REVIEW

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COVID-19 pathophysiology and ultrasound imaging: A multiorgan review

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Abstract

COVID-19 is a dynamic disease and may affect different tissues and organs as it progresses. Therefore, the impact generated by the disease in all its stages and organs requires a functional and versatile imaging technique able to detect particularities or artifacts dynamically. Ultrasonography fulfills all these requirements and exhibit several advantages relative to other imaging modalities, including portability, lower cost and biosafety. Throughout the COVID-19 pandemic, ultrasonography displayed a crucial role in the triage, monitoring, indicating organ damages and enabling individualized therapeutic decisions in COVID-19 patients. This review is dedicated to highlight the main pathological effects correlated with ultrasound changes caused by COVID-19 in the lungs, heart and liver.

KEYWORDS
COVID-19, echocardiography, multiorgan tropism, SARS-CoV-2, ultrasound

1 | INTRODUCTION

The coronaviruses are zoonotic viruses that belong to the *Nidovirales* order and *Coronaviridae* family that account with three already identified species—the etiologic agents of the severe acute respiratory syndromes (SARS).[1] The first coronavirus outbreak, caused by SARS-CoV-1, started in China in 2002 and caused more than 8.000 cases and 774 deaths in 27 countries.[2,3] After 10 years, a new outbreak, caused by MERS-CoV resulted in 1.728 confirmed cases and 624 deaths in 27 countries.[3,4] In 2019, the SARS-CoV-2 culminated in the current "Corona Virus Disease 2019" (COVID-19) pandemic, responsible for more than 200 million cases and more than 4 million deaths worldwide.[5,6]

The coronaviruses carry single-stranded ribonucleic acid with positive sense (+ssRNA), which express open-reading frames that encode for at least 27 proteins including 15 non-structural,

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8 auxiliaries and 4 structural (e.g., S "spike," M "membrane," E "envelope" and N "nucleocapsid" proteins).[7] To gain access to the host, the viral S protein interacts with the angiotensin II converting enzyme receptor (ACE2) and depends on auxiliary proteins located at the cell surface for successful invasion.[8] Among these peptides, the transmembrane serine protease 2 (TMPRSS2) is highlighted for its role in cleaving and activating the S protein of several classes of coronaviruses.[8] Furthermore, the furin protease mediates the binding of the S protein with ACE2 receptor.[8–10] After the viral particle's endocytosis process, its genetic material is released into the cytosolic environment for subsequent replication.[11]

The SARS-CoV-2 is transmitted via respiratory droplets and by contact with infected surfaces or objects.[12] Additionally, it might be detected in several samples, including spittle, feces and blood that may also contribute with the transmission.[13] The SARS-CoV-2 invasion occurs primarily along the respiratory tract and may be asymptomatic or symptomatic, displaying several symptoms, such as fever, cough, dyspnea, myalgia, fatigue, confusion, headache and sore throat.[14] In some cases, the infection might progress to severe symptoms and complications that include hypoxemia, respiratory or multiple organ failure, acute cardiac injury and secondary infections.[14–16] In the elderly and individuals with underlying comorbidities, such as diabetes mellitus, hypertension or cardiovascular disease, the infection may result in fatal complications.[14] The SARS-CoV-2 infection might affect multiple organs and the lungs play a central role on the symptomatology.[17]

The invasion process unbalances the renin-angiotensin pathway caused by ACE2 function disruption and induces lung endothelial, epithelial and alveolar damage mediated by immune cells that may lead to hypoxemia and fibrosis.[18,19] In addition, local endothelial nitric oxide production might also cause inflammation.[18,20] The effect of viral invasion on other structures, such as the brain, mouth, heart, kidneys, pancreas and the gastrointestinal tract is discussed in Reference 18.

Currently, few therapies have been identified, including dexamethasone, remdesivir, lopinavir, ritonavir, recombinant ACE2, interferon 1 and convalescent plasma.[21] However, the multiple organ tropism presented by SARS-CoV-2 requires an individualized assessment to personalize and establish efficient therapies.[22] To monitor pathological condition, several imaging techniques are fundamental for determining the clinical management of patients with COVID-19.[23]

1.1 | Ultrasonography applied to COVID-19

Medical imaging techniques present a fundamental role in the detection, monitoring and therapeutical choices regarding the multiple damages caused by SARS-CoV-2. Among them, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), X-ray (XR) and positron emission tomography (PET) display crucial importance in COVID-19 assessment. All are capable of revealing abnormalities in different organs as a result of the viral pathological process. In particular, chest CT allows the identification of precocious affections caused by COVID-19 and became an important tool for determining the progress and classification of disease stages.[24] However, the wide use of CT in patients with COVID-19 is discouraged due to the risk of cross-contamination associated with the need for prior hygiene for each patient.[25] Likewise, XR, MRI and PET techniques present the same risk, and their use is severely limited for such patients, especially for those allocated to the intensive care unit (ICU).[25–27]

Therefore, US has been increasingly employed as an imaging alternative to CT. US differs from other techniques for its portability, lower cost, easy transportation, sanitization and safety—a key factor to avoid viral contamination and enable imaging of patients in isolation—and, above all, US might provide images capable of indicating the nature of a wide variety of tissue damage in real-time over relatively fast examinations, a factor that may be crucial in urgent situations.[28–31]

