Post severe COVID-19 infection lung damages study. The experience of early three months multidisciplinary follow-up

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Abstract

The correct type and time of follow-up for patients affected by COVID-19 ARDS is still unclear. The aim of this study was to evaluate the survivors of COVID-19 ARDS requiring non-invasive respiratory support (NRS) admitted to a Respiratory Intensive care unit (RICU) from March 8th till May 31st 2020 looking at all sequelae via a comprehensive follow up. All patients underwent a multi-disciplinary instrumental and clinical assessment within three months form admission to evaluate all infection related sequelae. Thirty-eight patients were enrolled lung-ultrasound (LUS) showed an outstanding discrimination ability (ROC AUC: 0.95) and a substantial agreement rate (Cohen's K: 0.74) compared to chest CT-scan detecting improve-ment of lung consolidations. Youden's test showed a cut-off pres-sure of 11 cm H_2O ExpiratoryPAP-continuous-PAP-max (EPAP-CPAP) applied at the airways during hospitalization to be significantly correlated (p-value=0.026) to the increased pulmonary artery common trunk diameter. A total of 8/38 patients (21.8%), 2 of whom during follow-up, were diagnosed with pulmonary emboli (PE) and started anticoagulant treatment. Patients with PE had a statistically significant shorter length of time of hospitalization, time to negative swab, CPAP/NIV duration, P/F ratio and D-dimers at follow-up compared to non-PE.

A comprehensive approach to patients with ARDS COVID-19 requiring NRS is necessary. This study highlighted cardiopulmonary impairment related to the ARDS and to the high-EPAP-CPAP-max greater than 11 mmHg provided during admission, the usefulness of LUS in monitoring post-infection recovery and the correct identification and treatment of patients with PE during follow up.

Introduction

The COVID-19 infection has led to millions death worldwide [1]. The disease is responsible for the onset of acute hypoxemic respiratory failure (AHRF), due to a massive inflammatory body response and to a severe thromboembolic disease in the peripheral

capillary district [2-11]. These findings have led to the use of diverse anticoagulant, usually enoxaparin, which have improved the course of the illness reducing the mortality [12].

It is still unclear how to approach to the lung sequelae of COVID-19 in terms of screening tests, and timing to monitor survivors. The European Respiratory Society and American Thoracic Society coordinated an international task force suggesting a formal assessment of respiratory function, exercise capacity and a psychological evaluation already at 6-8 weeks from discharge [13], however other studies suggest a different approach [14,15]. Huang *et al*. [16], suggested that post-discharge care should be provided 6 months after symptom onset especially to patients who required respiratory support such as: high flow nasal cannula (HFNC), non-invasive ventilation (NIV), extracorporeal membrane oxygenation or invasive mechanical ventilation (IMV). Furthermore, possible onset of post-Covid Interstitial Lung Disease (ILD) justifies the pulmonary evaluation via lung function tests, (high resolution computed tomography) HRCT and quality of life (QoL) questionnaires [17-19]. Nevertheless, a comprehensive follow up cannot ignore the assessment of the potential damage occurred into the pulmonary circulation and the whole cardiovascular system, screening for the occurrence of chronic thromboembolic pulmonary hypertension (CTEPH).

Indeed, CTEPH can be assessed at least 3 months after pulmonary embolism (PE) [20,21]. Its incidence is usually estimated between 0.1 and 9% of the general population due to patients' non-specific symptoms and scarce adequate follow up and it may benefit from surgical and pharmacological treatment [21]. Moreover, several reports have described the onset of severe alopecia in COVID-19 survivors [22,23].

Therefore, the aim of this single centre prospective observational study was to screen all survivors to COVID-19 ARDS with severe cardio respiratory impairment requiring non-invasive respiratory support (NRS) *via* a multi-disciplinary clinical and radiological evaluation to categorize all sequelae related to the severe infection with particular interest to cardiopulmonary involvement.

Patients and Methods

This was a single centre prospective observational cohort study carried on among different Departments of the Policlinico of Bari. It was approved by the ethic committee (study number 6380, 12.05.2020) and all patients involved in the present study signed an informed and written consent before being enrolled. According to the Helsinki's Declaration all physicians agreed to participate in the study in compliance with the guidelines of Good Medical Practice.

