac output of 7 [6–9] L. As a result, systemic (SVR) and pulmonary vascular resistance (PVR) were 726 [615–1126] dyne/s/cm^{-5} and 173 [146–241] dyne/s/cm^{-5}. PAD/AA showed an inverse linear correlation with SVR (p = 0.012, R = -0.723) and mean arterial pressure (p = 0.019, R = -0.719), while a trend towards a positive linear correlation with cardiac output (p = 0.054, R = 0.549) and mean pulmonary pressure (p = 0.035; R = 0.592). According to abdominal CT variables, HA and GEA had an inverse linear correlation with mPHOP (p = 0.018, R = -0.750; 0.020, R = -0.847) and CVP (p = 0.013, R = -0.951; p = 0.039, R = -0.872).

4. Discussion

The present study on COVID-19 patients demonstrates a significant association between lung disease severity and splanchnic involvement. Concomitant pulmonary artery enlargement, enhanced portal visceral flow, and arterial remodeling are distinctive characteristics and suggest a common pathological pathway resembling portal hypertension's clinical trait. Based on multiple imaging techniques, laboratory, and vital parameters, the results confirm the systemic involvement of severe SARS-CoV-2 infection.

Over the last two decades, different respiratory viruses caused epidemic spreads [3,25]. Although during these viral infections a concomitant extra-pulmonary involvement has been frequently observed, no studies directly investigated the potential pathogenetic mechanisms that connect the thoracic and abdominal involvement. Therefore, in an attempt to clarify these mechanisms in COVID-19, we determined the clinicopathological modifications that concurrently happen above and below the diaphragm. The results, obtained by non-invasive techniques and confirmed with hemodynamic observations, depict a pattern of hyperdynamic porto-mesenteric flow in close association with respiratory and vascular thoracic parameters.

Among the several pathological conditions that affect thoracoabdominal circulation, portal hypertension is characterized by a hyperdynamic state with increased cardiac output and pulmonary pressure, splanchnic bed vasodilatation, low portal flow, and high portal pressure [26]. Even when normal portal resistances are restored, the hyperdynamic state sustains a high portal vein and hepatic artery flow, with liver damage persisting until flow normalization [27,28]. In our study, portal vein velocity was higher in the ICU-COV group compared to the MED-COV group, to non-COVID ICU patients, and healthy volunteers included in other studies [29,30]. We can hypothesize that the hyperdynamic state induced by COIVD-19 in combination with low hepatic resistances leads to a high portal vein velocity (in contrast to cirrhotic patients in whom the hepatic resistances are increased). Our idea is further supported by the higher HARI in the ICU-COV group, which could be secondary to the hepatic artery buffering response to high portal flow and subsequent upregulated angiogenesis [31-33]. As a result, liver injury occurs and could be perpetuated and exacerbated by COVID-19 events. Although the incidence of hepatic dysfunction found in this research is comparable to that observed in other studies [15], the significant correlation between altered abdominal circulation, liver damage, and respiratory failure is a novel observation. Indeed, despite pathological reports and imaging based large cohort studies highlighted both thoracic and abdominal damage in COVID-19 patients, no studies directly investigated their interplay.

Echocardiogram and CT-based studies disclosed a relation between thoracic vascular morphology, pulmonary hypertension, right ventricular dysfunction, disease severity, and survival [9,14]. In other studies, liver steatosis and damage were more frequently observed in ICU COVID-19 patients [34,35]. Our ICU COVID-19 patients showed all these thoracic and abdominal modifications and injuries. To further deepen these observations and try to offer a unique pathophysiological explanation, we decided to compare these cases with other well-studied disease: portal hypertension in cirrhotic patients and non-COVID ARDS.

Our findings (CT and US) highlighted a systemic flow remodeling that could be sustained by a portal hyperflow-like syndrome. Indeed, in patients affected by portal hypertension, an hyperdynamic circulatory state gradually develops with the possible consequent deterioration of lung function with hypoxia and respiratory failure [36]. This sustained hyperdynamic state lead to the development of pulmonary hypertension and progress up to porto-pulmonary hypertension [37]. Collectively, our hypothesis based on morphological observations and US liver hemodynamic was confirmed by the preliminary evaluation of systemic hemodynamic parameters in COVID-19 ICU patients. Indeed, hyperdynamic circulation, based on a high-output state, could result in the development of pulmonary hypertension and a reduction of systemic resistance. These hemodynamic modifications observed in COVID-19 ICU patients are typically observed in cirrhotic patients affected by portal-hypertension and portal-hyperflow.

