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CORONAVIRUS DISEASE 2019 PHENOTYPES, LUNG ULTRASOUND, CHEST COMPUTED TOMOGRAPHY AND CLINICAL FEATURES IN CRITICALLY ILL MECHANICALLY VENTILATED PATIENTS

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Abstract—Chest computed tomography (CT) may provide insights into the pathophysiology of coronavirus disease 2019 (COVID-19), although it is not suitable for a timely bedside dynamic assessment of patients admitted to intensive care unit (ICU); therefore, lung ultrasound (LUS) has been proposed as a complementary diagnostic tool. The aims of this study were to investigate different lung phenotypes in patients with COVID-19 and to assess the differences in CT and LUS scores between ICU survivors and non-survivors. We also explored the association between CT and LUS, and oxygenation (arterial partial pressure of oxygen [PaO₂]/fraction of inspired oxygen [FiO₂]) and clinical parameters. The study included 39 patients with COVID-19. CT scans revealed types 1, 2 and 3 phenotypes in 62%, 28% and 10% of patients, respectively. Among survivors, pattern 1 was prevalent (p < 0.005). Chest CT and LUS scores differed between survivors and non-survivors both at ICU admission and 10 days after and were associated with ICU mortality. Chest CT score was positively correlated with LUS findings at ICU admission (r = 0.953, p < 0.0001) and was inversely correlated with PaO₂/FiO₂ (r = −0.375, p = 0.019) and C-reactive protein (r = 0.329, p = 0.041). LUS score was inversely correlated with PaO₂/FiO₂ (r = −0.345, p = 0.031). COVID-19 presents distinct phenotypes with differences between survivors and non-survivors. LUS is a valuable monitoring tool in an ICU setting because it may correlate with CT findings and mortality, although it cannot predict oxygenation changes. (E-mail: my.davideorlandi@gmail.com) © 2021 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Lung ultrasound, LUS, COVID-19, SARS-CoV-2, CT scan, ICU, Phenotypes.

INTRODUCTION

A novel human coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified in Wuhan, China, in late 2019 (Huang et al. 2020). The pandemic is still ongoing in the majority of countries and has had a significant effect on national health care systems and general activities (Albano et al. 2020; Allam et al. 2020; Balestrino et al. 2020; Bandirali et al. 2020; WHO 2020). Coronavirus disease 2019 (COVID-19) is a new viral infection that commonly starts from the lower respiratory tract and further extends to other organs, making treatment options challenging (Gattinoni et al. 2020; Robba et al. 2020). More than 80% of confirmed COVID-19 cases present as a mild febrile illness. However, a small proportion of patients will experience critical illness, with many patients requiring mechanical ventilation (Chen et al. 2020) and multi-organ support (Katagiri et al., 2021). To date, the respiratory management of COVID-19 has relied on the general principles of acute respiratory distress syndrome (ARDS) management, and chest computed tomography (CT) may provide interesting insights into the pathophysiology and individualization of mechanical
ventilation in these patients (Chen et al. 2020; Lanza et al. 2020; Lu et al. 2020). However, chest CT is not suitable for a timely dynamic assessment of patients, particularly in patients who are critically ill. Chest X-ray can be performed at the bedside but has the drawback of low sensitivity (Bandiralli et al. 2020). In recent years, lung ultrasound (LUS) examination has become more widely used in the evaluation of lung diseases (Volpicelli et al. 2012), as it is a convenient, fast, non-invasive, readily repeatable tool and does not involve ionizing radiation. Hence, LUS should be considered a valid alternative to CT scans for characterizing COVID-19 pneumonia in an intensive care unit (ICU) setting and when difficulties occur with performing sequential CT scans (Allinovi et al. 2020; Soldati et al., 2020a).

The primary aim of this study was to investigate the presence at CT scan of different lung phenotypes in patients who are critically ill and affected by COVID-19, and to assess differences between ICU survivors and non-survivors in CT total severity score (TSS) and LUS scores. We also aimed to explore the possible association between chest CT scan and LUS, and between chest CT, LUS and oxygenation (arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2)), ventilation and clinical parameters.

