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Combined lung and cardiac ultrasound in COVID-related acute respiratory distress syndrome

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Abstract

Background Lung ultrasound (LU) is a useful tool for monitoring lung involvement in novel coronavirus (COVID) disease, while information on echocardiographic findings in COVID disease is to date scarce and heterogeneous. We hypothesized that lung and cardiac ultrasound examinations, serially and simultaneously performed, could monitor disease severity in COVID-related ARDS.

Methods We enrolled 47 consecutive patients with COVID-related ARDS (1st March–31st May 2020). Lung and cardiac ultrasounds were performed on admission, at discharged and when clinically needed.

Results Most patients were mechanically ventilated (75%) and veno-venous extracorporeal membrane oxygenation was needed in ten patients (21.2%). The in-ICU mortality rate was 27%%. On admission, not survivors showed a higher LUS score ($p=0.006$) and a higher incidence of consolidations ($p=0.003$), lower values of LVEF ($p=0.027$) and a higher RV/LV ratio (0.008). At discharge, a significant reduction in the incidence of subpleural consolidations ($p<0.001$) and, thus, in LUS score ($p<0.001$) and an increase in patter A findings ($p<0.001$) together with reduced systolic pulmonary arterial pressures were detectable. In not survivors at final examination, an increased in LUS score ($p<0.001$), and in RV/LV ratio ($p<0.001$) associated with a reduction in TAPSE ($p=0.013$) were observed. A significant correlation was observed between LUS and systolic pulmonary arterial pressure ($p=0.04$). LUS and RV/LV resulted independent predictors of in-ICU death.

Conclusions In COVID-related ARDS, the combined lung and cardiac ultrasound proved to be an useful clinical tool in monitoring disease progression and in identifying parameters (LU score and RV/LV ratio) able to risk stratifying these patients.

Keywords Echocardiography · Lung ultrasound · COVID · ARDS · Prognosis

Introduction

Coronavirus-19 disease (COVID) is an emerging worldwide pandemic, the clinical course of which can evolve in up to 15% of infected patients in a severe form of acute respiratory syndrome (ARDS) requiring mechanical ventilation and admission to Intensive Care Unit (ICU).

Lung ultrasound (LU) is recognized as a useful tool for monitoring lung involvement in COVID disease [1–3], though it has not been identified so far an ultrasound pattern pathognomonic of COVID infection [4–7]. To date, information on echocardiographic findings in COVID disease is scarce and heterogeneous, being performed in different degrees of disease severity [8].

We hypothesized that combined lung and cardiac ultrasound examinations, serially and simultaneously performed, could monitor disease severity in COVID-related ARDS. In particular, lung ultrasound could monitor lung disease progression/amelioration, while echocardiography simultaneously performed could add information on heart lung interactions (in terms of right ventricle dimension and function and systolic pulmonary arterial pressure).

We tested our hypothesis in 47 consecutive patients with COVID-related ARDS, consecutively admitted to our ICU from March 1st to May 31st 2020. We further assess the prognostic role of echocardiographic and lung ultrasound findings in these patients.

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Methods

In our case series study, we enrolled all patients with COVID-related ARDS consecutively admitted to our ICU (which is an ECMO referral center, Azienda Ospedaliero-Universitaria Careggi) from 1st March to 31st May 2020. The study protocol was approved by our Ethical Committee (n.17024, approved on March 31st 2020). The written inform consent for each patient was waived for emerging infectious disease.

According to our standard protocol, lung ultrasound and an echocardiogram [9] are performed on ICU admission, at discharge and whenever needed according to the clinician in charge's judgement.

All patients are in the supine position. For lung ultrasound examination, a scan of the three different areas of the thorax is performed as follows: anterior, lateral, and posterior, and then superior and inferior segments are performed. Thus, six specific regions for each lung are defined and categorized by one of the four different aeration patterns [10]. The lung ultrasound score (LUS) which proved to be a useful tool in intensive care (ICU) patients with ARDS [4] was calculated in each patient [11–14]. The following point scoring system was employed by region and ultrasound pattern as: A = 0 point, B1 = 1 point, B2 = 2 points, C = 3 points. Thus, a LUS of 0 is normal, and 36 would be the worst.

