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CTPA imaging findings, beyond pulmonary embolism, in patients with Severe Acute Respiratory Syndrome Corona Virus-2 infection and their relation to clinical outcome – a single center experience

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Abstract. – OBJECTIVE: The aim of our study was to investigate a potential association between the severity of COVID-19 disease and related 28-day mortality, with the presence of mediastinal lymphadenopathy, the extension of lung parenchymal infiltrates, the presence of pulmonary embolism, the density and distribution of mediastinal and subcutaneous fat, the inflammatory markers and the direct and indirect radiological signs of right heart overload and strain.

PATIENTS AND METHODS: We retrospectively included patients diagnosed with SARS-CoV-2 infection, who were admitted to the Departments of Internal and Respiratory Medicine of Patras University Hospital during the second pandemic wave (February 2021 up to July 2021) and underwent CTPA for routine diagnostic workup. Demographic characteristics, routine laboratory, radiological parameters and 28-day mortality were also recorded.

RESULTS: Fifty-three consecutive patients were included. The mean age was 64.47±17.1 years and 64,1% (n=34) were males. Pulmonary embolism (PE) (p=0.019), Right Ventricle-to-Left Ventricle Diameter (RV/LV) Ratio>1 (p<0.01), Reverse Flow in Hepatic Veins (RFHV) (p=0.019), higher density in subcutaneous fat (-99 HU *vs.* -104HU, p=0.016), increased Lactic Dehydrogenase (LDH), Polymorphonuclear cells (PMN), ferritin, and d-dimer levels (534 *vs.* 367 U/L, p=0.001, 9220 *vs.* 5660 K/μL, p=001, 956 *vs.* 360 ng/ml, p=0.005 and 2300 *vs.* 1040 μg/ml, p=0.003, respectively) were statistically significant related with worse 28-day mortality. Binomial multivariate regression analysis revealed that only RV/LV diameter>1, higher subcutaneous fat density and higher LDH values were independently associated with increased 28-day mortality (OR: 82.9, 95%CI: 1.334-5158, p=0.036, OR: 1.2, 95%CI: 1.016-1.426, p=0.032 and OR:1.016, 95% CI:1.004-1.029, p=0.011, respectively). Subgroup analysis revealed that mediastinal lymph node enlargement (EML) and PE were associated to increased Pulmonary Disease Severity Index (PDSI) score (p=0.042 and p=0.007, respectively), but not to mortality.

CONCLUSIONS: Our study showed that right heart strain as depicted by a RV/LV diameter>1, higher subcutaneous fat density and higher LDH values are independently associated with an increased 28-day mortality in our SARS-COV2 patient group.

Key Words:
COVID-19, Computerized Tomography Pulmonary Angiography, Mediastinal lymphadenopathy, Pulmonary embolism, Right heart strain.

Introduction

Severe Acute Respiratory Syndrome Corona-Virus-2 is the cause of the Coronavirus Disease 2019 (COVID-19) disease. Since the first cases were reported in Wuhan, China, the COVID-19 disease has spread rapidly worldwide[1]. COVID-19

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has progressed to an ongoing pandemic that remains a major health problem, with successively waves evolving worldwide[2-4].

COVID-19 has a variety of clinical manifestations ranging from asymptomatic infection to severe pneumonia. Older age, male gender, presence of comorbidities, higher C-reactive protein (CRP) and ferritin levels, pulmonary embolism and higher Pulmonary Disease Severity Index (PDSI) scores are among the well-known predictors of a worse outcome[5-9].

Radiological findings and patterns are also of interest since the extent of lung parenchymal infiltrates are highly correlated with laboratory prognostic factors, where vascular involvement predicts a rather dreadful outcome[4,7,8,10]. Ground-glass opacity is the most common radiological finding, followed by air bronchogram/consolidations/organizing pneumonia, crazy-paving pattern, and pleural thickening[7,8,11-15]. Enlarged mediastinal lymph nodes, defined as mediastinal lymph nodes ≥ 10 mm in short axis, was reported to be rare and atypical radiologic finding and its impact on the prognosis of COVID- 19 has not been well documented[1,8,11,16-18].