**MATERIALS AND METHODS**

This study was conducted in accordance with the current version of the Declaration of Helsinki. Informed consent was obtained from each enrolled patient. Our institutional review board of Liguria region, Italy, approved this current study (registry number 312/2020) that evaluated de-identified data and involved no potential risk to patients. To avert any potential breach of confidentiality, no link between the patients and the researchers was made available.

**Study description**

This is an observational retrospective cohort study of patients with COVID-19 admitted to two COVID-19—designated ICUs at Ospedale Evangelico Internazionale and San Martino Policlinico Hospital in Genova, Italy, from March 6, 2020, to April 17, 2020. Figure 1 represents the consort flow diagram of this study.

**Inclusion and exclusion criteria**

This study included critically ill patients with COVID-19, confirmed based upon a positive SARS-CoV-2 polymerase chain reaction assay, with available CT scan and/or LUS at ICU admission. All patients admitted to a COVID-19 ICUs were cared for by a standard ICU care team (i.e., pre-COVID) and staffing ratios. No critical shortages in medications, ventilators, dialysis machines or other critical care equipment were noticed.

**Chest CT**

Non-contrast chest CT scans were obtained using a 64-slice multi-detector CT (SOMATOM Sensation 64, Siemens Medical Solutions, Forchheim, Germany) and a 16-slice multi-detector CT (Lightspeed 16, GE Healthcare, Chicago, IL, USA) at ICU admission and about 10 d after admission. Other spot CT examinations were performed in some patients depending on specific conditions. In total, 94 CT scans were included.

COVID-19 chest CT in-hospital patterns were classified according to three main phenotypes recently proposed by Robba et al. (2020): (i) multiple, focal, possibly over-perfused ground-glass opacities with “crazy paving” appearance; (ii) in-homogeneously distributed atelectasis and peri-bronchial opacities with predominant lung consolidations and (iii) a patchy, ARDS-like pattern. Then, lobar involvement of each lung lobe was assessed for percentage and classified as minimal (1%—25%), mild (26%—50%), moderate (51%—75%) or severe (76%—100%), with corresponding scores of 1, 2, 3 or 4. The CT TSS was obtained summing the five lobe scores (range of 0—20), (Li et al. 2020). The classification and score of chest CT examinations was made by two radiologists with 5 and more than 20 y, respectively, of experience in chest CT (D. O. and G.B.) who were blinded to patients’ past medical history, vital signs, symptoms, laboratory measurements and previous scan results. Disagreement was solved by consensus, and in cases of persistent disagreement, we considered the classification and score performed by the most experienced operator.

**Lung ultrasound**

LUS examinations during ICU in-patient care were performed at ICU admission and at least every 2 d. In total, 362 LUS examinations were included.

We followed a 12-zone protocol (Mento et al. 2020). Each intercostal space of upper and lower parts of the anterior, lateral and posterior regions of the left and right chest wall were carefully examined, and findings (pleural effusion, confluent and isolated B-lines, irregular pleural line, consolidations) were recorded on 10 s video clips (Cantinotti et al. 2020; Perrone et al., 2021; Volpicelli and Gargani, 2020a; Volpicella, 2020b). For each of the 12 zones, a score from 0—3 was given according to the finding: irregular or isolated B-lines (1 point), confluent B-lines (2 points) and consolidations or pleural effusion (3 points). The total LUS score was calculated by summing the scores of all 12 zones (range of possible scores, 0—36). Scores from 1—10 were rated as mild, 10—20 as moderate and more than 20 as severe. The examinations were performed using a Mindray TE7 ultrasound system (Mindray Biomedical Electronic Co., Ltd, Shenzhen, China) and a Philips SparQ (Philips Healthcare, Bothell, WA, USA), equipped with a curvilinear array transducer (1.5—4.5 MHz) lung
pre-set. During the examination, the physicians were blinded to the patients’ past medical history, vital signs, symptoms, laboratory measurements and previous scan results. The LUS examinations of ICU patients were performed by three radiologists and one intensivist, blinded for review, with 5, 2, 1 and 2 y of experience in LUS, respectively, (G.B., D.O., T.M. and D.B.) who rotated individually in the ICU (G.B., D.O. and T.M.) or worked in the ICU (D.B.).