The main pathophysiological findings in patients with pulmonary involvement secondary to cirrhosis include enhanced inflammatory response, especially interleukin1 and 6, and endothelial damage due to shear stress with capillary obstruction (at autopsy). They could be considered as main drivers of vascular remodeling [38]. In addition, intussusceptive angiogenesis is another biological event observed in non-COVID patients affected by portal and pulmonary hypertension [39,40]. Interestingly, a recent pathological report on COVID-19 lung specimens reported capillary obstruction and intussusceptive angiogenesis [7,41]. This observation suggests a potential pathogenetic role for this process, in addition to a direct virus-driven effect and to the presence of lung peripheral microthrombi to cause respiratory failure in SARS-CoV-2 infection [42].

The concomitant visceral and chest vascular remodeling in the critically ill COVID-19 patients could depict a unique pattern of progressive systemic involvement in which a more pronounced portal hypertension/hyperlfow-like pattern persists in the early phase after lung recovery. Indeed, as elsewhere shown, those patients affected by a more severe lung dysfunction and admitted to ICU due to COVID-19 infection are more likely to pulmonary hypertension with incomplete recovery [43]. As a consequence, together with the optimization of ventilation setting to limit the impact of pulmonary hypertension [44,45], our observation should suggest an approach based on the modulation of the COVID-19 hyperdynamic circulation.

Among the etiopathogenetic mechanisms suggested to explain SARS-CoV-2-induced multiorgan injury, endothelial dysfunction and vascular inflammation are the main proposals. SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor that is expressed in the lung, heart, liver, kidney, intestine and in vascular endothelial cells [5]. ACE2 is an important regulatory component of the renin–angiotensin system. In fact, in physiological conditions, this receptor cleaves the vasopressor angiotensin-II (Ang II) into the vasodilatory and anti-inflammatory peptide angiotensin (1–7). Promoting endocytosis of ACE2, SARS-CoV-2 infection causes a local perturbation in Ang-(1–7)/Ang II ratio, that in turn elicits endothelial activation, cytokine release, leukocyte recruitment, and oxidative stress [46,47]. Sustained microvascular inflammation can cause dysregulated angiogenesis, deranged coagulation, and abnormal vascular tone regulation [48]. There is considerable evidence linking portal hypertension to renin–angiotensin system disturbances in cirrhotic patients [49]. Therefore, disruption of the renin–angiotensin system homeostasis and consequent vascular inflammation could explain the systemic hemodynamic alterations documented by the present research in COVID-19 (increased visceral flow and pulmonary hypertension pattern) and the

hypercoagulability previously described by our group in this disease [19]. SARS-CoV-2-induced cytokine storm [50] could further exacerbate endothelial dysfunction, leading to splanchnic and lung microcirculation derangement with possible multiorgan damage. Indeed, we found an association between liver and kidney function, lung and abdominal vascular remodeling and inflammatory biomarkers. Interestingly, due to pre-existing chronic inflammation and ACE receptor dysregulation, obesity and fatty liver, which were more common in the ICU-COV group, further exacerbate these COVID-19-related events [51]. Notably, the larger splenic diameter in the same group may be secondary to higher inflammatory activation and consequent hemodynamic activation in critically ill patients [52], although there are several possible concurrent causes.

Although our study included different imaging modalities to evaluate patients, US is known to be affected by intrinsic limitations. Portal velocity and splenic diameter may suffer from operator-dependent bias. To overcome this limitation, all US examinations were performed on the same US machine by two experienced operators. The results were consistent and confirmed by CT when possible, providing a unique pathophysiological explanation. In addition, the US measurements were performed for clinical purposes during the first COVID-19, in which the Italian health system was severely affected. For these reasons, the time of imaging examination was heterogeneous and some data (e.g. hepatic vein waveform) were not recorded in all patients.

This study discloses a significant association between lung disease and splanchnic alterations (Fig. 4). The research provides the evidence of portal hyperdynamic circulation in COVID-19 patients configuring portal hypertension-like features. This alteration could partly explain liver involvement and is closely associated with the degree of lung dysfunction. Pulmonary arteries are peculiarly enlarged in the critically ill patients and their changes are associated with the main abdominal damage biomarkers and vascular parameters. We suggest a correlation between thoracic and abdominal district alterations and that the portal hyperflow pathological pathway can contribute to this relationship. Occurrence of portal hypertension-like features in COVID-19 patients could suggest a more severe outcome and possibly be used to early predict progress to ARDS.