Pulmonary embolism is also a quite common, complication of the COVID-19 disease, associated with clinical severity and pulmonary vascular abnormalities, but with controversial correlation to survival[9,11,19-22]. On the other hand, cardiac Doppler Ultra Sound (U/S) confirmed right heart strain in patients with severe COVID-19 disease is associated with worse short-term mortality and long term consequences in COVID-19 survivors, and is considered to be the gold standard for the evaluation of right heart dysfunction[23,24]. Reverse Flow in Hepatic Veins (RFHV) is also a sensitive and specific radiological finding of right heart overload and strain in patients with pulmonary embolism, but has not been studied so far in hospitalized patients with COVID-19[25].

Fat deposition, density and distribution has a rather controversial role in COVID-19 disease. Obese patients with community acquire pneumonia may exhibit higher adipose tissue inflammation, (i.e., more dense adipose tissue in CT scans) but have surprisingly better survival rates[26]. Its association with COVID-19 survival rates is equivocal, since fat tissue can serve as an inflammation reservoir for the COVID-19 infection, but fat distribution has also a prognostic role[27,28].

The aim of our study was to investigate a potential association between the severity of COVID-19 disease and related 28-day mortality, with the presence of EML, PDSI, pulmonary embolism, mediastinal and subcutaneous fat density and distribution, inflammatory markers and direct and indirect radiological signs of right heart overload and strain.

Patients and Methods

We performed a retrospective study at University Hospital of Patras, Western Greece. From February to July 2021 all patients with SARS-CoV-2 infection who were admitted to the Departments of Respiratory and Internal Medicine (General Wards, non-ICU patients) of the University Hospital of Patras and underwent a CTPAs due to severe hypoxemia, hemodynamic instability, increased d-dimers were included into the study.

Demographic characteristics (age, gender), 28-day mortality, routine laboratory findings including white blood cells (WBC), polymorphonuclear cells (PMNs), absolute lymphocyte count (ALC), coagulation parameters (platelets-PLTs, fibrinogen, D-Dimers), C-reactive protein, ferritin, lactate dehydrogenase (LDH) and creatinine kinase (CPK) were recorded within 24 hours prior of the CTPAs.

All CTPA scans were performed using the standard protocol of our hospital. All CT images were reviewed independently by experienced radiologists (C.K., P.Z. & K.D) in consensus, using a Picture Archiving and Communication System (PACS). Each radiologist was also blinded with regards to clinical and laboratory findings of the patients. CT images were evaluated for the presence of central and/or peripheral emboli. Signs of right heart strain were also recorded for each patient such us Right Ventricle-to-Left Ventricle (RV/LV) Diameter Ratio>1, Ventricle Septal Deviation (VSD), Reverse Flow in Hepatic Veins (RFHV) and dilatation of azygos vein.

Using lung windows, the extend of the lung parenchymal involvement was also evaluated and the CT score was calculated by using a semi-quantitative scoring system[7,8]. The total CT score ranged from 0 (no involvement) to 25 (maximum involvement) and PDSI was defined as mild (1) for a score of 7or less, moderate (2) for a score of 8-17 and severe (3) for a score of 18-25[8].

Presence of liver steatosis, mediastinal and subcutaneous fat amount and density were also analyzed[29]. Mediastinal fat (MF) amount was estimated by using a semi-quantitative method and subsequently was categorized as low, me-

dium and high[30]. Subcutaneous fat (SF) amount was estimated by measuring its thickness. Measurement was performed in the posterior plane at the level of the lower chest between the skin surface and the tip of the T8th (8th thoracic) spinous process posteriorly. Patients were divided into three categories according to the SF thickness 1: less than 1cm, 2: between 1-3cm, 3: more than 3cm. Category 1 corresponds to underweight patients, though 2 to healthy weight and 3 to overweight /obese patients[28,31,32]. Fat quality and density analysis through CT attenuation measurement [mean density in HU] was also calculated by using an appropriate ROI. For MF density measurement, a ROI was placed at the level where fat was better seen, avoiding any artifacts. Subcutaneous fat density was calculated by placing a ROI in the anterior part of the chest wall to avoid incorrect measurements due to the dependent oedema usually seen in many long-hospitalized patients.

The presence of EML (short-axis of mediastinal lymph nodes >10mm) and of thymus was recorded for each patient[7,8,33]. Patients with known active malignancies were excluded.