Study design

The study enrolled patients admitted from March the 8th till May the 30th 2020 to the Policlinico of Bari with COVID-19 laboratory proven disease and AHRF secondary to the infection. All survivors were then screened with two negative swabs prior to be evaluated. The clinical and radiological evaluation was performed within 3 months from the admission. In case of persistent clinical symptoms or instrumental abnormalities, an appropriate treatment plan was initiated.

Study aims

Primary aims:

- To evaluate the presence of short-term outcomes of the pulmonary vascular bed and parenchyma looking for the type and severity of the interstitial lung disease, and PE;
- To characterize potential correlation between the echocardiographic sign of right heart overload and the pressures used during NRS (CPAP or BPAP).

Secondary aims:

- To verify the prevalence of development of CTEPH in this specific population;
- To describe dermatologic and any other long term clinical sequelae admission related.

Patients' selection and enrolment

Inclusion criteria were: age 18-75 years; patients admitted to Respiratory Intensive Care Unit (RICU) with laboratory proven diagnosis COVID-19 infection; the following symptoms were considered: fever, dyspnoea, respiratory rate greater than 30/min, peripheral oxygen saturation (SpO_2) lower than 93%, signs of lung consolidation at lung ultrasound (LUS) and Chest X-ray, AHRF with a PaO_2/FiO_2 ratio <300. Exclusion criteria were: known PH or lung fibrosis antecedent to the COVID 19 infection.

Data collection about hospitalization

The following data were collected: demographics, anamnesis and physical evaluation, treatment prior the admission, chest CT scan (if available), LUS (if available) and all blood results, arterial blood gas (ABG), PaO_2/FiO_2 ratio [Fio_2= fraction of inspired oxygen value measured *via* this formula FiO_2 = 20% + (4 x oxygen litre flow)], grading of severity of ARDS at admission, duration of hospitalization and RICU stay, and all medications' treatment received. Moreover, the use of NRS was recorded (i.e., high flow nasal cannula HFNC, CPAP or BPAP). The maximum expiratory positive airway pressure either during continuous pressure ventilation (CPAP) or end expiratory positive airway pressure (EPAP) during NRS defined as EPAP-CPAP-max applied to the airways during hospitalization was also recorded.

Cardiologic evaluation

Electrocardiography and echocardiography were performed. Echocardiography examinations were carried out *via* Philips IE 33 Ultrasound System (phased array probe, MHz 3-5). The images were independently reviewed by two operators (LDM and GG, senior specialist consultant and fellow, respectively) and final decision was reached by consensual discussion. As per the current guidelines [24], main right heart echocardiographic parameters considered were tricuspid annular plane systolic excursion (TAPSE), main pulmonary artery diameter (mPA-d), pulmonary acceleration time (PAT), tricuspidal S wave, right ventricle/right atrium (RV/RA) gradient and velocity and right heart chamber sizes such as right atrium (RA) area, right ventricle (RV) influx.

All these data were then specifically reviewed looking at the correlation between any right heart overload and the level of cmH2O of airway pressures applied via NRS during hospitalization.

Lung ultrasonography evaluation

LUS examinations were carried out *via* Philips IE 33 Ultrasound System (linear array probe, MHz 7.5-10), following the current literature [25]. LUS images were independently reviewed by two operators (LDM and GG) and final decision was reached by consensual discussion. Aeration pattern was recorded as per the current literature [26,27].

Respiratory evaluation

Full lung function tests with DLCO evaluation, arterial blood gas analysis, six minutes walking test (6MWT) were performed following the most recent guidelines [27-29]. NHYA scale was used to grade the dyspnoea reported by patients as per current guidelines [30].

Radiological evaluation

The CT scans were obtained with a 128 row multi-detector CT (Siemens Somatom Definition DS). An unenhanced scan in supine position from the jugular to the diaphragmatic domes was performed, followed by a CTPA. The CT images were independently reviewed by two radiologists (MDC and AM, senior specialist consultant and fellow, respectively) and final decision was reached by consensual discussion. CT images were analysed to identify pulmonary artery filling defect (PAFD) [31] and pulmonary parenchymal abnormalities (PPA).

