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Cardiovascular imaging evaluation in COVID-19 heart and vascular non-ischaemic involvement

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Abstract: Coronavirus Disease 2019 (COVID-19) is the pandemic challenge of the last year. Cardiovascular involvement is one of the main characteristics of this disease. Due to endothelial damage, consequent phlogosis may increase a thrombosis risk. Cardiac injury may occur in different ways. However, an ischemic involvement of the cardiovascular system is rarely implied. In this regard, direct and indirect effects of COVID-19 are described. Nonetheless, the possible evaluation of the cardiovascular system may require different modalities. The cardiovascular evaluation may be different in emergency compared to critical care, requiring different tools for each setting. The aim of this review is to explore these modalities according to the different involvement of the cardiovascular system.

Keywords: computerized tomography, coronavirus disease 2019, echocardiography, lung ultrasound

1. Introduction

COVID-19 is a pandemic challenge caused by the new coronavirus SARS-CoV-2[1]. It belongs to the Coronavirus family that includes the Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) viruses. The coronaviruses have a preferential tropism for lung cells[2]. SARS-CoV-2 enters the host cell using angiotensin-converting enzyme II (ACE2) as cell surface receptor[2]. Acute COVID-19 patients show a wide range of clinical manifestations, ranging from asymptomatic or mildly symptomatic (common cold), up to severe, often fatal disease. The latter form usually presents with bilateral interstitial pneumonia and moderate to severe oxygen desaturation and hypoxia. Many patients develop Respiratory Failure (RF) and Acute Respiratory Distress Syndrome (ARDS)[3], requiring prompt admission to intensive care unit (ICU). Since an acute cardiac involvement of COVID-19 infection[1] was observed, it has been hypothesized a direct effect of the virus on the myocardium and heart vessels[2,3]. There are many reports about the role on COVID-19 in spurring a diffuse
endothelial inflammation[2,4,5] as a result of virus tropism for ACE2. This enzyme is expressed by type II pneumocytes[6], which is anatomically close to the lung vascular network and is typically described to be hyperplastic in samples from COVID-19 patients[7–9]. The hyperplasia of endothelial cells is likely to be caused by lung tissue ischaemia due to small vessel congestion caused by inflammatory cells (so called “immunothrombosis”); a thrombosis of large vessels may occur as well[10]. Endothelial dysfunction has been suggested being an important pathophysiological event in infections by other coronaviruses, which can directly infect endothelial cells[11–14].

SARS-CoV-2 directly infects vascular endothelial cells and leads to cellular damage and apoptosis, thus decreasing the antithrombotic activity of the normal endothelium[10,15]. Alveolar damage, vessel wall oedema, hyaline thrombi, microhaemorrhage and diffuse thrombosis of peripheral small vessels have emerged as key features of COVID-19, all contributing to respiratory failure[16–18]. Endothelial cells of lung blood vessels can be activated by the high levels of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and ferritin in severe COVID-19[19,20]. The role of inflammation has been also related to prognosis in COVID-19[21,22] and to cardiovascular involvement. Recent in-vitro studies have related the myocardial involvement to a direct SARS-CoV-2 action on cardiomyocytes in the form of diffuse cardiovascular involvement[23,24].

Demises related to cardiovascular disease increased during COVID-19 pandemic in both swab negative[25] and positive patients[26]. However, COVID-19 patients with cardiac involvement have a high mortality rate[27,28].

This review focuses on images that have proved to be very useful for the evaluation of cardiovascular involvement in the COVID-19 patients.

2. COVID-19 cardiovascular involvement

Cardiovascular disease is the major comorbidity of COVID-19 patients, and it is closely related to the disease severity. It is likely related to lung failure and COVID-19 disease progression[27,29]. However, cardiovascular involvement may arise also in children,[30] indicating that the heart involvement should be described also in patients without cardiovascular risk factors. The myocardial involvement may be considered as a part of the COVID-19 disease. In many patients, the initial clinical manifestation of COVID-19 presents with cardiovascular symptoms such as heart palpitations and chest tightness.[31–33] COVID-19 can also exacerbate a preexisting cardiovascular disease and cause new cardiovascular disorders, as showed in several studies[1,34]. Described mechanisms of myocardial injury include imbalance of oxygen supply–demand, direct viral myocardial invasion, inflammation, coronary plaque rupture with acute myocardial infarction, microvascular thrombosis, and adrenergic stress. In COVID-19 patients, the myocardial injury ranges between 9.6 and 46.3%[35]. Myocardial injury can be detected in about 25% of hospitalized patients affected by COVID-19, and is associated with an increased risk of mortality[36]. It causes worse prognosis, higher mortality rate (RR 5.54, 95% CI 3.48–8.80), and more ICU admissions (RR 3.78, 95% CI 2.07–6.89)[35].