Statistical Analysis

Statistical analysis was performed using the SPSS-25.0 (IBM Inc., Armonk, NY, USA) statistical software. The level of statistical significance (p-value) was set at 0.05. Descriptive statistics were used to summarize and describe the variables in our dataset. For continuous variable comparison, Student t-test and Mann-Whitney U test were performed as appropriate. Chi square test was used for categorical variables. A binomial multivariable regression analysis was applied in biologically plausible variables identified by univariate analysis ($p < 0.1$) accounting for potential confounders.

Results

Fifty-six consecutive patients during the second pandemic wave (February to July 2021), who underwent CTPA, were included. The main outcome was the 28-day mortality (survivors and non-survivors groups). Three patients were excluded from the analysis due to concurrent thoracic malignancy. All patients were receiving the standard protocolized in-hospital treatment for COVID-19 including dexamethasone, remdesivir, tocilizumab and prophylactic low molecular weight heparin. Out of 53 patients that underwent CTPAs, 27 (50.9%) had died by day 28. Eleven out of 53 CTPAs (20.8%) were diagnostic for PE. Age, gender, PDSI and EML distribution were not statistically different between the two groups (Table I).

Pulmonary embolism incidence was more common in the non-survivors group (9/26-34% *vs.* 2/27-7%, p= 0.019). Additionally, RV/LV >1 and RFHV were more common in the non-survivors' group (11/26-42% *vs.* 2/27-7%, p=0.004 and 9/26-34% *vs.* 3/27-11%, p=0.019, respectively). Subcutaneous fat was denser in the non-survivors' group (-99HU±7 *vs.* -107HU±7, p=0.016). Liver steatosis and mediastinal fat density was not different among groups (Table I). Statistically significant increased LDH, PMNs, ferritin and d-dimers levels were noticed in the non-survivors group (534 ± 218 U/L *vs.* 367 ± 146 U/L, p=0.001, 9220 *vs.* 5660 K/μL, p=001, 956 *vs.* 360 ng/ml, p=0.005 and 2300 *vs.* 1040 μg/ml, p=0.003, respectively) (Table I).

Multivariate regression analysis revealed that RV/LV diameter>1, increased subcutaneous fat density and higher LDH values were independently associated with increased 28-day mortality (OR: 82.9, 95%CI: 1.334-5158, p=0.036, OR:1.2, 95%CI: 1.016-1.426, p=0.032 and OR:1.016, 95%CI: 1.004-1.029, p=0.011 respectively). No other common laboratory and radiological signs were associated with 28-day mortality (Table II). Subgroup analysis revealed that EML and PE were related to increased PDSI scores (p=0.042 and p=0.07, respectively), but not to 28-day mortality.

Discussion

Our study showed that increased RV/LV>1, as measured in CTPA images, increased subcutaneous fat density and higher LDH levels are independently associated with 28-day mortality in hospitalized patients due to COVID-19 disease. According to our knowledge no previous study has showed analogous combined results[22,34-36].

Many patients with severe COVID-19 have RV dilatation and dysfunction, but LV dysfunction is less common[24,37,38]. In our patient population, RV/LV >1, reflecting a severe RV dysfunction, was independently statistically related with worse 28-day mortality, unrelated to the presence of PE, possibly representing an increased microcirculation thrombotic load[39]. In a recent study where 28 critically ill

Table I. Univariate analysis of demographics, radiological patterns, and laboratory parameters.