Despite the several advantages of the technique, there are important diagnostic limits that prevent its wider use in cases of COVID-19: the number of qualified professionals to interpret the test is limited during the pandemic; it is not possible to perform a "risk assessment" of the patient; mechanically ventilated patients suffer from the "curtain effect" caused by increased lung insufflation, which reduces the echocardiographic windows; and, logistically, the demand for the exam may be greater than the number of devices.[32]

In the particular case of the lungs, it was recently verified that US has an accuracy similar to chest CT in pointing out elements suggestive of COVID-19 (e.g., 100% sensitivity, 78% specificity and positive and negative predictive value of 92% and 100%, respectively).[33] A good correlation between US and CT is also observed for other organs, establishing US as an important tool in the evaluation of COVID-19 patients.[29,33] Finally, US is the imaging methodology that best satisfies several requirements imposed by COVID-19 and enable monitoring of different tissues, determine the degree of local lesion and enable the choice of therapies in an individualized manner according to the particularities of the pathological mechanism affecting different organs.[24,28] This review is dedicated to highlight the main US changes caused by COVID-19 in the lungs, heart and liver.

2 | LUNGS

2.1 | Pulmonary pathophysiology

The lungs are the most affected organs by COVID-19.[34] Recent studies indicate that the SARS-CoV-2 infection affects many cells along the proximal (e.g., cilia and goblet cells) and distal (e.g., type I and II pneumocytes) air tracts, especially on type 2 alveolar cells (AT2) that exhibit a high expression rate of ACE2 ($\sim$83%)[19] and TMPRSS2.[35–37] The infection in AT2 cells is one of the main mechanisms that triggers SARS in severe cases of COVID-19, characterized by the accumulation of fluids in the alveolar sacs and consequent reduction in gas exchange.[38,39]

After the viral infection, pattern recognition receptors (PRRs) detect the pathogen replication and act as "sentinels" that undergo oligomerization due to the interaction with invasive RNA structures.[40,41] This process generates transcription factors (e.g., NF-κB), which induce the expression of types I and III interferons (IFN) that interfere with the viral replication.[42] The IFN activate the JAK–STAT signaling pathway and induce the expression of antiviral genes, whose products (i) restricts the viral replication within infected cells, (ii) induces an "antiviral state" in the tissue by recruiting cells of the innate immune system and (iii) prepare an adaptive immune response.[43]

However, the SARS-CoV-2 infection is effective in delaying or preventing the production of immune responses associated with types I and III IFN, thus enabling the viral replication to proceed uncontested and delay the activation of the innate immune system.[44]This effect is particularly associated with severe cases of the disease with a high mortality risk.[45]

Nonetheless, the response to the viral infection is multifaceted and a second defense strategy is mediated by the recruitment of specific leukocyte subtypes capable of releasing a wide variety of pro-inflammatory cytokines and chemokines.[46] Therefore, the innate immune system is activated via interaction with damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs; e.g., SARS-CoV-2 orf8b).[47] The exposure to PAMPs activates NLRP3 receptors which, in turn, recruit the enzyme caspase-1, a pore-forming protein that causes pyroptosis—cell death induced by the synthesis and activation of IL-1β, IL-18, TNF-α and gasdermin-D—a phenomenon observed in >82% of patients.[10,48] Different mechanisms linked to NLRP3 activation have been reported (e.g., induction of inflammasomes and consequent initiation of an inflammatory response correlated to cell death patients [[49,50]]), though only one has been so far associated with the SarS-CoV-2 infection.[51]

The release of IL-1β and TNF-α activates Th17 cells, which secrete pro-inflammatory cytokines that provoke an event defined as "cytokine storm."[52] Among them, IL-17, IL-21, IL-22 and GM-CSF stand out, as they are responsible for the induction of neutrophils and other immune cells (e.g., CD68⁺ macrophages), blood-air barrier remodeling, fever, hypoxemia and edema.[53] Recent studies suggest that due to the imbalance of the immune response caused by SARS-CoV-2—as it delays or prevents the preparation of an adaptive response—it triggers an exacerbated expanding response in an attempt to control the infection.[44] This response, however, results in a broad pulmonary immunopathology characterized by the elevation of neutrophils in the lung tissue, particularly in the most severe cases.[51]

Although the molecular mechanisms of pulmonary pathophysiology are still unclear, multiple factors are under consideration. Among them, the functional loss and reduction of ACE2 expression upon its binding with the S protein of SARS-CoV-2 stands out, as it disturbs the renin-angiotensin-aldosterone system (RAAS) responsible for maintaining the blood volume and electrolyte concentration.[54] The consequent ACE2 blockage significantly reduces the conversion of angiotensin II—a potent vasoconstrictor and oxidizing action—into angiotensin 1–7, which interacts with the *Mas* receptor and stimulates vasodilation and antiproliferative effects.[55]

Since the lungs are the main location of angiotensin II synthesis, its unregulated effects cause local vasoconstriction, which culminates in edema, loss of lung function, diffuse alveolar damage, AT2 cell hyperplasia, fibrin deposition in the interalveolar space and lymphocytic inflammation.[56,57] Another pathological mechanism of SARS-CoV-2 is the activation of coagulation pathways due to cellular apoptosis resulting from the inflammation of viral replication: with the loss of the air–blood barrier's integrity, the resulting exposure of thrombogenic substrates (e.g., membrane and other components of lysed cells) initiate coagulation and form microthrombi that occlude the alveoli and blood vessels.[57] This effect raises D-dimer values up to five times and may cause disseminated intravascular coagulation.[57] Additionally, respiratory tract infection affects the vascular endothelium and smooth muscles of pulmonary arteries and arterioles, which may impact pulmonary perfusion and obstruct gas exchange by inhibiting smooth muscle contraction and reduce the concentration of nitric oxide.[58,59]

