A multisystem approach by bed-side ultrasound in patients with COVID-19 infection: a case series

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ABSTRACT

Recent epidemiological reports on Chinese population affected by novel coronavirus showed a wide spread of clinical and biochemical alterations, suggesting a relationship between progression of lung damage to acute respiratory distress syndrome and the systemic inflammatory response, triggering an irreversible multiple organ damage and disseminated intravascular coagulation. Bedside ultrasound assessment provides integrated information, describing a multisystemic and dynamic clinical scenario for every patient. Furthermore, this approach allows to concentrate multiple information in the hands of a single operator, also limiting the risk of exposure to infection for healthcare professionals. As per our experience, herewith reported, we described the characteristics of 10 patients with SARS-CoV-2 infection. Ultrasound findings were related to clinical information, blood test analysis, and results of instrumental tests, such as chest X-ray and chest computed tomography. According to our ultrasound data, COVID-19 appears to be a systemic pathology even in those cases of mild to moderate disease. By this multisystem ultrasound approach, we could immediately recognize patients with a diffuse organ involvement and a more severe clinical pattern; moreover, we can protect healthcare workers and limit infection within health facilities.

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Consent: patients gave their informed consent to participate in the study.

Ethics: practice described for every single patient is consistent with our standard clinical care and comply with the Declaration of Helsinki.

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Introduction

The main cause of admission to the emergency room for COVID-19 patients is the presence of respiratory failure. An extensive lung involvement is the principal cause of clinical aggravation and admission to Intensive Care Unit (ICU).[1-3]

Due to progressive clinical instability, and high contagiousness, patients with COVID-19 cannot be easily moved from one setting to another in hospital facilities.[4] For this reason, ultrasound method represents a fundamental resource in all the phases of their clinical management.

Scientific evidence showed the high reliability and sensitivity of ultrasound assessment as point-of-care in the critically ill patient.[5] In particular, point-of-care ultrasound was the gold standard for clinical management in ICU and Emergency Department (ED).[6] Moreover, several reports described the great efficiency of ultrasound in hemodynamic assessment and monitoring after therapy.[7]

The role of ultrasound in pneumonia diagnosis is well known.[8]

Recent epidemiological reports on Chinese population affected by novel coronavirus showed a wide spread of clinical and biochemical alterations, suggesting a relationship between progression of lung damage to acute respiratory distress syndrome (ARDS)[9] and the systemic inflammatory response, triggering an irreversible multiple organ damage and disseminated

intravascular coagulation.[10] In this regard, the role of an increased prothrombotic response in COVID-19 pneumopathy and the frequent finding of pulmonary thromboembolism in patients with severe clinical course, may not be considered as a random association, but aspects of the same disease.[11]

Bedside ultrasound assessment provides integrated information, describing a multisystemic and dynamic clinical scenario for every patient. Furthermore, this approach allows to concentrate multiple information in the hands of a single operator, also limiting the risk of exposure to infection for healthcare professionals.[6,12]

Case Report

The aim of our study was to describe ultrasound findings in COVID-19 patients, in relation to clinical severity and instrumental and biochemical parameters.

The study population consists of 10 consecutive patients, affected by COVID-19, belonging to the ED of the SS Cosma and Damiano Hospital in Pescia, Italy, after the onset of fever and dyspnea.

According to current protocols we performed biochemical exams (whole blood cells count, transaminases, D-dimer, creatinine, C reactive protein, procalcitonin, high-sensitivity troponin, brain natriuretic peptide), arterial blood gas analysis, in order to assess respiratory function and lactate levels, and bedside chest X-ray.

Bedside ultrasound evaluation comprised the assessment of lung, cardiac function, liver parenchyma, diameters, and collapsibility of the inferior vena cava; it was performed during medical examination in the emergency department, by the same expert operator, using a 'ESAOTE MyLab 75' ultrasound, with a 3.5-MHz convex probe.

Lung ultrasound was performed according to a method described elsewhere.[13-15] During each exam 8 scans were obtained, 4 for each hemithorax, evaluating the upper and lower part of anterolateral regions.

Cardiac ultrasound assessment was performed according to the traditional transthoracic method.