Dermatological evaluation

Full dermatologic and trichological examination was provided to each patient during follow-up by a specialist physician. The aim was to look for the presence of alopecia and to provide a differential diagnosis among the different pattern of hair loss. Among different type of alopecia secondary to COVID-19 infection, telogen effluvium, androgenic alopecia and alopecia areata were the most described and object of this evaluation.

Statistical analysis

Data were described as mean (standard deviation) for parametric variables. The Chi-square test and Fisher's variant were used for the comparison of dichotomous variables. The comparison of the subpopulations was carried out *via* Mann-Whitney's U test for the non-parametric parameters. The intra-group comparison for paired data was performed with the Wilcoxon test. Spearmann correlation tests were performed between the parameters under study. Starting from the receiver operating characteristic (ROC) curve, the cut-off was then calculated using the Youden test. The diagnostic performance and accuracy of LUS in discriminating patients with and without ILD *versus* chest CT was evaluated through ROC curve analysis and Cohen's kappa (K) test; p-values <0.05 were considered significant.

Results

The flow chart diagram (Figure 1) describes the follow up approach offered. Out of 97 patients admitted from March 8th till May 30th 2020, 20 (20.6%) patients died, 37 (38.1%) were transferred to RICU, 2 (0.02%) patients denied further follow-up, and a total of 38 (39.2%) patients were enrolled. The patient's characteristics are shown in Table 1; mean time from diagnosis (COVID-19 laboratory proven disease) to hospital admission was 8.03 (±5.44) days and mean length of stay in RICU was 17.41 (±7.70) days. Mean time elapsed from admission to follow-up evaluation was 85.34 (±11.53) days. The dyspnea was the only symptom which persisted significantly (38/38, 100%) during follow up although with a reduced NYHA stage (mainly NYHA I with 7/38, 63.6%). Another remarkable symptom reported by COVID-19 survivors post AHRF was alopecia (27/38, 71%). Different alopecia patterns were identified such as telogen effluvium, androgenic alopecia and alopecia areata. These patterns were alone or in combination among them with the highest percentage represented by telogen effluvium present in 19/27 (70.4%) patients. Respiratory and imaging outcomes are shown in Table 2. Echocardiographic findings were described looking at the low-intermediate/high probability of PH based on current literature [24]. Multi-parametric correlations of right heart findings are shown in Table 3. Youden's test showed that the pressure of 11 cmH_2O of EPAP-CPAP-max applied to the airways during hospitalization was significantly correlated (p value: 0.026) to an increased main pulmonary artery diameter (mPA-d) found at echocardiographic follow-up (Figure 2). Lung ultrasound (LUS) showed an outstanding discrimination ability (ROC AUC: 0.95) and a substantial agreement rate (Cohen's K: 0.74) compared to the chest CT scan (gold standard technique) in the assessment and grading of ILD in our study population (Supplementary Table 1 and Supplementary Figure 1). The flow chart diagram (Figure 1) describes the follow up approach offered.

Discussion

In this study a comprehensive approach to survivors to COVID-19 with severe AHRF requiring NRS is described and its main findings detailed. In particular, the persistence of dyspnoea (38/38, 100% patients) may be related to the DLCO reduction and to the presence of GGO at the CT scan. The LUS findings were confirmed by CT scan as previously reported [32]. Moreover, persistence of PE and association between high end expiratory pressure applied to the airways and right heart overload was found. Indeed, pulmonary emboli (PE) was found in 8/38 patients (21%), of whom 2/38 (0.05%) during follow up. This underlines the importance of D-Dimer monitor and subsequent CTPA during follow up of these patients. These data are similar to other studies on PE in patients with COVID-19 [33,34]. However, patients with PE diagnosis at follow-up, showed statistically significant difference in terms of length of hospitalization, time to negative swab and duration of NRS treatment. We speculated that subjects in the