Therefore, the SARS-CoV-2 infection induces a pro-thrombotic state at the pulmonary level—not usually observed in other airway infections (Figure 1)—characterized by an increase in the levels of fibrinogen, Von Willebrand factor and D-dimer.[61] The local hypercoagulability response is a defense mechanism aimed at preventing the entry and limit the spread of pathogens.[62]

2.2 | Pulmonary ultrasonography in patients with COVID-19

The strategy of employing pulmonary ultrasonography (PUS) to monitor the disease evolution over the lungs revealed itself as an effective
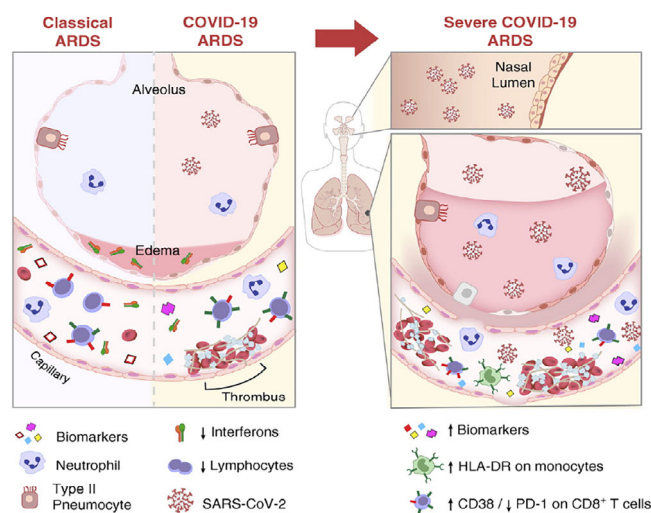
FIGURE 1 Representation of the airway and alveolar's biochemistry during classic acute respiratory distress syndrome (ARDS) and in COVID-19-induced ARDS. In both syndromes, the alveolar-interstitial-capillary structure is similarly affected. There is an increase in pro-inflammatory biomarkers, endothelial and capillary permeability, in addition to an increase in inflammatory cells (neutrophils, monocytes and macrophages) in vessels and alveoli. However, the increased biomarkers in the two syndromes are distinct. Image adapted from[60]

alternative for generating clinically useful images and minimize the risk of infection for the patient and/or health professional.[63] Despite the preference of CT for pulmonary diagnosis, PUS has the potential to accurately distinguish varied ultrasonic signs and patterns associated with COVID-19,[64,65] as well as perform functional assessment of the tissue and the capacity for gas exchange.[66]

The ultrasonographic examination of patients with COVID-19 is characterized by the following patterns: (i) the effusion, thickening and fragmentation of the pleural and subpleural lines; (ii) the disappearance of the A lines (suggesting air content reduction); (iii) the appearance of B lines (indicating air volume reduction and local density increment), which may be separated or coalescent; (iv) consolidations in different areas and locations at different stages of the disease, which is associated with air bronchograms and whitish pulmonary pattern; (v) a "light beam signal," which is a vertical band-shaped artifact that moves with the pulmonary sliding during breathing—a result of the onset of interstitial involvement.[67] The observation of these patterns with bilateral pulmonary involvement was verified in >75% of COVID-19 cases.[68]

Both the A and the B lines are unique lung artifacts that are not exclusively related to COVID-19 and may also suggest lung impairment by distinct pathologies. The A lines indicate the amount of air in the alveolar spaces and are hyperechoic horizontal arcs formed at identical intervals and parallel to the pleura and skin line, due to the repeated reflection of the transducer/skin and pleura interface (Figure 2A,B).[68,69] The B lines are hyperechoic and vertical to the pleura (also called "comet tails") that move along with the pulmonary sliding. The B lines extend from the pleural line to the edge of the ultrasound image and eliminate the A lines as a result of the reverberation of the PUS bundles with edema in the alveoli (Figure 2B,C).[68–70]

The B lines indicate the degree of pulmonary impairment: the presence of up to 2 B lines per intercostal space suggests non-severe alveolar damage; the presence of three or more lines with greater thickness point indicate compromised pulmonary aeration and a moderate reduction in compliance, as a result of interlobular septa thickening and alteration of the pulmonary interstitium[71] Another usual finding employed to indicate the evolution of the pathology are the pleural irregularities, which are associated with interstitial thickening resulting from edematous alveolar damage.[72] Subpleural consolidation indicate loss of local aeration, characterized by edema resulting from

the inflammatory process.[28,73] In PUS, their texture is similar to the liver tissue.[73] Furthermore, large consolidations are identified by an important reduction in lung aeration.[28]

As previously mentioned, PUS has excellent correlation with CT and other chest imaging techniques.[33] The evolution of the pulmonary status of patients affected by COVID-19 monitored by PUS and CT is shown in Figure 3.[28] The following continuous monitoring shows the progressive reduction in lung capacity, revealing coalescent B lines (Figure 3B,C) compatible with ground-glass opacification in CT.[28] The evolution of pulmonary impairment (between 9 and 13 days) leads to an increase in the area covered by the B lines and is usually followed by consolidations—initially small and restricted to the subpleural space (Figure 3D,E), but prone to evolve into other areas and locations depending on the intensification of the pathological process.[66] Thereby, by specifying the pulmonary disease of COVID-19 through ultrasonographic images, it is possible to differentiate the disease from other pathologies, such as bacterial pneumonia, cardiogenic pulmonary edema, pulmonary fibrosis or respiratory distress syndrome.[28]