According to our standard protocol [8, 9, 15, 16], an echocardiogram is performed on ICU admission, at discharge and, on clinical judgment, as previously described [15]. The right ventricle size is assessed by the RV end-diastolic area (EDA) and the ratio between EDAs of the right and left ventricles was calculated (RVEDA/LVEDA). Systolic pulmonary artery pressure (sPAP) is obtained using the simplified Bernoulli's equation: 4 • (*V*max tricuspid regurgitation)^2 + central venous pressure (CVP). Each measure is performed three times, and the mean value was recorded. Tricuspid Annular Plane Excursion (TAPSE) is also measured, as the difference of displacement during diastole and systole.

All ultrasound (lung and cardiac) procedures are performed using the necessary protective equipment for professionals. Dedicate machines are used in the COVID ICU and transducers are wrapped in single-use plastic covers [15].

Statistical analysis

Data were processed with IBM-SPSS 20 statistical package (SPSS Inc, Chicago, IL). Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean ± standard deviation (SD). Data of subgroups were reported as frequencies (percentages) or means ± SD; comparisons were performed by chi-square test (or Fisher's exact test, when appropriate) for categorical variables and with Student's *t* test for continuous data. Pearson's regression analysis was performed to assess whether LUS score was related to systolic pulmonary arterial pressure (sPAP). Multivariate linear regression analysis was performed to identify predictors for in-ICU mortality. Considering the low number of events, a limited number of covariates were entered in the multivariable model (to avoid overfitting). Results of logistic regression are reported as adjusted OR (odd ratio) and 95% confidence interval (CI). A *p* value less than 5% has been taken as statistically significant.

Results

Our population was constituted by 47 patients with COVID-related ARDS, consecutively admitted to our ICU (Table 1). Twelve patients (25.5%) were transferred from spoke hospitals. Males were the majority (82.9%) and hypertension was the most frequent risk factor (87%), while diabetes was observed in about one third of the entire population (32%). Most patients were mechanically ventilated (75%) and veno-venous extracorporeal membrane oxygenation (ECMO) was needed in ten patients (21.2%). Veno-arterial ECMO was used for refractory cardiac arrest in one patient who developed multiorgan failure. The in-ICU mortality rate was 27% (13/47). When compared to survivors, patients who did not survive were older ($p < 0.001$), with a higher SAPS ($p < 0.001$) and a lower tidal volume ($p = 0.042$). Not survivors were more frequently treated with prone positioning ($p = 0.011$) and ECMO support ($p = 0.022$).

Table 2 shows lung and cardiac ultrasound findings on ICU admission in the comparison between survivors and not survivors. In our series, we performed 148 echocardiograms, among whom 18 were transesophageal ones (11 for ECMO implantation, five to rule out endocarditis, two for technical difficulties). At lung ultrasound, not survivors showed a higher LUS score ($p = 0.006$) and a higher incidence of consolidations ($p = 0.003$).

Pattern A was detectable only in survivors. At echocardiogram, survivors exhibited higher values of LVEF ($p = 0.027$) and a lower RV/LV ratio (0.008). At first echocardiography, three patients showed localized segmental LV abnormalities which were previously known since all these three patients had previously known ischemic heart disease.

When examining at discharge ultrasound findings in the 29 discharged patients (Table 3), we observed a significant reduction in the incidence of subpleural consolidations ($p < 0.001$) and, thus, in LUS score ($p < 0.001$) and an

Table 1 Clinical characteristics of the study population

		Survivors	Not survivors	
Number	47	34	13	
Age (mean ± SD, years)	63 ± 11	60 ± 9	71 ± 10	< 0.001(*t*)
Males (*n*.%)	39 (82.9%)	26 (73%)	13 (100%)	0.21*
SAPSII	46 ± 16	42 ± 16	58 ± 3	< 0.001(*t*)
Comorbidities (*n*.%)				
Hypertension	41 (87%)	28 (82%)	13 (100%)	0.689*
Cardiovascular disease	11 (23%)	9 (26%)	2 (15%)	0.174*
Diabetes	15 (32%)	7 (20%)	8 (62%)	0.007*
Malignancy	3 (6%)	3 (8%)	0	0.942*
COPD	3 (6%)	0	3 (7%)	0.945*
Chronic kidney disease	1 (2%)	0	1 (7%)	0.870*
Autoimmune disease	3 (6%)	2 (5%)	1 (7%)	0.820*
Other	4 (8,5%)	3 (8%)	1 (7%)	0.897*
Respiratory support				
Non invasive	12 (25%)	12		
Invasive	35 (75%)	22	13 (100%)	
PEEP cmH2O (median, range)	12 (8–18)	12 (8–16)		0.690KW
TV (median, range) ml	570 (160–710)	493 (300–730)		0.042KW
P/F (median, range)	115 (69–264)	121 (69–264)		0.143KW
Prone position (*n*, %)	31 (65%)	18	13	0.011*
ECMO	11 (23.4%)	5	6	0.022*
Transferred from peripheral hospitals (*n*.%)	12 (25.5%)	8	4	0.611*
LOS (median, range) days	12.5 (2–58)	15 (2–58)	10 (8–30)	0.541KW
In-ICU mortality (*n*.%)	13 (27.6%)			