**Data collection**

Patient data, including sociodemographic information, clinical data and laboratory data, were obtained from the electronic medical record. Diagnostic imaging data were obtained from the radiology information system and picture archiving and communication system (RIS-PACS) system. Data concerning LUS and chest CT scan at ICU admission and during the critical phase of the disease (around 10 d after ICU admission during the multi-systemic clinical syndrome with impaired/disproportionate and/or defective immunity) were collected (Turk et al. 2020).

**Statistical analysis**

Data were collected until June 28, 2020. No sample size calculation was performed a priori for this exploratory and descriptive study. Baseline characteristics are presented as mean and standard deviation for continuous variables and count and proportions for categorical variables. Statistical analysis of the obtained data was performed using a Cohen’s Kappa (κ) test to compare chest CT abnormal findings to LUS and chest X-ray abnormal findings. Data distribution of continuous variables was assessed by Shapiro-Wilk tests, and parametric and non-parametric tests were performed in accordance to the test results. Pearson’s correlation tests were applied to test correlation between continuous variables, and unpaired Student’s t test (or Mann-Whitney U tests) were used to
evaluate the possible differences in these variables between ICU survivors and non-survivors. Fisher’s exact test was used to compare the proportion of categorical variables between groups. Generalized linear regression models were used to assess the influence of each parameter and their combination on ICU survival. Statistical significance was set at a p value of <0.05. Calculations were performed using R software v. 4.0.3 (R Core Team, Wien, Austria).

**Results**

The study period included 39 adults who were critically ill with SARS-CoV-2 infection (Fig. 1a). The mean patient age was 63.2 ± 13.4 y (standard deviation), with seven patients (18%) who were aged 75 y or older. There were 9 women (23.1%), and the majority of patients were white (30 [76.9%]). Cardiovascular diseases were the most common comorbid condition (17 [43.6%]), followed by diabetes (15 [38.4%]). Nine patients (23.1%) had a body mass index (BMI) of 30 kg/m² or greater. ICU admission occurred at 11.3 ± 8.9 d from symptom onset; the PaO₂/FiO₂ ratio was 204.8 ± 111.4 and the mean C-reactive protein (CRP) value was 139.5 ± 95.1 mg/L (upper limit of normal 10 mg/L). Demographics are fully reported in Table 1.

All patients included in the study had recent chest X-rays; 83% had chest a CT while 34% had LUS. The subgroup analysis, performed in survivors and non-survivors, showed a nearly significant older age of non-survivors’ group, with a significant higher incidence in the sub-group of patients aged more than 75 y (71% non-survivors).

The mean ICU stay period was 18.3 ± 12.1 d, and patients who survived had significantly longer ICU stays compared with non-survivors (18.8 ± 9.0 d vs. 11.8 ± 5.6 d, p = 0.001). Thirty-two patients (82.0%) received invasive mechanical ventilation, and 28 patients (72%) received at least one pronation cycle (Guérin et al., 2013).

**COVID-19 phenotypes**

Patients received chest CT scans at ICU admission: 24 patients (62%) presented with type 1 pattern; 11 patients (28%) presented with type 2 pattern; and 4 patients (10%) presented with type 3 pattern. Among survivors, 20 patients (71%) presented with type 1 phenotype, 7 patients (25%) with type 2, and 1 patient (4%) with type 3; whereas among non-survivors, types 1, 2 and 3 occurred in 4 (36%), 4 (36%) and 3 patients (27%), respectively, with a significant prevalence of type 1 pattern in the survivors’ group (p < 0.005).

**Chest CT and LUS scores**

At ICU admission, the mean CT TSS score was 11.6 ± 3.7, and mean LUS score was 22.4 ± 7.5. Initial ICU clinical findings, critical care interventions and outcomes are summarized in Table 2.