To obtain effective results via PUS examination in the management of cases of infection, it is necessary to establish protocols to visualize different lung regions (Figure 4).[74] Lung division may be performed into 12 or more zones, 6 for each lung.[75] A careful analysis of the back region is suggested, as the histopathology of COVID-19 is prominently manifested in the posterior regions.[76] It is recommended that the patient remains seated with their back to the operator.[77] However, in more severe cases, in which the patients are lied at the supine position and presents no mobility, the back areas of the lung are not visible and, therefore, the viewing should be directed close to the posterior axillary line.[74] Other ultrasound protocols include the evaluation from 10 to 14 different lung areas.[78]

In conclusion, the advantages of PUS in the examination of COVID-19 patients are the following: portability, possibility of bedside assessments, biosafety and availability to repeat the examination during follow-ups with no exposure to radiation.[65,74] In addition, this imaging method allows for the assessment of tissue damage and the degree of pulmonary impairment caused by COVID-19.[28,72,78] Finally, PUS offers the physician a practical and safe method to obtain information during case monitoring, therapeutic response and even adaptations to mechanical ventilation.[64,65,74,79]
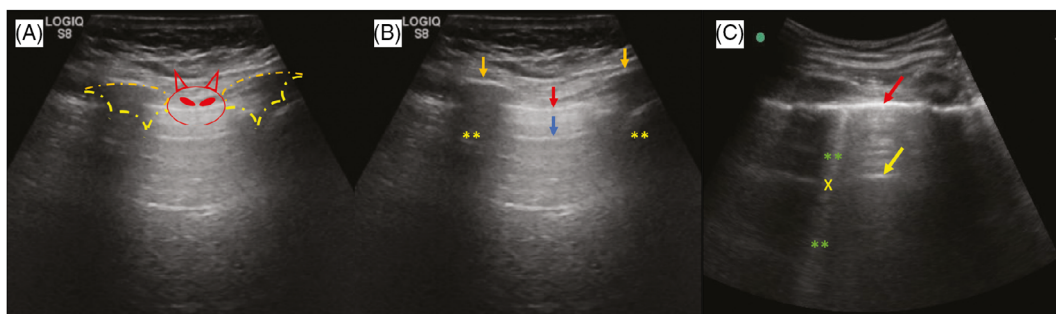
FIGURE 2 Longitudinal section of chest B-mode ultrasound imaging. The association of ribs and pleural line generate a solid landmark called the "bat sign" (A). The A lines (blue arrow), ribs (orange arrows) and their respective acoustic shadows (asterisks) are represented in image B. The B lines (asterisks) eliminate the A lines (yellow arrow) when they cross (x) (C). Adapted from[66]
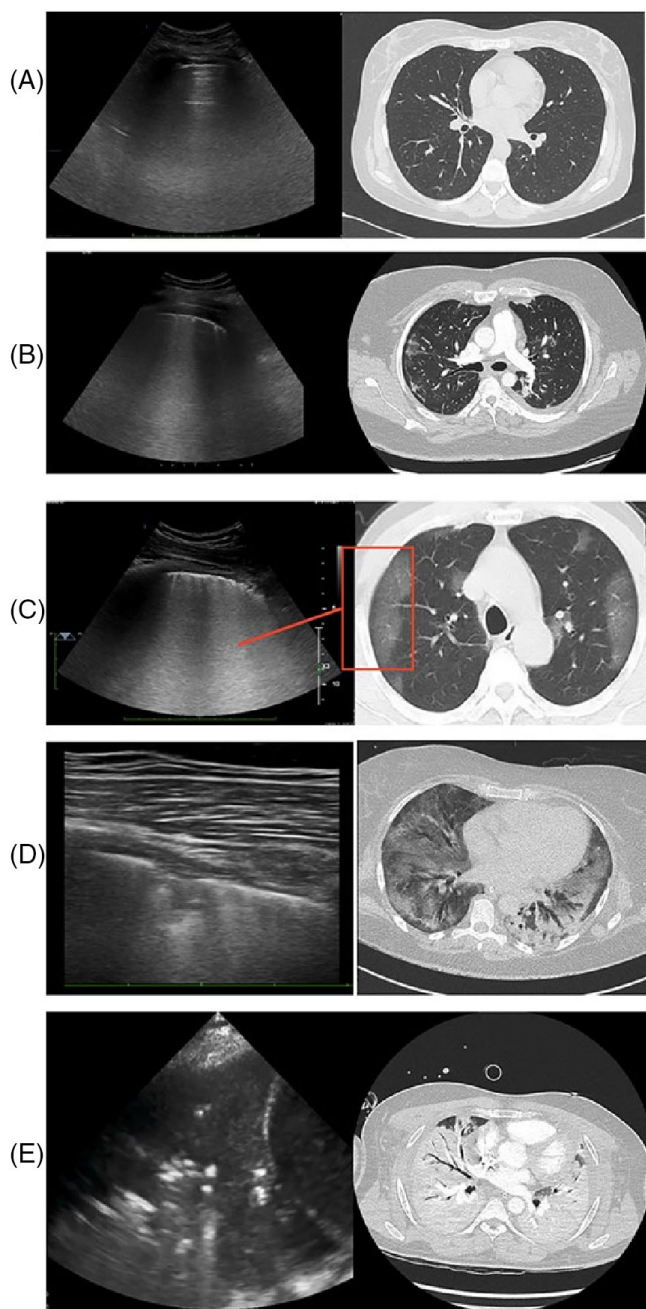
FIGURE 3 PUS and CT images of the lungs of individuals affected by COVID-19 at different stages, from normal aeration (A), progressive deaeration states (B and C) small and peripheral consolidation (D) and large consolidation (E). Adapted from[28]