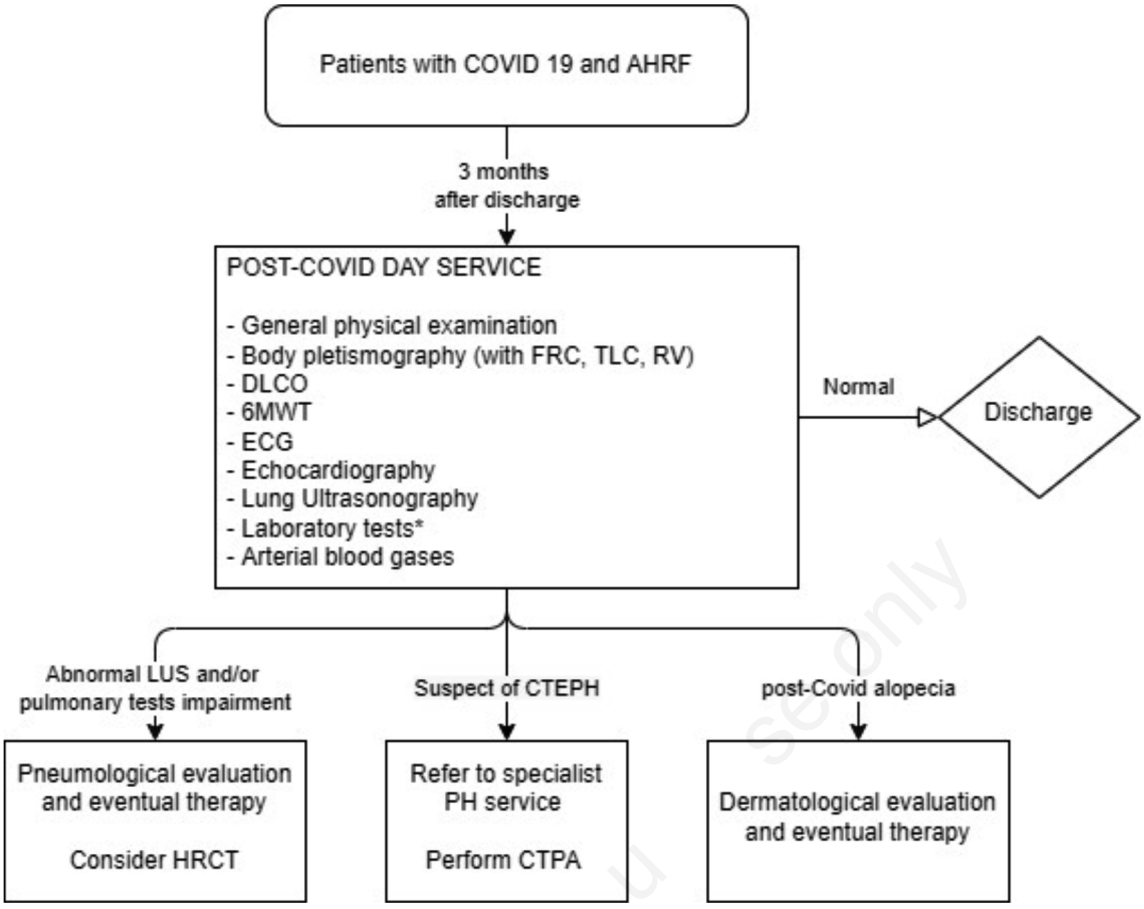

Figure 1. Flow diagram of the study. Laboratory test performed were: hemoglobin, white blood cell, neutrophils, lymphocytes, platelets, creatinine, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, pro hormone BNP, C-reactive protein, ferritin, high-sensitivity troponin I, D-dimers, fibrinogen, prothrombin time international normalized ratio, soluble suppression of tumorigenesis-2, SARS-CoV-2 immunoglobulin G and SARS-CoV-2 immunoglobulin M. FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; 6MWT, 6 minutes walking test; LUS, lung ultrasound; HRCT, high-resolution computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; CTPA, computed tomography pulmonary angiogram.

group without PE during admission may have had still small thromboembolic involvement of the pulmonary circulation which was not clearly visible on CTPA scan performed and found during follow up as reported elsewhere [35].

As showed in Tables 2 and 3, increased inflammatory response found with high ferritin level and lymphopenia statistically directly correlated to the several markers of cardiac congestion at the echocardiography and CT follow up.