The high inflammatory burden due to cytokine release can significantly hit the patients’ cardiovascular systems[37–40]; it can induce arrhythmias, myocarditis, coagulation abnormalities with venous thromboembolism, Takotsubo cardiomyopathy, Kawasaki-like disease and multisystemic inflammatory syndrome,[41] leading directly or indirectly to cardiogenic shock[42]. SARS-CoV-2 uses the ACE2 as the receptor to enter the host cell[43,44], that requires its binding to the viral spike protein (Fig. 1). The spike protein priming is mediated by the host cell serine proteases TMPRSS2, cathepsin B and cathepsin L[45,46]. TMPRSS2 is present on lung cells that express ACE2 and is mandatory for viral entry. Additionally Nicin et al.[47] showed that cardiac cells, (which include cardiomyocytes, pericytes, fibroblasts, endothelial cells and leukocytes from patients with heart failure and reduced ejection fraction or with aortic stenosis), hugely express ACE2. The entry of SARS-CoV-2 into the lungs and heart could be facilitated by an underlying renin-angiotensin system (RAS)-related, pathophysiology of the cardiovascular disorders
and chronic use of pharmacologic RAS inhibitors which both induce an increase of the ACE2 levels\[48\]. Thus, the infection may have a direct impact on cardiovascular diseases[41]. However, ACE2 reduces the levels of angiotensin II, a potent proinflammatory agent in the lungs, which can contribute to lung injury. RAS inhibitors may block the production or function of angiotensin II and potentially increase the levels of ACE2, thereby indirectly inhibiting angiotensin II[49].

Figure 1: COVID-19 heavily affects patients' cardiovascular system: it can induce direct damages, leading to arrhythmias and myocarditis, and indirect damages, mediated by cytokine storm, systemic vasculitis and vascular thrombosis. The indirect damage contributes to the development of myocarditis and leads to Kawasaki-like Disease and Multisystem inflammatory syndrome, coagulation abnormalities and venous thromboembolism, and Takotsubo cardiomyopathy. ACE2: Angiotensin Converting Enzyme 2; IFN-γ= interferon-γ, MCP1= monocyte chemoattractant protein 1, MIP1-α= macrophage inflammatory protein 1-α; ROS= Reactive Oxygen Species; TMPRSS2: Transmembrane protease, serine 2; TNF-α= tumour necrosis factor-α;
2.1 Myocarditis

SARS-CoV-2 infection affects the myocardium in the form of myocarditis (Fig. 1). As mentioned before, ACE2 is used by SARS-CoV-2 as receptor to initiate the COVID-19 infection, playing an important role in viral pathogenicity. The receptorial machinery may lead to a down-regulation of ACE2. This down-regulation produces toxic overaccumulation of angiotensin II and induces fulminant myocarditis, similar to acute respiratory distress syndrome[41]. Other studies suggest that angiotensin II plays an important pathophysiological role in viral myocarditis.[50] An extremely robust cytokine storm given by interleukin-1 (IL-1), IL-2, IL-6, IL-8, TNF-α, and MCP-1 is also the core pathophysiological mechanism of fulminant myocarditis[19,34,51].

Severe myocarditis with reduced systolic function has been reported after COVID-19.[52,53] Some patients died of fulminant myocarditis or virus-activated “cytokine storm syndrome”, suggesting a high inflammatory burden and a possible increase in myocarditis-related cardiac events.[54] Furthermore, sporadic autopsy cases suggest infiltration in the myocardium of interstitial mononuclear inflammatory cells, especially when fulminant myocarditis occurs.[9,55]

Guo et al. reported that 28% of 187 patients hospitalized with COVID-19 had an acute myocardial injury, defined as elevation of troponin T. Patients with high troponin T levels also had higher inflammatory biomarkers, such as leukocytosis, lymphopenia, D-dimer, C-reactive protein, and pro-calcitonin.[56,57] Thus, myocardial injury is mostly associated with infection-related myocarditis. Ruan et al.[34] found that, on a sample of 150 patients with laboratory-confirmed COVID-19, the ones who died had higher levels of troponin, myoglobin, C-reactive protein, serum ferritin, and IL-6: among 68 deaths, 7% were attributed to myocarditis with circulatory failure and 33% were cases in which myocarditis might have played a contributing role in the patient’s demise.