To assess inferior cava vein measurements, the probe was positioned at the level of the subxiphoid region, with the patient in supine position. To acquire standardized measurements, the inferior vena cava (IVC) diameter was measured 2 cm from the junction between the inferior vena cava and the right atrium, recording in M-mode every 10 seconds, and including 2-3 cycles respirators. The inspiratory and expiratory diameters of the IVC were evaluated by measuring the lumen of the vein within the same respiratory cycle, measuring from the internal wall to the opposite internal wall. The measurements were collected in M-mode.[16,17] We defined the inferior vena cava as collapsible in relation to the cut-off for the collapsibility index equal to 40%, according to the literature data.[17]

The liver ultrasound evaluation was dedicated to the study of different parenchymal features on suspicion of acute organ damage. We assessed liver echogenicity in comparison with the renal parenchyma, pattern of homogeneity and inhomogeneity, visibility of vascular structures, visibility of the diaphragm, possible presence of portal vein thrombosis diaphragm.[18]

Based on our experience, we described the characteristics of 10 patients with SARS-CoV-2 infection. Ultrasound findings were related to clinical information, blood test analysis, and results of instrumental tests, such as chest X-ray and chest computed tomography (CT).

ICU admission was required for five patients due to the progressive worsening of respiratory failure.

Clinical, biochemical and instrumental characteristics of the study group were reported in Table 1.

ICU patients already showed severe hypocapnic respiratory failure upon presentation at emergency room; significant alterations on biochemical exams were found, in comparison with non-ICU patients. Chest X-rays showed widespread pulmonary thickening and interstitial plot reinforcement in ICU patients, while in others only uncommon mild interstitial disease was found.

In patients with more severe clinical impairment, ultrasound assessment discovered marked signs of organ damage. Ultrasound findings were reported in Table 1.

An extensive pulmonary involvement consisted in diffuse and confluent B lines, irregular pleural line and thickness, subpleural consolidations. Similar findings were described elsewhere for H1N1 pneumonia.[8] Myocardial alterations, including wall brightness end pericardial effusion, were reported.

We did not find signs of hypovolemia; upon the assessment of vena cava diameters and collapsibility, we found a central venous overload, frequently associated with altered cardiac kinetic and a slight enlargement of right chambers. We excluded pulmonary embolism by CT angiography.

Non-ICU patients showed a mild respiratory involvement and minor biochemical alterations, requiring ordinary hospitalization. Chest X-ray was unremarkable; sporadic thickened pleural and rare subpleural consolidations, as well as isolated ground glass areas were reported on CT scan. Ultrasound evaluation was able to recognize signs of initial lung involvement even in patients with mild disease, showing sporadic non-confluent B lines, uncommon subpleural consolidations, and sporadic pleural thickening. Similar findings were described elsewhere.[19] Cardiac function and central venous pattern were unremarkable in non-ICU patients.

Ultrasound assessment of liver parenchyma showed irregular non-homogeneous brightness. On Doppler examination, demodulation of portal flow was also described. These findings were reported in ICU patients, but mild hyperechoic appearance of liver in comparison with renal parenchyma was also described in others. Ultrasound findings were shown in Figures 1 to 5.

Discussion

Novel coronavirus infection has been associated with widespread clinical presentation, ranging from respiratory and gastrointestinal symptoms, neurological and cardiological signs, suggesting a diffuse pattern of organ damage. COVID-19 pneumonia is the most widely described condition; other diseases related to novel coronavirus infection are lacking in evidence in recently published reports. However, a detailed investigation of the patient with advanced COVID-19 is not always possible due to the instability of the clinical conditions and the high risk of contagion for the clinical staff.

Bedside lung ultrasound could increase the quality of clinical information in the hands of the emergency physician, also limiting the exposure to the biological risk for healthcare professionals. Several studies

Table 1. Characteristics of study population.

	Non-ICU patient (n=5)	ICU patient (n=5)
PaO_2, mmH_2O (mean±SD)	69±5	49±7
$PaCO_2$, mmH_2O (mean±SD)	35±3	24±4
D-dimer, mcg/ifEU (mean±SD)	750±78	1820±250
CRP, mg/dL (mean±SD)	5.3±2.3	20.6±6.8
HS troponin, pg/mL (mean±SD)	32.7±9	100±12
AST, U/L (mean±SD)	55±8	160±15
ALT, U/L (mean±SD)	80±15	230±21
LDH, U/L (mean±SD)	312±32	530±37
WBC, 1000/mm×3 (mean±SD)	4.1±0.3	3.5±0.4
Lactate levels, mmol/L (mean±SD)	1.2±0.2	3.1±0.4
Lung ultrasound		
B lines	Regional asymmetrical distribution; focal pattern, non- confluent lines	Diffuse, non-homogeneous, asymmetrical distribution, *spared areas* of normal parenchyma; multifocal pattern, confluent lines
Pleural thickening	Regional distribution	Irregular thickened fragmented pleural line, findings diffuse on different quadrants
Consolidations	Uncommon	Anterior sub-pleural consolidations
Pleural effusion	No	Uncommon
Cardiac ultrasound		
Pericardial effusion	No	Frequent, non-circumferential, non-hemodynamic
Kinetic	No alterations	Regional hypokinesis
Chambers	No alterations	Slight increase in the right sections
Myocardium	No alterations	Diffuse echo-bright appearance of the myocardium
IVC ultrasound		
Diameter, mm (mean±SD)	17±3	22±3
Collapsibility index, % (mean±SD)	Normal, >40%	Venous congestion, reduced collapsibility index, <40%
Liver ultrasound		
Parenchymal pattern	Hyperechogenic areas with regional distribution, predominantly normal parenchyma	Significant hepato-renal difference, hyperechogenic areas with diffuse distribution, inhomogeneous areas of the parenchyma with regional distribution