Chest CT scores and LUS scores significantly differed between survivors and non-survivors. In a multiple regression model considering all the elements at admission (CT, LUS, age, BMI, PaO₂/FiO₂, CPR, interleukin-6, ferritin, sex, race and temperature) as possible predictors of ICU death, only chest CT and LUS significantly influenced outcome (p < 0.0001).

The evolution over time of LUS score, CPR levels and PaO₂/FiO₂ ratio were different between survivors and non-survivors. In fact, LUS and CRP showed an increasing trend among patients who died in ICU, while a decreasing trend was observed in those who survived (p = 0.009 and p < 0.0001, respectively). Conversely,

| Demographics               | Overall (n = 39) | ICU survivors (n = 28) | ICU non-survivors (n = 11) | p value |
|----------------------------|------------------|-----------------------|---------------------------|---------|
| Age, mean (SD)             | 63.2 (11.0)      | 61.0 (10.5)           | 68.8 (10.9)               | 0.056*  |
| Sex                        |                  |                       |                           |         |
| Men                        | 30 (76.9%)       | 21 (75%)              | 9 (81.8%)                 | 0.974†  |
| Women                      | 9 (23.1%)        | 7 (25%)               | 2 (18.2%)                 |         |
| Race                       |                  |                       |                           |         |
| White                      | 30 (76.9%)       | 20 (71.4)             | 10 (89%)                  | 0.380†  |
| Latin Americans            | 9 (23.1%)        | 8 (28.6)              | 1 (11%)                   |         |
| BMI, mean (SD)             | 26.2 (5.1)       | 26.1 (4.5)            | 26.5 (6.5)                | 0.886*  |
| Cardiovascular diseases    | 17 (43.6%)       | 10 (35.7%)            | 7 (63.6%)                 | 0.114†  |
| Chronic kidney disease     | 6 (15.4%)        | 3 (10.7%)             | 3 (27.3%)                 | 0.197†  |
| Diabetes mellitus          | 15 (38.4%)       | 8 (28.6%)             | 7 (63.6%)                 | 0.043†  |
| Asthma                     | 5 (12.8%)        | 5 (17.9%)             | 0                        | 0.439†  |
| Chronic obstructive pulmonary disease | 7 (17.9%)   | 5 (17.9%)             | 2 (18.2%)                 | 0.981†  |

Data are expressed in percentages or in mean and SD.
BMI = body mass index; ICU = intensive care unit; SD = standard deviation.
* Student’s t test
† X²
during the ICU stay, the PaO2/FiO2 ratio was reduced in non-survivors compared with survivors ($p = 0.003$).

**Association between chest CT, LUS scores, and oxygenation, ventilation and clinical parameters**

We found a significant direct correlation between chest CT and LUS scores at ICU admission ($r = 0.953$, $p < 0.0001$), a significant inverse correlation between admission CT TSS score, LUS score and PaO2/FiO2 ratio ($r = -0.375$ and $r = -0.345$, with $p = 0.019$ and $p = 0.031$, respectively) and a significant direct correlation between chest CT at ICU admission with TSS score and CRP levels ($r = 0.329$, $p = 0.041$) but not between LUS score and CRP levels ($r = 0.266$, $p = 0.102$) (Figs. 2 and 3).

**DISCUSSION**

In our cohort of patients who were critically ill with COVID-19, we found the following: (i) On ICU admission, phenotype 1 was found most frequently on chest CT scan, followed by phenotypes 2 and 3. Among survivors, we observed almost the same distribution of overall findings, with a significant prevalence of phenotype 1. No significant phenotype prevalence was seen among non-survivors. (ii) Chest CT and LUS scores differed between survivors and non-survivors both at ICU admission and at 10 days after admission. (iii) Chest CT strongly correlated with LUS findings. (iv) Chest CT inversely correlated with PaO2/FiO2 ratio and CRP, while LUS PaO2/FiO2 ratio only. (v) In a multiple regression model, chest CT and LUS were the best parameters individually associated with clinical, laboratory and ventilatory parameters.