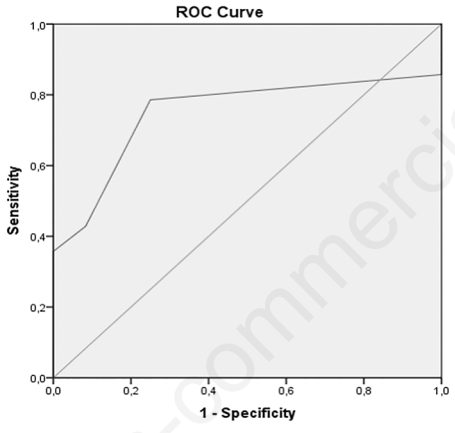

Figure 2. Receiver operating characteristic (ROC) curve showing the correlation between EPAP-CPAP-max applied to the airways and the increased main pulmonary artery (mPA) diameter (mPA-d) found at follow-up. Youden test looking at the cut off of positive airway pressure applied at the airways during hospitalization correlated with an increased main pulmonary artery diameter (mPA-d) found at follow-up (cut-off value ≥25 mm, as per the current guidelines). ROC, receiver operating characteristic; mPA-d, mean pulmonary artery diameter; EPAP-CPAP-max, expiratory PAP-continuous PAP-max (maximum positive expiratory pressure applied to the airways).

	Increased mPA-d (≥25 mm)	Normal mPA-d (<25 mm)	p-value
EPAP-CPAP-max, mean ±SD (cmH_2O)	13.29±3.63	10.67±1.30	**0.026**

Youden index: 11 cmH_2O (sensitivity: 0.750; p=0.031)

Table 1. Population of our study.

Sex, male, n (%)	27 (71.1%)		
Age, yr, mean (SD)	60.6±10.4		
BMI, kg/m^2, mean (SD)	27.5±4.1		
Comorbidity, n (%)	34 (89.5%)		
Hypertension, n (%)	21 (55.3%)		
Dyslipidaemia, n (%)	8 (21.1%)		
Obesity, n (%)	7 (18.4%)		
Overweight, n (%)	19 (50%)		
Diabetes mellitus, n (%)	6 (15.8%)		
CKD, n (%)	6 (15.8%)		
Chronic CHD, n (%)	5 (13.2%)		
Malignancy, n (%)	5 (13.2%)		
Thyroid disease, n (%)	4 (10.5%)		
OSAS, n (%)	3 (7.9%)		
Asthma, n (%)	1 (2.6%)		
COPD, n (%)	1 (2.6%)		
Smoker, n (%)	18 (47.4%)		
Current smoker, n (%)	2 (5.3%)		
Ex-smoker, n (%)	16 (42.1%)		
Clinical symptoms	**Hospitalization**	**Follow-up**	**p-value**
Fever, n (%)	24 (82.8%)	0	-
Asthenia, n (%)	34 (89.5%)	5 (13.2%)	<0.01
Recent syncope, n (%)	5 (13.2%)	2 (5.2%)	0.28
Dyspnea, n (%)	38 (100%)	38 (100%)	1
NYHA I (%)	0	7 (63.6%)	-
NYHA II (%)	0	2 (18.2)	-
NYHA III (%)	0	2 (18.2)	-
NYHA IV (%)	38 (100%)	0	-
Cough, N (%)	24 (63.2%)	5 (13.2%)	<0.01
Hemoptysis, n (%)	1 (2.6%)	0	-
Sore throat, n (%)		5 (13.2%)	0 -
Diarrhea, n (%)	5 (13.2%)	0	-
Vomiting, n (%)	1 (2.6%)	0	-
Anosmia, n (%)	8 (21.2%)	1 (2.6%)	0.03
Ageusia, n (%)	13 (34.4%)	1 (2.6)	<0.01
Arthralgia, n (%)	10 (26.6%)	1 (2.6)	0.01
Alopecia, n (%)	0	27 (71%)	-
Laboratory tests	**Hospitalization**	**Follow-up**	**p-value**
HB, mean ±SD (g/dl)	13.62±1.44	13.85±1.40	0.50
WBC, mean ±SD (106/ul)	6.33±2.75	5.99±1.30	0.50
Neutrophils, mean ±SD (%)	76.18±8.69	55.45±7.92	<0.01
Lymphocytes, mean ±SD (%)	16.45±6.73	35.05±7.22	<0.01
PLT, mean ±SD (103/ul)	217.81±85.55	250.66±59.52	0.06
Creatinine, mean ±SD (mg/dl)	0.89±0.28	0.80±0.16	0.07
AST, mean ±SD (U/l)	58.31±51.18	19.49±4.40	<0.01
ALT, mean ±SD (U/l)	67.00±83.54	25.50±6.63	<0.01
GGT, mean ±SD (U/l)	76.44±54.01	28.45±17.99	<0.01
proBNP, mean ±SD (pg/ml)	217.41±586.64	75.82±85.94	0.15
C-PR, mean ±SD (mg/ml)	136.48±61.85	3.33±1.40	<0.01
Ferritin, mean ±SD (ng/ml)	565.19±370.99	77.00±104.16	<0.01
D-dimers, mean ±SD (ug/l)	4307.59±12590.68	312.14±218.06	0.05
Fibrinogen, mean ±SD (mg/dl)	503.72±183.36	256.81±39.01	<0.01
Hs-TnI, mean ±SD (pg/ml)	17.46±16.08	8.82±6.44	<0.01
PT INR, mean ±SD	3.98±16.43	1.41±2.06	0.34
Sst2, mean ±SD (ng/ml)	-	34.80±15.14	-
IgM SARS-CoV-2, mean ±SD	-	0.71±0.22	-
IgG SARS-CoV-2, mean ±SD	-	14.76±18.31	-