CRediT authorship contribution statement

Daniele Dondossola: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft. **Caterina Lonati:** Methodology, Resources, Visualization, Writing – original draft. **Alessia Pini:** Conceptualization, Data curation, Formal analysis, Software. **Daniela Bignamini:** Data curation, Investigation, Methodology. **Alberto Zanella:** Data curation, Formal analysis, Project administration, Supervision. **Rosa Lombardi:** Data curation, Formal analysis, Investigation. **Vittorio Scaravilli:** Conceptualization, Investigation, Methodology, Visualization, Writing – review & editing. **Vincenzo La Mura:** Formal analysis, Methodology, Writing – review & editing. **Laura Forzenigo:** Formal analysis, Methodology, Software. **Pierpaolo Biondetti:** Formal analysis, Investigation, Software, Validation. **Giacomo Grasselli:** Funding acquisition, Supervision, Writing – review & editing. **Anna Fracanzani:** Funding acquisition, Supervision, Writing – review & editing. **Chiara Paleari:** Data curation, Formal analysis, Investigation. **Annalisa Cespiati:** Data curation, Formal analysis, Investigation. **Serena Todaro:** Data curation, Formal analysis, Investigation. **Emanuele Cattaneo:** Data curation, Formal analysis, Investigation. **Marianna Di Feliciantonio:** Data curation, Formal analysis, Investigation. **Giordano Sigon:** Data curation, Formal analysis, Investigation. **Carlo Valsecchi:** Data curation, Formal analysis, Investigation. **Amedeo Guzzardella:** Data curation, Formal analysis, Investigation. **Michele Battistin:** Data curation, Formal analysis, Investigation. **Federica Iuculano:** Data curation, Formal analysis, Investigation.

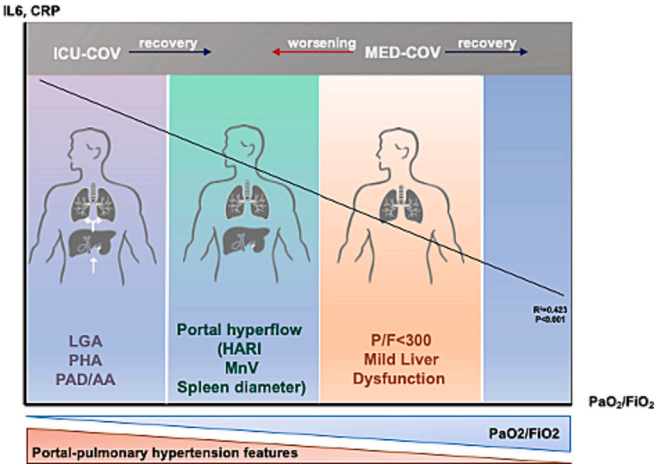

Fig. 4. Graphical representation of the main findings of the study. The effect of inflammation, liver injury, portal inflow, and vascular remodeling parameters of lung and abdomen was further evaluated using multiple regression models, using the quantity PaO_2/FiO_2 as dependent variable (Appendix Table 7). Inflammatory activation is associated to a more severe COVID-19 respiratory involvement ($R^2 = 0.423$; $p < 0.001$) up to ARDS onset and need of mechanical ventilation. The peculiar COVID-19 endothelial damage could sustain the inflammatory activation and the systemic involvement of the disease. Indeed, our data show a progressive development of portal hypertension-like features ($R^2 = 0.493$; $p < 0.001$) with hyperdynamic abdominal flow associated to respiratory disease severity: from mild liver damage in mild pneumonia patients to chest and visceral vascular remodeling in the critically ill patients. In the ICU-COV patients, the hyperdynamic flow could cause and sustain a vicious cycle that resemble porto-pulmonary hypertension and that could partially explain the unusual COVID-19 ARDS features. It is sustained by hyperdynamic circulatory state, organ damage and inflammatory dysregulation ($R^2 = 0.508$; $p = 0.012$). All these phenomenons were observed in the ICU-COV group, supporting our hypothesis. LGA, left gastric artery; PHA, proper hepatic artery; PAD/AA, pulmonary artery diameter/ascending aorta ratio; HARI, hepatic artery resistance index; MnV, mean portal vein velocity; P/F, PaO_2/FiO_2 ratio.

Declaration of competing interest

All authors declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154759.

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