3 | HEART

3.1 | Cardiac pathophysiology

The heart is heavily affected by COVID-19.[75] The SARS-CoV-2 infection might damage the cardiac tissue in multiple ways and may cause a myriad of pathological events, such as myocardial damage, myocarditis, sudden cardiac arrest, heart failure and varying stages of shock.[80] According to epidemiological data, the following heart diseases were observed in patients with COVID-19: myocarditis (7–17%), heart failure (24%), arrhythmias (17%) and thrombotic events (31%).[75,81] Such findings are associated with higher mortality rates and several complications, which include malignant arrhythmias, acute kidney injury and coagulation disorders.[80,82,83]

Furthermore, the viral infection is aggravated for those patients with previous cardiovascular disease (estimated 85% more risk of fatality and a mortality rate of 10.5%, compared to 2.3% for individuals without heart disease), which is the third most prevalent comorbidity in patients hospitalized with COVID-19.[84] As demonstrated by Zhou et al., patients with cardiac complications (pre-existing or due to infection) exhibit higher risk of rapidly changing from a stable to an unstable condition.[85]

Although still not fully understood, the pathogenesis of cardiac damage caused by SARS-CoV-2 is multifaceted and may be caused by direct viral infection or via indirect events. The myocardial damage caused by direct virus infection is indicated by the release of troponin T/I and detection of the viral genome in the heart.[86] Recently, Mitrani et al. revealed that almost a third of the patients exhibit some cardiac complications and the high mortality rate is associated with previous cardiovascular disease.[87] Moreover, a study by Maccio et al. showed that the endothelial cells of cardiac capillaries and epicardial nerves are the main targets of the virus due to increased ACE2 expression.[88] As a result, the infection might cause cardiac damage through several mechanisms, such as induction of cell death, inflammatory response and impairment of electromechanical functions.[89]

The viral infection may provoke microvasculature impairment, particularly at the small epicardial capillaries (that display elevated ACE2 expression), which may cause vasculitis along the capillaries, arterioles and cardiac venules.[88] Therefore, patients infected by SARS-CoV-2 are more likely to develop thromboembolic conditions.[90] As previously discussed, the downregulation of ACE2 resulting from viral infection causes an increase in angiotensin-II levels and a reduction in angiotensin 1–7 and 1–9 levels, which display cardioprotective effects.[75] Elevated levels of angiotensin-II are responsible for the genesis of a cascade of cytokines via NF-kB, IL-6, TGF-β and vascular endothelial growth factor (VEGF), which promote inflammation and fibrosis of the pericardial serous layer.[91,92] COVID-19, as well as diabetes and atherosclerosis are ACE2 inhibitory factors, thus all these pathologies are correlated with the occurrence of myocardial ischemia and ventricular dysfunction.[91]

The most frequent arrhythmia in patients with COVID-19 is sinus tachycardia—a homeostatic response to any infection or inflammatory response whose mechanism is, however, not fully understood—though atrial fibrillation and ventricular tachycardia are also observed.[93–95] Among the mechanisms causing this condition, electrolyte imbalance, lung damage, drug side effects and cell signaling cascades after viral infection stands out.[75] In addition, hypoxia due to ARDS is correlated with an increased risk of arrhythmia.[96] Medicines such as azithromycin and lopinavir/ritonavir may also contribute to trigger arrhythmias by prolonging the QT interval.[97]

The indirect effects of COVID-19 might induce myocardial injury via systemic inflammatory response generated by the "cytokine

FIGURE 4 Detailing of the lung zones for the recommended PUS scan in patients with COVID-19. Adapted from[74]

(A) **anterior chest wall** (B) **lateral chest wall** (C) **posterior chest wall**
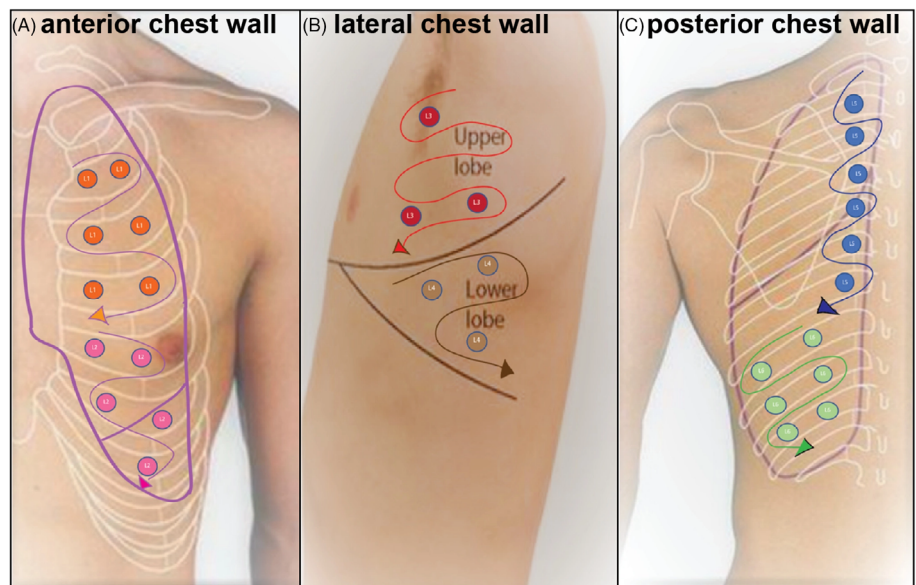
storm," characterized by high levels of IL-1, IL-6, IL-1β, IFNγ, MCP-1 and IP-10.[98,99] The cytokines contribute to cardiomyopathy by facilitating the release of radical oxygen species (ROS), nitric oxide and superoxide anions.[100] Additionally, damage-associated molecular proteins (DAMPs; e.g., heat shock proteins, oxidized lipoproteins and nuclear proteins HMGB1 proteins) are released from the damaged myocardium and induces inflammation and cardiomyopathy, establishing a continuous inflammatory cycle, resulting in septic cardiomyopathy due to COVID-19 and hemodynamic instability.[75,100]