BMI, body mass index; CKD, chronic kidney disease; CHD, coronary heart disease; OSAS, obstructive sleep apnea syndrome; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; HB, hemoglobin; WBC, white blood cell; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, -glutamyl transferase; proBNP, pro hormone BNP; CPR, C-reactive protein; hs-TnI, high-sensitivity troponin I; PT INR, prothrombin time international normalized ratio; sST2, soluble suppression of tumorigenesis-2; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; IgM, Immunoglobulin M.

Table 2. Respiratory and imaging outcomes.

Pneumological evaluation	Hospitalization (n=38)	Follow-up (n=38)	p-value
AHRF, N (%)	38 (100%)	-	-
ARDS, N (%)	25 (65.8%)	-	-
Mild (P/F: 200-300), N (%)	11 (28.9%)	-	-
Moderate (P/F: 100-199), N (%)	11 (28.9%)	-	-
Severe (P/F: <100), N (%)	3 (7.9%)	-	-
NRS, N (%)	38 (100%)	-	-
CPAP, N (%)	26 (68.4%)	-	-
HFNC, N (%)	8 (21.1%)	-	-
BPAP, N (%)	4 (10.5%)	-	-
EPAP-CPAP-max (cmH2O)	11.3±1.9	-	-
FIO_2, mean ±SD (%)	59.6±19.1	21±0	<0.01
PAO_2, mean ±SD (%)	137.2±73.9	83.5±14.2	<0.01
P/F ratio, mean ±SD	218.2±81.2	405.7±50.5	<0.01
6MWT, mean ±SD (meters)	-	517.5±93.2	-
Delta SpO_2, mean ±SD (%)	-	0.84±1.0	-
FEV1 of predicted, mean ±SD (%)	-	101.3±14.2	-
Tiffenau Index %, mean ±SD (%)	-	79.4±4.4	-
TLC, mean ±SD (L)	-	92.4±20.8	-
DLCO, mean ±SD (mL/min/mmHg)	-	87.0±12.7	-
DLCO VA, mean ±SD (mL/min/mmHg/L)	-	99.7±12.9	-
Echocardiographic pulmonary hypertension assessment	**Patients with low probability (29/38, 76.3%)**	**Patients with intermediate-high probability (9/38, 27.3%)**	**p-value**
RA area, mean ±SD (cm^2)	14.69±2.94	17.89±3.52	0.009
RV/LV diameter ratio, mean ±SD	0.85±0.09	0.99±0.11	0.0004
RV inflow, mean ±SD (mm)	34.66±4.16	41.33±4.30	0.0002
TAPSE, mean ±SD (mm)	21.03±2.09	21.89±2.37	0.31
RV/RA gradient, mean ±SD (mmHg)	19.66±5.13	26.78±7.51	0.003
RV/RA max velocity, mean ±SD (m/s)	2.16±0.31	2.52±0.36	0.006
mPA diameter, mean ±SD (mm)	24.69±2.69	26.00±3.16	0.22
PAT mean ±SD (ms)	111.45±19.75	89.56±16.25	0.005
LV tele-diastolic eccentric index, mean ±SD	0.94±0.05	0.96±0.05	0.34
LVFE mean, mean ±SD (%)	60.83±8.46	62.11±5.01	0.67
E/A ratio, mean ±SD	0.73±0.24	0.77±0.13	0.69
E/e' ratio, mean ±SD	5.37±1.58	5.41±1.68	0.09
LA volume indexed, mean ±SD (ml/m^2)	26.21±6.39	28.86±9.29	0.34
BMI score, mean ±SD (kg/m^2)	26.56±2.86	30.70±5.93	0.0067
Lung ultrasound score, mean ±SD	2.83±3.51	6.33±3.84	0.0147
Total severity score on CT, mean ±SD	2.79±3.71	4.44±2.07	0.21
CT evaluation of pulmonary embolism	**Patients without PE (30/38, 79.0%)**	**Patients with PE (8/38, 21.0%)**	**p-value**