SD standard deviation, *SAPS* simplified acute physiologic score, *ECMO* extracorporeal membrane oxygenation, *TV* tidal volume, *PEEP* positive end expiratory pressure, *LOS* length of stay, *ICU* intensive care unit. (*t*): Student *t* test, *: chi-square test, KW: Kruskal–Wallis test

increase in pattern A ($p < 0.001$) in comparison with admission findings. At discharge echocardiography, systolic pulmonary arterial pressures significantly reduced ($p < 0.01$), while RV wall thickness increased ($p < 0.01$). The development of pericardial effusion (> 5 mm) was observed in about one third of patients (27.5%) with no hemodynamic impact.

As depicted in Table 4, at final lung examination, not survivors showed a significantly increased in LUS score ($p < 0.001$) and all patients developed consolidations and pleural effusions. At final echocardiogram, not survivors showed an increased of RV/LV ratio ($p < 0.001$) associated with a reduction in TAPSE ($p = 0.013$) and an increased in sPAP ($p = 0.05$) and RV wall thickness ($p < 0.01$). Acute cor pulmonale was detected in six patients (46%), among whom four were on ECMO support.

At Person's regression analysis, LUS score was directly related to sPAP ($R = 0.296$, $p = 0.04$).

At multivariate linear regression analysis (Table 5), different models were performed to avoid overfitting. LUS resulted an independent predictor of in-ICU death in two models; while, among echocardiographic parameters, RV/LV ratio was independently related to early death when adjusted for sPAP.

Discussion

This is the first investigation, assessing the clinical significance of combined lung and cardiac ultrasound in COVID-related ARDS. The main finding of the present investigation, performed in 47 consecutive COVID-related ARDS patients requiring ICU admission, is that a combined ultrasound approach (lung and cardiac) is able to monitor lung COVID disease progression. A reduction in the incidence of subpleural consolidations and in systolic pulmonary arterial pressures and the re-appearance of A-lines characterize patients at ICU discharge. On the contrary, worsening of lung consolidations, RV dilatation and dysfunction (as indicated by TAPSE) associated with a significant increase in systolic arterial pressures characterized not survivor patients. RV dilatation and LUS score resulted independent predictors of in-ICU death in COVID-related ARDS. The

Table 2 Ultrasound findings on ICU admission: comparison between survivors and non-survivors

	Survivors	Not survivors	
Number	34	13	
LUS			
LUS score	22 ± 5	26 ± 1	0.006(*t*)
Subpleural consolidations (*n.*%)	24 (82.7%)	12(92%)	0.418#
Consolidations (*n.*%)	6 (20.6)	8 (62%)	0.003#
Pleural effusion (*n.*%)	1 (3.4%%)	2 (15%)	0.764#
Pattern A (*n.*%)	3 (10.3%)	0	0.937#
LV dimension (mm/m^2)	27.3 ± 2	28 ± 1	0.236(*t*)
LV ejection fraction (%)	59.5 ± 9	53 ± 8	0.027(*t*)
LV segmental abnormalities (*n.*%)	3	1	
RV/LV	0.37 ± 0.05	0.43 ± 0.10	0.008(*t*)
RV wall thickness (mm, mean ± SD)	5.3 ± 0.5	5.6 ± 0.5	0.072(*t*)
SPAP (mmHg, mean ± SD)	49.7 ± 6	50 ± 6	0.878(*t*)
TAPSE (mm)	22 ± 2	21 ± 2	0.132(*t*)
PE > 5 mm (*n.*%)	0	0	

chi square test

LV left ventricle, *RV* right ventricle, *sPAP* systolic pulmonary arterial pressure; *TAPSE* tricuspid plane systolic annular excursion; *PE* pericardial effusion, (*t*): Student *t* test, *: chi-square test

latter finding strongly suggests the potential role of a combined ultrasound approach in risk stratifying these patients.