The proinflammatory cytokine response mediates atherosclerosis and contribute to plaque disruption by provoking local inflammation.[101] Thereby, the exaggerated release of these inflammatory agents causes important hemodynamic changes, increasing the probability of ischemia, thrombosis, pulmonary embolism and may induce multiple organ dysfunction or disseminated intravascular coagulation.[91,102] Patients with more severe cases of COVID-19 exhibit higher levels of inflammatory markers, such as C-reactive protein, ferritin, interleukin 6, TNF-α and thrombotic markers such as D-dimer.[103,104] In addition, elevated cardiac troponin is indicative of myocardial damage, which is recurrent in COVID-19 patients and associated with worse outcomes.[104] The increase in the level of brain natriuretic peptide (BNP) is correlated to the presence of diastolic abnormalities, right ventricular enlargement and a more severe prognosis.[104,105]

The hypoxemia in the cardiac tissue, a condition resulting from pulmonary obstruction and consequent reduction in gas exchange is an aggravating prognosis.[106] The cellular damage caused by anaerobiosis, acidosis and ROS are also associated with an increased risk of acute myocardial infarction (AMI).[89,107,108] Moreover, patients with previous heart diseases are more susceptible to cardiac tissue damage—probably due to the inflammation caused by COVID-19—and pre-existing target organ damage due to cardiovascular risk factors also weakens the hearts resistance against the disease.[109–111]

According to Capotosto et al., cardiac complications may also be related to acute pulmonary damage, causing right ventricular failure, pulmonary hypertension (with high mortality rate, up to 46%) or acute pulmonary embolism after disturbances in the coagulation and venous thromboembolism.[32] Additionally, a higher risk of death for patients with COVID-19 who had previous coronary artery disease is observed, as the viral infection might trigger AMI.[112–114]

## 3.2 | Echocardiography in patients with COVID-19

Echocardiography is widely recommended and has become part of the routine for the diagnosis and monitoring of cardiac complications caused by SARS-CoV-2. It is useful to indicate a wide variety of cardiac alterations caused by the infection (Figure 5) and may also suggest degeneration or necrosis of parenchymal cells as well as the formation of hyaline thrombi.[85] Thereby, the technique has a crucial role in the assessment of patients severely affected by the virus and with pre-existing cardiovascular diseases (e.g., heart failure, cardiomegaly, and arrhythmias).[116]

Echocardiography evaluation is fundamental to set individualized therapeutic interventions, such as protective ventilation to the right ventricle, therapy with anticoagulants, pulmonary vasodilation or extracorporeal oxygenation.[117] Therefore, echocardiography enables adequate management of a patient with heart failure and other complications.[118–120] Several findings from the clinical practice suggest this imaging modality when the patient display symptoms compatible with heart failure, high levels of BNP and pneumonia.[120,121] In fact, the echocardiography exam led to therapeutical modifications of 45% of COVID-19 patients due to significant alterations.[122]