P/F ratio at follow-up, mean ±SD (mmHg)	397.37±48.93	436.88±46.53	0.048
D-Dimers at follow-up, mean ±SD (ng/ml)	331.88±234.41	199.12±120.60	0.038
FVC, mean ±SD (L)	3.52±0.93	4.39±0.78	0.0399
FEV1, mean ±SD (L)	2.89±0.67	3.53±0.60	0.04
Time of negative swab, mean ±SD (days)	27.23±14.62	10.13±11.83	0.004
Time of hospitalization, mean ±SD (days)	28.37±12.27	11.13±12.60	0.005
NRS treatment duration, mean ±SD (days)	16.33±7.77	9.83±2.86	0.011

AHRF, acute hypoxaemic respiratory failure; ARDS, acute respiratory distress syndrome; NRS, non-invasive respiratory support; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; BPAP, bilevel positive airway pressure. EPAP-CPAP-max, expiratory PAP-continuous PAP-max (maximum positive expiratory pressure applied to the airways); FiO_2, fraction of inspired oxygen; PaO2, partial arterial pressure of oxygen; P/F ratio, partial arterial pressure of oxygen/fraction of inspired oxygen ratio; 6MWT, six minutes walking test; SpO_2, peripheral capillary oxygen saturation; FEV1, forced expiratory volume in 1 second; TLC, total lung capacity; DLCO, Diffusing capacity of the lung for carbon monoxide; VA, alveolar volume; RA, right atrium; RV, right ventricle; LV, left ventricle; TAPSE, Tricuspid annular plane systolic excursion; mPA, mean pulmonary artery; PA, pulmonary artery; LVFE, left ventricle ejection fraction; LA, left atrium; BMI, body mass index; FVC, forced vital capacity.

Table 3. Multi-parametric correlations of right heart echocardiographic findings.

Right heart echocardiographic parameters	Correlation	R	R^2	P value
RA area	RV influx diameter	0.581	0.337	<0.001
	Lymphocytes control	-0.357	0.127	0.028
	EPAP-CPAP-max	0.339	0.115	0.090
RV influx diameter	Ferritin entrance	0.554	0.307	0.014
	Lymphocytes control	-0.393	0.154	0.015
mPA diameter	RV influx	0.428	0.183	0007
	Age	0.338	0114	0.038
	WBC entrance	-0.466	0.217	0.016
	EPAP-CPAP-max	0.404	0.163	0.040
	PA diameter on CT	0.445	0.198	0.005
TAPSE	FEV_1	0.333	0.111	0.048
RV-RA gradient	ProBNP control	0.353	0.125	0.030
Tricuspidal S wave	RV-RA gradient	0.357	0.127	0.028
PAT	RV-RA gradient	-0.459	0.210	0004
	RV-RA velocity	-0.478	0.228	0.002

RA, right atrium; RV, right ventricle; mPA, mean pulmonary artery; TAPSE, tricuspid annular plane systolic excursion; PAT, pulmonary acceleration time; EPAP-CPAP-max, expiratory PAP-continuous PAP-max (maximum positive expiratory pressure applied to the airways); WBC, white blood cell; P max airways TOT; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; proBNP, pro hormone BNP.