ICU, Intensive Care Unit; SD, standard deviation; PaO_2, partial arterial pressure of O_2; $PaCO_2$, partial arterial pressure of CO_2; CRP, C reactive protein; HS troponin, high-sensitivity troponin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, white blood cells; IVC, inferior vena cava.

showed the accuracy of lung ultrasound in detecting and monitoring lung diseases, such as pneumonia and ARDS.[5,20] Furthermore, ultrasound is extremely sensitive in distinguishing initial alterations from widespread organ alteration and it could be used as a gravity screening, selecting candidate patients for second level diagnostic procedures. Our data confirm the results of the literature, suggesting that ultrasound is superior in comparison with radiography, in defining lung damage. In addition, recent studies suggest that the ability of chest CT to identify suspected cases for interstitial pneumonia is not superior to pulmonary ultrasound.[19,20]

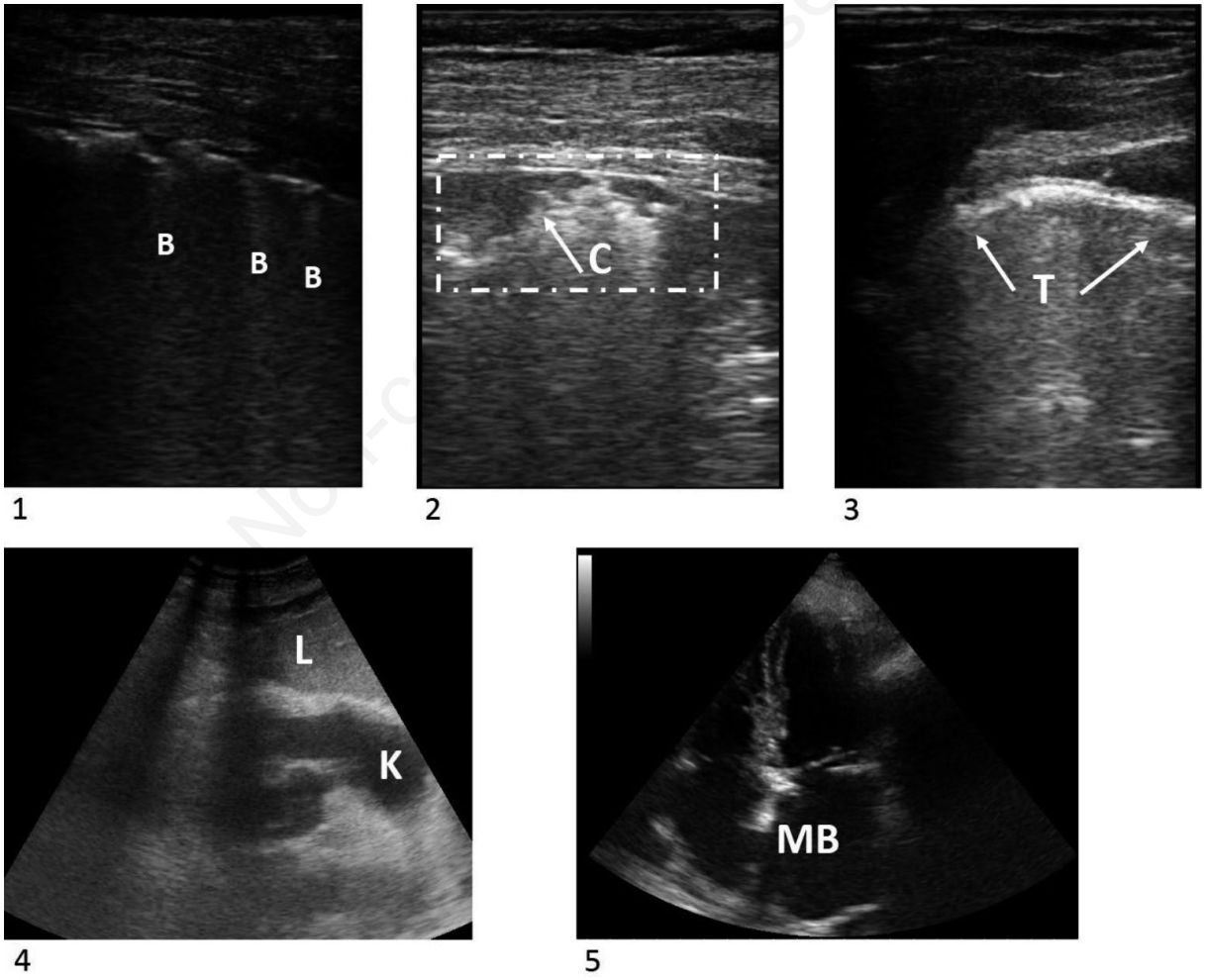
In addition to respiratory tract involvement, myocardial damage has been reported. Epidemiological reports revealed elevated levels of myocyte necrosis markers, such as creatine kinase-MB, N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin. Arrhythmias were described in 16.7% of the 138 hospitalized COVID-19 patients at Zhongnan Hospital of Wuhan University.[21] Moreover, macroscopic alterations of the myocardium and pericardium have been described by Liu *et al*. however, due to the limited clinical data, the certainty of the relationship between myocardial changes and COVID-19 requires further investigation.