**COVID-19 phenotypes**

One of the aims of the present study was to characterize and classify patients according to CT findings. In this setting, distinct phenotypes at chest CT scan were identified, as previously described (Gattinoni et al. 2020; Robba et al. 2020). Phenotype 1/L, with multiple focal possibly over-perfused ground glass opacities, was observed in 62% of cases; inhomogeneously distributed atelectasis and peri-bronchial opacities were observed in 28% (phenotype 2/L), while a patchy ARDS-like pattern was detected in 10% of cases (phenotype 3/H). In a previous report, Gattinoni et al. (2020) showed that phenotype 3/H was present in 20%—30% of critically ill patients, which is slightly higher compared with our overall results (Gattinoni et al. 2020). However, looking at the non-survivor’s sub-group, we observed comparable results (27%).

Doubts remain regarding the existence of COVID-19 phenotypes (Gattinoni et al. 2020b; Tobin, 2020;
Despite variable respiratory system elastance, lungs recruitability and clinical course, the current literature seems to agree that COVID-19 phenotypes are phases of a single disease, characterized by distinct host responses to the virus and different levels of lung damage (Chiumello et al. 2020; Mauri et al. 2020; Ball et al. 2021). However, post-mortem findings have previously confirmed the existence of distinct chest CT phenotypes between COVID-19 survivors and non-survivors (Carsana et al. 2020; Jin et al. 2020; Pan et al. 2020; Robba et al. 2020), which is in accordance with our findings.

Our cohort survivors showed residual lung alterations at chest CT and LUS at the time of ICU discharge, which confirms the existence of distinct phenotypes as different phases of the same disease. As previously described by Gaspardone et al. (Gaspardone et al., 2021), these findings suggest a slow lung anatomic healing after ARDS because of severe viral pneumonia. This finding supports the concept that an appropriate follow-up of residual pulmonary lesions after ICU discharge should be pursued. In this setting, LUS could be of valuable help thanks to its easier application in a low-resource setting (Allinovi et al. 2020).

Furthermore, our data confirm that the worse the CT pattern, the harder the clinical course (Cartocci et al. 2020; Song et al. 2020; Turcato et al. 2020), raising concerns about potential therapeutic strategies being different in each phase of the disease (Battaglini et al. 2020; Robba et al. 2021).

Fig. 2. Correlation between CT and LUS score at admission (a); correlation of CT or LUS scores and PaO2/FiO2 ratio (b, d) and CPR (c, e) at admission. CT = computed tomography; CRP = C-reactive protein; FiO2 = fraction of inspired oxygen; LUS = lung ultrasound; PaO2 = arterial partial pressure of oxygen.
Chest CT and LUS scores

Chest CT scan revealed a pivotal role in diagnosis and treatment of patients with severe COVID-19, possibly influencing individualized therapeutic strategies (Garg et al. 2021). However, chest CT scan may be difficult to perform in patients who are critically ill owing to possible clinical instability, which can make transfer to the CT room a contraindication. In this setting, other simpler tools like LUS have been proposed to better characterize COVID-19 patterns, with the limitation of less specificity and operator dependency, but with the advantages of bedside availability and not exposing the patient to ionizing radiation (Chen et al. 2020; Lu et al. 2020; Lanza et al. 2020).

In our study, chest CT and LUS scores significantly differed between survivors and non-survivors, confirming that both may be considered essential tools for patients’ outcome stratification at ICU admission and on follow-up (Feng et al. 2020; Hu et al. 2020; Pan et al. 2020; Rojatti et al. 2020). This has been previously confirmed by Pan et al. (2020), who found that persistent progression with predominant crazy-paving pattern was the major manifestation of COVID-19 in non-survivors. Several other studies investigated the role of chest CT and LUS for detecting patients at risk of death. A recent report found that higher LUS scores could predict 30-d mortality (Borghesi et al. 2020), although this point is still debated (Colombi et al. 2020a). However, qualitative and quantitative chest CT assessments associated with clinical data may be considered an optimal tool for the stratification of survival. In fact, pneumonia extent (greater than 40%) was detected as a possible predictor of outcome in patients with COVID-19 (Colombi et al. 2020b).