Moreover, the right atrium area correlated significantly with lymphocytes (p=0.028) while mPA-d to white blood count (p=0.016). This is in line with the right heart engagement in ARDS, with major inflammatory lung damage which relates to an inotropic right ventricular response (increased TAPSE, active response) and an increased mPA-d and right heart chamber sizes (passive response). Further analysis pointed out that a direct correlation between TAPSE at the echocardiographic exam and FEV_1 was detected (p=0.048) which confirms the coupling of these two systems heart-lung with shared similar functional impairment. Direct correlations between the tricuspidal maximum velocity regurgitation and proBNP at follow-up blood tests (p=0.03) was found, highlighting the pulmonary vascular engagement during moderate to severe ARDS (PAPs incremented). Another extremely important finding is the direct correlations between the mPA-d and EPAP-CPAP-max applied to the airways via NRS during hospitalization (p=0.04). This is further confirmed by the increased right atrium area which significantly correlated to the EPAP-CPAP-max (p=0.09). Jardin *et al*. highlighted that during pulmonary hyperinflation, the transmural pressure increases [36]. This entails a rise of flow resistances in pulmonary circulation adherent to the alveolar wall with a consequent capillaries collapse. This phenomenon combined with the micro-emboli COVID-19 related and hypoxic vasoconstriction in the lung, leads to increase afterload of the right ventricle and to increase of mPA-d [37,38]. Therefore, patients were divided into two groups according to the mPA-d cut off (25 mm), comparing the maximum EPAP-CPAP pressure applied to the two groups (statistically significant difference with p=0.026). ROC curve and Youden's test were then performed (Figure 2) in order to establish a cut off of the maximum pressure that should be applied to the airways, which was found to be ~11 cmH_2O (ROC sensitivity 0.750; p=0.031). This enhances the importance not to use a maximum pressure higher than 11 cmH_2O in order to avoid over distension of the lungs as it directly correlates to right heart overload [2,35].

Lastly, a dramatic incidence of alopecia was described in our patients' population may be related to the persistent severe hypoxia and insufficient blood supply to the scalp tissues and the prolonged use of tight mask head support [22].

At the moment, 12-week time point is considered to be optimal in providing sufficient time for imaging resolution while also ensuring that non-resolving changes are addressed sufficiently early [15,32]. In case of persistent clinical symptoms earlier evaluation after discharge may be considered. However, considering all these findings, 3 months after discharge should be considered the longest time before re-evaluation in particular if AHRF occurred.

This study has some limitations, first the small number of patients considered which however allowed to fully and comprehensively perform a clinical and radiologic review of all patients. Second, patients were all admitted to RICU with AHRF COVID-19 related, thus does not allow to generalize these findings to all COVID-19 admitted patients. Third, it is a tertiary hospital experience with many available specialists' consultations that it may not be available in many other hospitals. The major strengths of this study are first, the peculiar comprehensive follow-up offered to all patients which allow to detail many long-term post COVID-19 findings. Second, the cardiorespiratory and dermatologic sequelae highlighted in these patients with more severe cardio-respiratory disease's involvement allowed to initiate specific specialist treatments allowing their better prognosis. Last, this study underlined the power of a strong collaborative approach that transversely may involve many specialists who look after patients during and after admission for COVID-19 severe infection.

Conclusions

In summary, this study describes the importance of a structured comprehensive approach to patients admitted with AHRF COVID-19, requiring NRS. Results highlighted the cardio-pulmonary impairment resulting from the severity of lung infection and the high EPAP-CPAP-max greater than 11 cmH_2O provided during admission. Further studies with larger numbers will be warranted to deeply appreciate the details of the COVID-19 cardio pulmonary sequelae.

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