	Survival	Death	p
N (%)	27 (50.9)	26 (49.1)	
Age (iqr)	67 (48-76)	68 (53-76)	Ns
Gender			
Male/Female (%)	17 (63)/10 (37)	17 (65)/9 (34)	Ns
Radiological Parameters			
EML (%)	17(63)	16 (61)	Ns
PDSI (1/2/3) (%)	4 (14)/18 (66)/5 (18)	4 (15)/12 (46)/10 (38)	Ns
Thymus (%)	0	3 (11)	Ns
Liver Steatosis (%)	3 (11)	6 (24)	Ns
PE (%)	2 (7)	9 (34)	**0.019**
RV/LV >1 (%)	2 (7)	11 (42)	**0.004**
VSD (%)	5 (18)	7 (27)	Ns
Azygos Dilatation (%)	1 (3.7)	2 (8)	Ns
RFHV (%)	3 (11)	9 (35)	**0.019**
Mediastinal Fat Density(sd)	-99 (12)	-95 (14)	Ns
Subcutaneous Fat Density (sd)	-104 (7)	-99 (7)	**0.016**
Laboratory Parameters			
WBC (iqr)	7410 (5700-10890)	12160 (6500-19275)	Ns
PMN (iqr)	5660 (4230-9280)	9220 (5940-17625)	**0.01**
ALC (iqr)	860 (710-1140)	680 (455-1230)	Ns
MONO (iqr)	430 (370-590)	640 (340-1075)	Ns
PLTs (iqr)	241 (163-293)	194 (138-318)	Ns
DD (iqr)	1040 (620-1690)	2300 (1390-7400)	**0.003**
CPK (iqr)	74 (42-223)	100 (57-327)	Ns
LDH (sd)	367 (146)	534 (218)	**0.001**
FER (iqr)	360 (231-1264)	956 (591-1602)	**0.005**
CRP (iqr)	4.3 (0.7-7.8)	4.1 (0.57-7)	Ns
Fibrinogen(sd)	510 (187)	427 (177)	Ns

IQR: interquartile range, SD: Standard deviation, PE: Pulmonary Embolism, RV/LV: Right ventricle to Left ventricle Diameter Ratio, CRP (mg/dL): C-reactive protein, WBC (K/μL): White Blood Count, PMN (K/μL): Polymorphonuclear cells, ALC (K/μL): Absolute Lymphocyte Count, MONO (K/μL: Mononuclear cells, PLTs (K/μL): Platelets, DD (μg/ml): D-dimers, LDH (U/L): Lactate Dehydrogenase, FER(ng/ml): Ferritin, RFHV: Reverse Flow in Hepatic Veins, EML: mediastinal lymph node enlargement, VSD: Ventricle Septal Deviation.

patients died from COVID-19, 14 had U/S confirmed RV abnormality, but only 2 had LV impairment. Therefore, a strong relation between RV dysfunction and poor prognosis might exist, which is in concordance with our results[40]. Assessment of RV function is essential for managing ARDS, acute pulmonary embolism, and pulmonary hypertension. A full understanding of the pathophysiology and a prompt diagnosis of right heart strain by the increased RV/LV may be helpful for early identification and precise treatment, improving mortality[37]. CTPA can play a key role in that view since it is readily available, but cardiac U/S remains the gold standard to evaluate RV strain. RV disfunction, as depicted by sensitive cardiac U/S parameters like tricuspid annular plane systolic excursion, S'peak systolic velocity, fractional area changes and right ventricular free wall longitudinal strain, is associated with increased mortality[34]. A reliable identification of RV dysfunction can prompt physicians to limit high positive end expiratory pressures and preserve right heart afterload. RFHV was also related to worse 28-day mortality in our patient group, reflecting the negative effect of severe right heart strain on survival, but its statistical importance did not remain in the multivariate analysis[25]. Of note, in the paper by Planek et al[35], RV dysfunction defined as the blood reflux in the inferior vena cava, but not the RV/LV were associated with 60-day mortality. Nevertheless, in this paper the RV/LV might have been underestimated, due to limitations in performance of the measurements in the axial plane.

Pulmonary embolism is also a frequent complication in severe COVID-19, despite the prophylactic anticoagulant therapy, particularly in patients with radiologically extensive disease[22]. Of note 11/53 of our patients that underwent CTPAs, were diagnosed with PE, which is in concordance with the literature[41,42]. More severe disease is associated with a higher inci-

Table II. Multivariate analysis of univariate significant parameters.

	Univariate analysis			Multivariate Analysis		
	Survival	Death				
N (%)	27 (51)	26 (49)				
			p	O.R.	C.I	p
PE (%)	2 (7)	9 (34)	0.019			
RV/LV >1(%)	**2 (7)**	**11 (42)**	**0.004**	**82.9**	**1.334-5158**	**0.036**
RFHV (%)	3 (11)	9 (35)	0.019			
Subcutaneous Fat Density (sd)	**-104 (7)**	**-99 (7)**	**0.016**	**1.2**	**1.016-1.426**	**0.032**
PMN (iqr)	5660 (4230-9280)	9220 (5940-17625)	0.01			
LDH (sd)	**367 (146)**	**534 (218)**	**0.001**	**1.016**	**1.004-1.029**	**0.011**
FER (iqr)	360 (231-1264)	956 (591-1602)	0.005			
DD (iqr)	1040 (620-1690)	2300 (1390-7400)	0.003			