Association between chest CT, LUS scores and oxygenation

In our cohort of COVID-19 critically ill patients, we observed a strong correlation between chest CT and LUS at ICU admission ($r = 0.953$, $p < 0.0001$), suggesting the possible utility of LUS technique in cases of contraindications or impossibility to perform chest CT, and for daily clinical assessment of pneumonia progressions (Chen et al. 2020). Similarly, Volpicelli et al. (2021) found a strong correlation between LUS and CT imaging, thus confirming our results. However, other authors concluded that admission chest CT showed better performance than LUS for COVID-19 diagnosis, at varying disease prevalence (Colombi et al., 2020a). In fact, the main LUS limitation is related to its poor specificity, with findings overlapping with those from other pneumonia or lung pathologic conditions (e.g., chronic heart failure or pulmonary fibrosis) (Tung-Chen et al., 2020).

Chest CT was inversely correlated with admission PaO$_2$/FiO$_2$ ratio ($r = -0.375$, $p = 0.019$), and CRP ($r = 0.329$, $p = 0.041$), while LUS showed an inverse correlation with admission PaO$_2$/FiO$_2$ ratio ($r = -0.345$, $p = 0.031$) but did not correlate with CRP. These data suggest that the lower the oxygenation, the worse the chest CT and LUS profile, confirming the association between clinical features and radiographic or ultrasonographic images (Cartocci et al 2020; Song et al. 2020; Turcato et al. 2020). Similarly, in non-COVID-19 ARDS settings,
LUS was adopted for detecting improvement in oxygenation, confirming that it could be promising for monitoring aeration at bedside, but not for predicting oxygenation response (Haddam et al. 2016). Additionally, LUS can predict response to the prone position in awake, non-intubated patients with COVID-19-associated ARDS (Avdeev et al. 2021).

We acknowledge that we present a lower LUS PaO2/FiO2 ratio correlation compared with other similar studies (Perrone et al., 2021; Soldati et al. 2020b). However, this reflects our experience during the first strike of the pandemic, and our results were obtained in patients who were mechanically ventilated and critically ill with COVID-19 and possibly with both pneumonia and ventilatory-related lung changes, which are frequently not distinguishable. These findings are also consistent with other previously published series performed on comparable patients (Millington et al. 2018; Rojatti et al 2020; Dargent et al. 2020).

Limitations

This study has some limitations, the first of which is the retrospective design. Chest CT images were assessed basing on clinical necessity and patients’ status, making it impossible to perform regular imaging at the same time. Second, chest CT scans were performed at patient ICU admission and during ICU stay. However, being critically ill, many patients could not receive a chest CT scan during their acute phase because of their clinical instability, limiting a possible transport to the CT room. To reduce this heterogeneity bias, most of the chest CT scans performed during ICU stay were assessed during a critical phase of the disease (during the multi-systemic clinical syndrome with impaired/disproportionate and/or defective immunity) corresponding to 10 d after ICU admission, if deemed feasible. Third, chest CT scans were reviewed by experienced radiologists using the CT TSS. However, this method could be affected by interpretation bias; nonetheless, computer-aided quantitative analysis of the CT examination (Quantitative Computed Tomography) was also recently used for this purpose, showing a promising role in predicting COVID-19 clinical outcome (Lanza et al. 2020). Fourth, other possible confounding factors were not considered in the multivariate analysis (i.e., multiple organ dysfunction) for data unavailability.

CONCLUSIONS

In patients with COVID-19 who are critically ill and mechanically ventilated, chest CT and LUS scores at ICU admission significantly differed between survivors and non-survivors. We also observed a significant correlation between admission clinical, oxygenation and imaging findings and between CT and LUS scores during patients’ follow-up. In conclusion, although chest CT scans cannot be replaced by LUS in the diagnostic process, LUS should be considered as a valuable complement to diagnosis and follow-up in an ICU setting because it has many advantages such as being convenient, fast, non-invasive, readily repeatable and does not involve ionizing radiation.

DECLARATION OF COMPETING INTEREST

All authors have no conflict of interest to disclose.

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