As already discussed, US alterations may suggest particularities of COVID-19, such as the extension or evolution of the pulmonary damage caused by the SARS-CoV-2 infection. For example, modest and
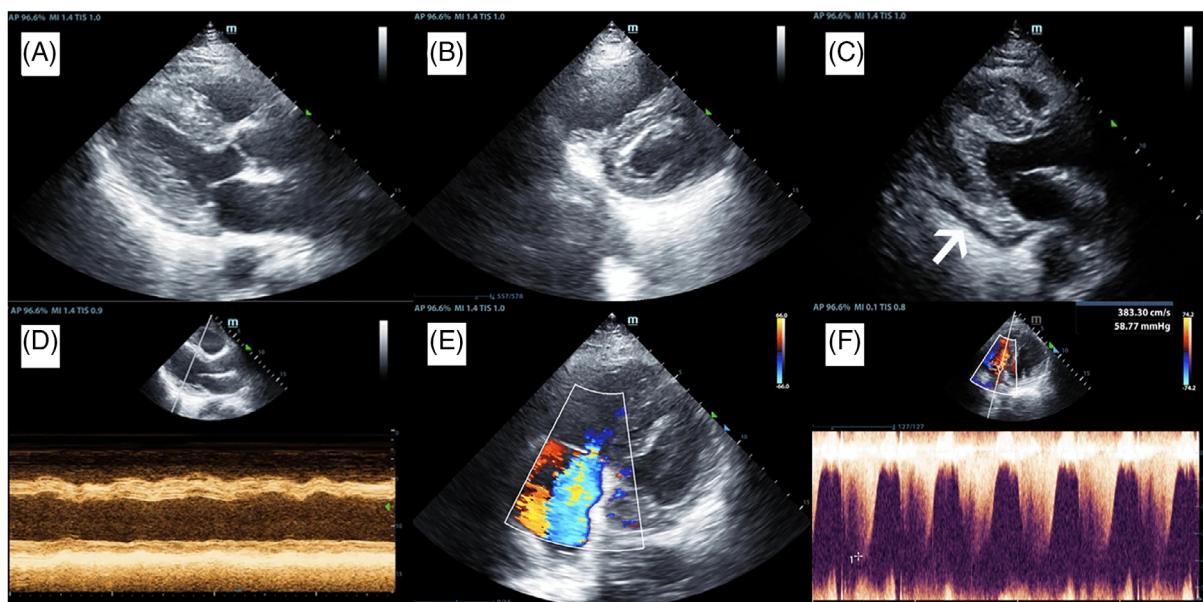
FIGURE 5 Echocardiography images of a patient with COVID-19. The images display the thickening of the left ventricular wall (A), widening of the right ventricle and thickening of the left ventricular wall (B), pericardial effusion (indicated by the white arrow) (C), M-mode graph of the left ventricular base with marked dyskinesia (D), Color Doppler mode showing tricuspid valve regurgitation (E) and continuous Doppler mode of the tricuspid regurgitation indicating pulmonary hypertension (E). Image adapted from[115]
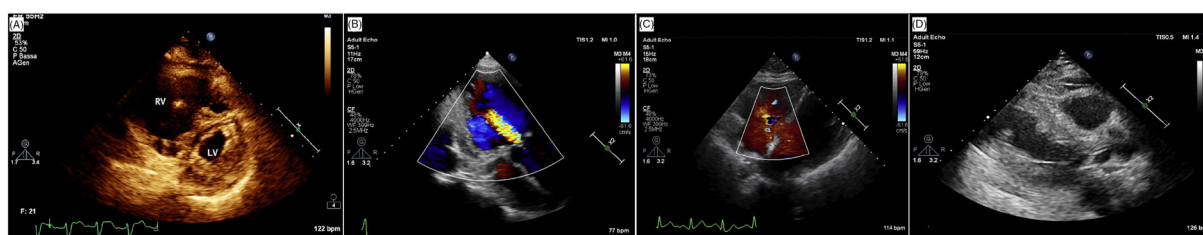
FIGURE 6 Echocardiography of a patient infected with SARS-CoV-2 indicating right ventricular dilatation with minor secondary left ventricular compression due to mechanical ventilation (A). Image adapted from.[118] Echocardiography images highlighting moderate aortic regurgitation (B), right ventricle and tricuspid valve regurgitation (C) and wall thickening with moderate impairment of systolic function and movement abnormality of the anterior basal wall (D). Adapted from[120]

severe viral infections cause local edematous foci in the interstitial pulmonary pleura, seen as "ground glass lesions" on CT and coalescent B lines on PUS.[118] In these situations, echocardiographic findings indicate ventricular interdependence, septal displacement ventricular diastolic, left ventricular hypodiastole and reduced cardiac output—caused by greater respiratory effort and higher ventilation rate per minute.[118,123] Moreover, the necessity of mechanical ventilation causes several functional changes that require close monitoring, such as dilation, tricuspid valve insufficiency, reduced right heart systolic capacity and left heart compression as represented in Figure 6A.[124]

To illustrate the relevance of echocardiography, Zhang et al. reported the use of the technique in several cases throughout 2020. In all their cases, the patients presented fever, pneumonia and high levels of BNP.[120] The cardiac alterations included left ventricular enlargement, reduced ventricular ejection fraction and mitral valve regurgitation (Figures 6B,C). In severe cases, they detected abnormalities in the movement of the anterior walls, apical aneurysm with

thrombosis and AMI. These assessments reinforce the discussion of Guarracino et al. that suggest a greater impairment of the right heart during COVID-19 respiratory complications.[118]

In addition, COVID-19 patients with vein thrombosis exhibit increased risk of thromboembolism and are more susceptible to damage from this pathology.[118,125] Pulmonary embolism might result in pulmonary hypertension, right ventricular enlargement and tricuspid valve regurgitation.[126] According to Anile et al., around 18% of patients who manifest thromboembolic events are referred to the ICU, of which around 40% end up dying.[127]

Thereby, one of the main uses of echocardiography in patients affected by COVID-19 (especially for intubated patients) is the detailing of the right ventricular dimensions and function, usually overloaded due to pulmonary hypertension induced by (i) higher pulmonary vascular resistance, (ii) pulmonary thromboembolism or (iii) the introduction of high positive final expiratory pressures caused by mechanical ventilation.[128]

This monitoring is essential to target the accurate therapy by differentiating between cases of pneumonia with or without the presence of thrombi, cases of biventricular or isolated right ventricular failure and cases with primary or secondary right ventricular dysfunction.[117] Additionally, the assessment of left ventricular function and other cardiac structures (e.g., diameter of the right heart chambers) via US is important for monitoring hemodynamic and thromboembolic phenomena, especially due to recent correlations between progressive tissue dysfunction and the worsening of the disease.[129]

Therefore, the echocardiographic modality displays a paramount importance to evaluate and monitor COVID-19 patients. This technique is relevant for the diagnosis, prognosis and treatment of any patient, as cardiac complications are not necessarily related to previous cardiovascular disease.[115,128] By evaluating the right ventricle, it is possible to avoid worse cardiac (e.g., regurgitation, dilation or decreased ejection fraction) and pulmonary (e.g., hypertension or lung damage) consequences.[117,121]