IQR: interquartile range, SD: Standard deviation, PE: Pulmonary Embolism, RV/LV: Right ventricle to Left ventricle Diameter Ratio, CRP (mg/dL): C-reactive protein, PMN (K/μL): Polymorphonuclear cells, DD (μg/ml): D-dimers, LDH(U/L): Lactate Dehydrogenase, FER (ng/ml): Ferritin.

dence of pulmonary embolism, endothelial damage and coagulopathy[14,22,41,43,44]. Pulmonary embolism is related to alveolar damage, small airways disease, vessel wall oedema, hyaline thrombi, microhemorrhage, and subsequent diffuse thrombosis of peripheral small vessels that have emerged as key features of COVID-19 pathophysiology of tricompartmental disease, finally contributing to respiratory failure[43,45]. Nevertheless, in our patient group multivariate analysis showed that PE was not independently associated with 28-day mortality, probably reflecting its prompt diagnosis and treatment. Our results are in concordance with a recent metanalysis, where PE in COVID-19 patients, was associated with worse clinical parameters but not mortality[22].

It is already known that distinctive types of adipose tissue density and distribution may have different roles in affecting COVID-19 infection rates and outcomes[28]. Our study showed that higher subcutaneous adipose tissue density, but not distribution, was independently associated to increased 28-day mortality, which is in concordance with already existing literature, where fat tissue density reflected increased viral shedding and augmented systematic inflammatory response, most probably due to local overexpression of Angiotensin Converting Enzyme II receptors in fat tissue[27,28,46].

SARS-CoV-2 can affect some routine blood parameters: decreased ALC, and albumin, and up-regulated PMNs, ferritin, D-dimer, creatinine, LDH, and CK levels are distinguishing features of the critically ill patients[43]. LDH is a laboratory parameter that provides valuable prognostic information for mortality and/or severe COVID-19 disease, as in our study[41,42].

In the beginning of the pandemic, mediastinal lymphadenopathy did not appear to be a common clinical or radiologic finding, and was detected in only 1.3% of patients with COVID-19[13,18]. Nevertheless, more recent retrospective studies showed that the prevalence of EML was ranging from 18.2% to 54.8, which is in agreement with our results[16,17]. Our data showed that EML on CT scans was statistically significantly associated with more extensive pulmonary disease, but not with worse 28-day mortality. A study including 189 patients reported that MLE was significantly more frequent in critically ill patients than in non-critically ill patients (51.9% *vs.* 18.5%, $p<0.05$)[46]. Valette et al[47] found that EML was identified in 66% of critically ill patients who were admitted to intensive care unit. Although atypical radiological findings are less taken into account, enlarged mediastinal lymphadenopathy may be useful in predicting severity, and should no more considered as atypical[1,18].

Our study has many limitations. It has a small number of included patients and invasive microbiological sampling was also not routinely performed and therefore coexisting bacterial, fungal, and mycobacterial infections could not be ruled out. We also were unaware of patients' previous RV functionality that might have affected the RV/LV ratio, and we have not validated RV strain with cardiac U/S.

Conclusions

Our study has showed that CTPAs, beyond PE, can provide valuable prognostic information

with regards to right heart strain and systematic inflammatory response as depicted by the RV/LV and adipose tissue density, respectively.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Informed Consent

Not applicable. Data is anonymized and retrospectively collected.

Availability of Data and Material

Data is available upon request.

Authors' Contributions

Dr Sampsonas had the inception of the project and wrote the manuscript. Dr Lagadinou collected the data and edited the manuscript. Drs Kalogeropoulou, Zampakis and Dionysopoulos reviewed and evaluated the anonymized radiological data. Drs Karampitsakos, Papaioannou, Malakounidou, Katsaras, Zarkadi, provided and evaluated anonymized patient clinical data. Dr Karamouzos provided the statistical analysis. Drs Velissaris, Marangos and Stratakos provided a thorough critical review of the manuscript. Dr Tzouvelekis provided the final review and critical evaluation of the manuscript.

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Ethical Approval

University Hospital of Patras, Ethics committee & Study approval No. 223/14-5-2021.

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