2.2 Coagulation abnormalities and venous thromboembolism

COVID-19 patients are more likely to be exposed to an elevated risk of arterial and venous thromboembolism (VTE) due to a state of endothelial dysfunction, vascular inflammation, and hypercoagulability associated with the SARS-CoV-2 infection.[58] Patients have abnormal coagulation parameters, such as prothrombin time, fibrin degradation products, activated partial thromboplastin time, and D-dimer. In particular, increased levels of fibrin degradation products and D-dimer are closely associated with poor prognosis.[58,59] In a cohort of 1099 Chinese patients, 60% had severe illness and 46% had elevated D-dimer levels (>0.5 mg/l).[60] Other studies demonstrate that hospitalized patients with severe COVID-19 disease have abnormal coagulation parameters[59,61]. The increased risk of venous thromboembolism poses a considerable challenge to caring for 31-40% of critically ill COVID-19 patients.[62,63]

Tang et al.[59] showed that fibrin degradation products and D-dimer levels were significantly higher in COVID-19 non-survivors compared to survivors, and 71.4% of non-survivors met clinical criteria for disseminated intravascular coagulation (DIC) during the disease course. The DIC patients had high venous thromboembolism rates, elevated D-dimer levels, high fibrinogen levels, low antithrombin levels, and pulmonary congestion with microvascular thrombosis and occlusion. Fibrin deposition in the pulmonary microvasculature contributed to ARDS in patients with concomitant diagnoses of DIC[64].

A severe inflammatory state with hypercoagulability instead of acute DIC was described by Panigada et al. among 24 COVID-19 patients hospitalized in ICU [65]. They described increased C-reactive protein, normal or increased platelet count, near-normal prothrombin time and activated partial thromboplastin time, increased fibrinogen, and dramatically increased D-dimer. Factor VIII and von Willebrand factor increased, as well as protein C, while antithrombin marginally decreased.[65]
Moreover, the hypercoagulable changes of microthrombi are noted in pulmonary capillary vessels and are thought to represent megakaryocytes’ overexpression and platelet adhesion.

Thus, current recommendations are favoring platelet inhibitors. Hence, patients with severe respiratory failure, bilateral pulmonary infiltrates and D-dimer >3 times the upper limit of normal were treated with antiplatelet therapy. The therapy usually includes acetylsalicylic acid, clopidogrel, tirofiban, and fondaparinux, which showed to be effective in improving hypoxemia and successful in weaning ventilator.[66]

2.3 Takotsubo cardiomyopathy

Takotsubo cardiomyopathy (TCM), also known as stress-induced cardiomyopathy, may be associated with the SARS-CoV-2, considering its increased incidence in the COVID-19 patients[67] (Fig. 1). It is characterized by a transient reversible wall motion abnormality of the left ventricle in the absence of significant obstructive coronary artery disease, with acute left ventricular dysfunction usually in the setting of physical or emotional stress[68]. Apical TCM is the most common form (>80%) followed by the midventricular form[68]. It is typically associated with intense emotional or physical stress, and most commonly seen in women (>90%)[69]. There is very little literature on TCM pathophysiology, although conditions of acute stress leading to catecholamine surge have been suggested as pathophysiological mechanisms[70]. Severe systemic inflammation and cytokine storm could lead to acute stress and injury, evident from elevated markers of myocardial injury such as C-reactive protein, pro-calcitonin, creatine kinase, myoglobin, and N-terminal pro b-type natriuretic peptide (NT-proBNP).[71] “Cytokine storm syndrome” in COVID-19 patients overlaps cytokine release syndrome;[72] it has been observed that cytokine release syndrome is accompanied by catecholamine surge[73], which can predispose to the TCM.