Our findings confirmed data reported in recent studies describing an involvement of the myo-pericardial tissue related to coronavirus infection, suggestive for a myopericarditis.[22]

The pathogenetic link between coronavirus infection and cardiovascular disease is widely debated.[23]

Authors described multiple mechanisms, including direct viral damage, hypoxemia for severe lung involvement, and systemic inflammatory reaction[24] related to cytokine storm.[25] The role of the ACE2 enzyme in the pathogenesis of cardiovascular complications has been suggested recently, in particular for the evidence relating to SARS.[25,26]

The evaluation of the hemodynamic status in the



Figures 1-5. Ultrasound findings in COVID-19 patients, admitted to Intensive Care Unit. 1) B lines (B) and irregularities of the pleural line; 2) Sub-pleural consolidations (C); 3) Pleural thickening (T); 4) Inhomogeneous hyperechogenicity of the hepatic parenchyma (L) in comparison with the renal parenchyma (K); 5) Myocardial brightness (MB).

critically ill patient is a key element of correct therapeutic management. Detailed reports on the hemodynamic status in patients with pneumonia due to COVID-19 are lacking. Several studies evaluated diagnostic utility of combined cardiac and thoracic critical care ultrasonography in optimizing differential diagnosis among the causes of respiratory failure, with particular reference to ARDS and pulmonary edema. Large IVC minimal diameter and diffuse B lines were associated with cardiogenic edema, whereas a low B-line ratio was predictive of ARDS.[27] In this report, we found a reduced collapsibility index and large diameter of IVC in patients with extensive pulmonary involvement; central venous congestion, not related to pulmonary edema, and a slight increase in the right sections could be associated with a diffuse pulmonary microvascular thrombotic damage, as suggested elsewhere.

Recent studies described gastrointestinal manifestations, including anorexia, nausea, vomiting and diarrhea; the possibility of fecal-oral transmission was suggested after detection of SARS-CoV-2 in the stool of infected patients.[28] Varying degrees of abnormality in liver function indexes are frequently reported, and are apparently related to the systemic inflammatory state.[29] Clinical implications of liver changes are not fully known, and there are no imaging investigations aimed at studying the liver parenchyma during coronavirus infection. In this case report, ICU patients showed ultrasound alteration of the hepatic parenchyma, which appeared hyperechoic, with an inhomogeneous structure. These structural changes are associated with alterations in liver function indexes. Further studies are needed to understand the role of these alterations at clinical level and to better understand the structural alterations of liver parenchyma.

Conclusions

According to our ultrasound data, COVID-19 appears to be a systemic pathology even in those cases of mild to moderate disease.

The multisystem ultrasound approach could provide essential information on the patient clinical condition and disease progression. For this purpose, the usefulness of chest radiography is limited, as the lesions are mainly evident in case of more advanced disease; chest CT, on the other hand, while providing a clear description of lung parenchyma, is not always executable, depending on the patient clinical condition, and does not provide dynamic indications. By this multisystem ultrasound approach, we could immediately recognize patients with a diffuse organ involvement and a more severe clinical pattern; moreover, we can protect healthcare workers and limit infection within health facilities.

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