In our series, on ICU admission, the most common findings were a high proportion of subpleural consolidations and increased systolic pulmonary arterial pressures. At lung ultrasound, subpleural consolidations were described in COVID-19 pneumonitis [2, 16–19], although they are non-specific, since they can be detected at some degree in all forms of pneumonia. In our patients (all requiring ICU admission and mostly mechanically ventilated), they can be interpreted as the progression of the interstitial syndrome, characterizing COVID lung infection.

While the re-appearance of pattern A characterized lung ultrasound in discharged patients (in keeping with previous findings [2]), indicating the resolution/amelioration of lung disease, the progression towards lung consolidations and the development of pleural effusions distinguished the final lung ultrasound in not survivors. These findings strongly suggest that serial lung ultrasound could monitor COVID lung disease identifying two different trajectories, the first characterized by the development/re-appearance of Pattern A and the second one by lung extensive consolidations.

Few papers performed a systematic echocardiographic assessment in COVID patients, suggesting a relationship between systolic pulmonary arterial pressure and disease severity [20–23]. In 200 non-ICU patients [20], patients with pulmonary hypertension had signs of more severe COVID-related lung disease. In a series of 28 patients with COVID disease requiring Intensive Care Unit (ICU) admission, by means of serial echocardiograms we observed that systolic pulmonary arterial pressures were increased in all patients on ICU admission but significantly decreased during ICU stay [15]. A lower incidence of pulmonary hypertension was reported by Deng et al. [21], probably because their series was constituted mainly by patients with milder COVID disease. In agreement with these findings, Szekely et al. [21] observed that patients with worse clinical grade had shorter

Table 3 Comparison between ultrasound findings on ICU admission and at discharge in the 29 discharged patients

	On ICU admission	At discharge	
Lung ultrasound			
LUS score	22 ± 5	12 ± 4	< 0.001(*t*)
Subpleural consolidations (*n.*%)	24 (82.7%)	8 (27.5%)	< 0.001#
Consolidation (*n.*%)	6 (20.6)	2 (6.9%)	0.254#
Pleural effusions (*n.*%)	1 (3.4%%)	7 (24.1%)	0.055#
Pattern A (*n.*%)	3 (10.3%)	22 (75.9%)	< 0.001#
LV dimension (mm/m^2)	27.3 ± 2	28.4 ± 4	0.190(*t*)
LV ejection fraction (%)	59.5 ± 9	55 ± 12	0.111(*t*)
LV segmental abnormalities (*n.*%)	3	3	
RV/LV	0.37 ± 0.05	0.36 ± 0.06	0.493(*t*)
RV wall thickness (mm, mean ± SD)	5.3 ± 0.5	5.7 ± 0.5	< 0.01(*t*)
SPAP (mmHg, mean ± SD)	49.7 ± 6	43 ± 6	< 0.01(*t*)
TAPSE (mm)	22 ± 2	23 ± 2	0.062(*t*)
PE > 5 mm (*n.*%)	0	8	

chi square test

LV left ventricle, *RV* right ventricle, *sPAP* systolic pulmonary arterial pressure; *TAPSE* tricuspid plane systolic annular excursion; *PE* pericardial effusion, (*t*): Student *t* test, *: chi-square test

Table 4 Comparison between ultrasound findings in the 13 non-survivor patients

	On ICU admission	Final exam	
n.13			
Lung ultrasound			
LUS score	26 ± 1	31 ± 0.5	< 0.001(*t*)
Subpleural consolidations (*n*.%)	12 (92%)	13 (27.5%)	
Consolidation (*n*.%)	8 (62%)	13 (100%)	
Pleural effusions (*n*.%)	2 (15%)	13 (100%)	
Pattern A (*n*.%)	0	0	
Echocardiography			
LV dimension (mm/m^2)	28 ± 1	27.8 ± 1	0.434(*t*)
LV ejection fraction (%)	53 ± 8	50 ± 8	0.330(*t*)
LV segmental abnormalities (*n*.%)	1	1	
RV/LV	0.43 ± 0.10	0.54 ± 0.08	0.001(*t*)
RV wall thickness (mm, mean ± SD)	5.6 ± 0.5	6.7 ± 0.6	< 0.01(*t*)
SPAP (mmHg, mean ± SD)	50 ± 6	55 ± 7	0.05(*t*)
TAPSE (mm)	21 ± 2	19 ± 2	0.013(*t*)
PE > 5 mm (*n*.%)	0	9	

LV left ventricle, *RV* right ventricle, *sPAP* systolic pulmonary arterial pressure; *TAPSE* tricuspid plane systolic annular excursion; *PE* pericardial effusion, (*t*): Student *t* test, *: chi-square test