4 | LIVER

4.1 | Hepatic pathophysiology

The SARS-CoV-2 infection can also affect the liver tissue directly or indirectly. The direct infection is characterized by the invasion and replication of the virus in the hepatocytes[130] via ACE2 interaction, which may progress to acute liver damage.[131] However, the hepatocyte's expression of ACE2 ($\sim$2.6%) is lower compared to cholangiocytes ($\sim$59.7%).[19] Therefore, the most probable infection process starts in the bile duct and spreads to the liver by the breakage of intratissue barriers—via reduction of tight junction proteins, an effect already demonstrated in vitro for claudin 1.[132–134] Furthermore, only 0.03% of hepatocytes from healthy patients co-express ACE2 and TMPRSS,[135] reinforcing the hypothesis of a higher probability of invasion via bile duct. It is important, however, to highlight that this percentage still represents millions of cells susceptible to viral invasion.[136]

The SARS-CoV-2 infection causes several changes in hepatic function tests (TFH; e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gammaGT, albumin and other laboratory and imaging exams).[132,137,138] The number of patients affected by COVID-19 that showed liver impairment ranges between 15% and 78%.[137] More severe cases exhibit liver damage with higher incidence when compared to moderate cases.[139]

The associated liver damage potentializes and affect more severely individuals that are already afflicted with liver disease (e.g., non-alcoholic fatty liver disease [NAFLD] or associated metabolic comorbidities).[132,134,140] For example, the lipogenesis that characterizes steatosis is increased by injury and dilation of the endoplasmic reticulum of hepatocytes caused by SARS-CoV-2.[132] According to Medeiros et al., patients with COVID-19 are 4.7 times more likely to develop hepatic steatosis.[141] Consequently, patients with hepatic steatosis display higher risk to undergo intubation, ICU hospitalization or require dialysis.[142]

The indirect impact of COVID-19 in liver disease is identified by systemic inflammation, thromboembolism, local hypoxia, and drug use (e.g., azithromycin or remdesivir).[132,143,144] Post-mortem histological analyses of the liver revealed the presence of vascular abnormalities, such as partial portal microthrombosis (present in 50% of cases), micro and macrovesicular steatosis (45%), portal inflammation ($\sim$65%) and portal fibrosis (60%).[145] The reason for the predisposition of thrombosis formation is the exacerbated production of pro-inflammatory cytokines, which result in increased inflammation, platelet activation and endothelial dysfunction as previously discussed.[146]

4.2 | Hepatic ultrasonography in patients with COVID-19

US can detect anatomical and/or physiological changes in the liver tissue (e.g., biliary tree obstructions, hepatic steatosis or portal fibrosis). Therefore, it is an important alternative technique for the diagnosis and monitoring of several hepatic comorbidities induced and/or potentialized by COVID-19 since $\sim$37% of patients are affected by viral infection at the abdominal level.[147]

The main findings in the liver US in COVID-19 patients include hepatomegaly, changes in the liver echogenicity (suggesting hepatic infarction or hepatic steatosis), heterogeneity of hepatic parenchyma, signs of necrosis, increased gallbladder thickness and drastic reduction in the Doppler signal imaging in the hepatic arteries and portal vein.[148] All such US alterations may be induced either by direct or indirect SARS-CoV-2 infection.[148]

The increase in cases of portal vein thrombosis (PVT) is an alarming complication observed in COVID-19 cases, which may trigger intestinal infarction and ischemia.[149] Even with prophylactic measures in the ICU, the frequency of thrombotic complications in critically ill patients is around 30%.[150] The cytokine storm associated with patient immobilization and hypoxia is believed to be the cause of PVT and its primary diagnosis is performed via US and Doppler or CT due to initial complaints of abdominal pain.[151]

However, the utilization of liver US usually involves the identification of consequences caused by COVID-19, such as hepatic steatosis and fibrosis.[152] The US B-mode is the most recommended method for diagnosis and classification of hepatic steatosis,[153] an important tool to evaluate the consequences of COVID-19.[138] US provides useful images for the diagnosis and therapy of steatosis, especially for moderate or severely affected liver.[153] Its overall sensitivity and specificity are of 85% and 93%, respectively.[153] However, mild steatosis recognition is still poor, with 60% sensitivity.[154] More precise identification of steatosis may be performed by liver elastography that displays reduced elastic modulus due to the pathological process.[155] Inflammation and consequent elevation of transaminases is directly related to the disease's progression ([154,155]).

Furthermore, a study by Abdelmohsen et al. showed that US diagnosis in COVID-19 patients of hepatomegaly and biliary disease was found in 56% and 41% of imaging exams, respectively.[156] US is further used for the primary analysis of hepatobiliary alterations and,

therefore, may be used in cases of damage associated with cholangiocytes and cholestasis.[148]

5 | CONCLUSION AND PERSPECTIVES

The SARS-CoV-2 multiorgan tropism as well as its indirect effects might be elucidated throughout or after the infection with high sensitivity and specificity by ultrasound imaging. The ultrasonographic analysis of the lungs, heart and liver of COVID-19 patients reveal specific artifacts that may determine the prognosis or therapy. Therefore, ultrasound, previously regarded as a complementary technique in the assessment of these patients, might be included as a key imaging modality in COVID-19. The widespread use of ultrasound imaging, however, still requires standardization to determine specific technical settings (e.g., scanner, probes and ultrasound frequency) as well as to improve accuracy, reproducibility, scoring systems and predictive value in COVID-19 patients.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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