Table 5 Multivariate analysis

Model 1				
	OR	95% CI	*p* value	Wald
Age (1 year step)	1.076	0.990–1.169	0.085	2.969
SAPS (1 unit step)	1.273	0.999–1.621	0.051	3.815
Model 2				
	OR	95% CI	*p* value	Wald
LUS (1 unit/ step)	1.960	1.057–3.636	0.033	4.556
sPAP (VD/AD) (1 mmHg step)	0.911	0.815–1.018	0.100	2.711
Model 3				
	OR	95% CI	*p* value	Wald
LUS (1 unit step)	1.398	1.017–1.923	0.039	4.247
TAPSE (1 mm step)	0.784	0.555–1.107	0.167	1.910
Model 4				
	OR	95% CI	*p* value	Wald
RV/LV (100 unit step)	1.154	1.016–1.311	0.028	4.838
ssPAP (VD/AD) (1 mmHg step)	0.934	0.839–1.039	0.208	1.585

SAPS simplified acute physiologic score; *LUS* lung ultrasound score; *sPAP* systolic pulmonary arterial pressure; *RV/LV* right/left ventricle ratio; *OR* odd ratio; *CI* confidence interval

pulmonary accelerating times suggesting increased RV afterload. In COVID ARDS, the finding of increased systolic arterial pressures may be multifactorial. First, hypoxic pulmonary vasoconstriction, known to characterize COVID-related ARDS [23], is probably the main factor.

Second, lung disease (and progression) contributes to alterations in pulmonary circulation since atelectasis and consolidations exert mechanical compression of pulmonary vessels.

Similarly, the role of pulmonary embolisms/thrombosis, not infrequent of COVID disease, cannot be rule out [24–26]. Finally, ventilation (specifically positive end expiratory pressure and driving pressures) is known to affect RV afterload. In this setting, the right ventricle has to face an augmented afterload, so it seems advisable to monitoring pulmonary arterial pressure by means of echocardiography to early detect right ventricle dilatation and/dysfunction in these patients [8, 16]. Further research is needed to evaluate whether pulmonary arterial hypertension and RV dysfunction may represent therapeutic targets in COVID disease. In this context, nitric oxide was proposed as a rescue therapy in the Surviving Sepsis Campaign Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 [27].

In a series of one hundred consecutive patients with COVID infection, RV dilatation and dysfunction were a common finding, being detectable in the 39% and in the small subset of patients who clinically deteriorated (20%) showed RV function deterioration [20]. We extend these findings documenting that RV/LV ratio was an independent predictor of ICU mortality in severe COVID patients and acute cor pulmonale was detectable in about half of not survivors at final echocardiogram The prognostic role of RV dilatation was previously reported by us [28] and others in severe ARDS [29, 30].

The direct correlation between LUS score and sPAP we documented strongly support the notion that these two methodologies, when combined, are able to monitor both the

involvement of lung parenchyma (LUS score) and pulmonary circulation (sPAP) in COVID-related ARDS. In daily practice, in these patients, combined lung and cardiac ultrasound represents a clinical useful tool in monitoring disease severity and heart–lung interactions.

Moreover, according to our data, serial echocardiographic examination in COVID-related lung disease should focus on RV dimension and function, and on systolic pulmonary arterial pressures.

Limitation of the study

The present investigation may be limited by the limited number of patients enrolled in a single-center study. However, serial examinations were performed in the single patients by means of simultaneous lung and cardiac ultrasound, thus providing a more complete picture and assessment of COVID lung disease and its impact on disease progression and prognosis. Mechanical ventilation (increased intrathoracic pressures) is known to influence heart–lung interactions and RV dimensions. However, in our series, the majority of patients were mechanically ventilated and serial ultrasound (lung and cardiac) examinations were performed and results compared in the single patient.

Conclusions

Overall, our findings suggest that an "ultrasound combined approach", that is simultaneous lung and cardiac ultrasound examinations, proved to be a useful clinical tool in monitoring disease progression, assessing heart–lung interactions and in identifying parameters (LU score and RV/LV ratio) able to risk stratifying these patients. Further investigations are, however, needed to confirm these findings in larger cohorts of patients and to specifically assess the effects of therapeutic interventions, in primis prone positioning.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statement All procedures were performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Due to the peculiar conditions of COVID pandemia informed consent was waived (all patients sedated and mechanically ventilated).

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