Therefore, the association between TCM and COVID-19 may be explained by potential pathophysiological links between the two conditions. Though these direct connections are not fully understood, they may be attributable to three factors: the overactive immune response from cytokine storm, the sympathetic nervous system surge, and the development of microvascular dysfunction noted in SARS-CoV-2 infection.[67]

2.4 Kawasaki-like disease and multisystemic inflammatory syndrome

SARS-CoV-2 is associated with sharp increase in the incidence of Kawasaki-like Disease (KL)[74–76] (Fig. 1). The Kawasaki disease is a systemic vasculitis with predilection for coronary arteries mostly affecting children <5 years of age. Although it may be a self-limited febrile illness, it is the most common cause of acquired heart disease in childhood in Japan, North America, and Europe[77,78]. Furthermore, coronary artery aneurysms (CAAs) from the Kawasaki disease affect patients in adult life, especially those with missed diagnosis or delayed treatment, placing them at risk for coronary artery thrombosis, myocardial ischemia and infarction, and accounting for 5% of acute coronary syndromes[79]. The main features are high fever, extensive skin rash, cheilitis with red, cracking, bleeding lips and strawberry tongue, conjunctivitis, erythema and induration of hands and feet, subsiding with periungual peeling, cervical lymphadenopathy, and coronary artery dilation/aneurysms[80]. The causes of Kawasaki disease is unknown, but it is generally accepted that viral agents can trigger it, as seasonal peaks of the disease parallels with seasonality of common respiratory infections.[80]

SARS-CoV-2 can infect endothelial cells and cause endothelial cell damage and thrombosis. In children presenting with chilblains, skin biopsy showed endothelial cell damage, thrombosis and the coronavirus in endothelial cells.[81]

COVID-19 was initially reported as affecting children only mildly, as showed in an epidemiologic survey including 2135 SARS-CoV-2-exposed children according to the Chinese Centre for Disease Control and Prevention as well as in other studies[82–85].
Later cases series reported outbreaks of a severe multisystemic inflammatory syndrome in children exposed to the virus during the progression of the COVID-19 pandemic in Europe and USA. This syndrome has been called “Multisystem Inflammatory Syndrome In Children” (MIS-C) by the World Health Organization (WHO) and the Centre for Disease Control (CDC).[86] It shares features with staphylococcus aureus toxin-mediated toxic shock syndrome[26] and atypical Kawasaki disease[87,88]. MIS-C is a cytokine storm syndrome induced by SARS-CoV-2 with very high inflammation markers: C-reactive protein, pro-calcitonin, neutrophilia, lymphopenia, pro-inflammatory cytokine levels, mainly IL-6 and IL-10, soluble IL-2 receptor, ferritin, and D-dimers[89,90], and frequently fulfils criteria for macrophage activation syndrome (MAS) of children with juvenile idiopathic arthritis/Still’s disease.[91] SARS-CoV-2 binds to ACE2 leading to excessive angiotensin II signaling, which activates STING pathway. STING is a cytosolic DNA sensor and adaptor protein in type I Interferon (IFN) and nuclear factor (NF)-κB pathway; an over-activation of the STING pathway leads to hyper-coagulopathy through release of IFN-β and tissue factor by monocytes-macrophages.[92] MIS-C is characterized by multi-organ dysfunction, high fever rash hypotension, gastrointestinal symptoms, conjunctivitis, and mucosal changes, including also high frequency of myocarditis and shock from either acute myocardial dysfunction or systemic hyperinflammation. As a result, cardiac manifestations, including myocardial and coronary involvement, are frequent in children with COVID-19 related Kawasaki-like disease and/or MIS-C, and need to be carefully identified and monitored over time.

2.5 Arrhythmias

Arrhythmias are another example of common cardiovascular problems in patients with COVID-19. High prevalence of arrhythmias in patients with or without a prior cardiovascular disease might be partly attributable to metabolic disarray, hypoxia, neurohormonal or inflammatory stress in the setting of the viral infection. Myocardial injury is associated with impairment of cardiac function[57]. Specifically, fulminant myocarditis with cardiogenic shock is associated with atrial and ventricular arrhythmias[49,52,93], considering that a new onset of malignant tachyarrhythmias in the setting of troponin elevation should raise suspicion for an underlying myocarditis[94,95]. In a cohort of 137 COVID-19 patients, heart palpitations were part of the presenting symptomology in 7.3% of them[49], which indicates the possibility of arrhythmia caused by the SARS-CoV-2 infection. Fatal outcomes of COVID-19 also have a significant association with myocardial injury and cardiac disfunction, leading to arrhythmias[57]. Wang et al.[96] reported that among 138 patients hospitalized with COVID-19, cardiac arrhythmia was revealed in 16.7% and contributed to the transfer to the ICU of 44% of the patients. Of note, in patients with COVID-19 the manifestations related to arrhythmia may be masked by respiratory symptoms.

3. Cardiovascular imaging in emergency

Given the need for the healthcare system to evaluate a huge number of patients with suspected COVID-19 infection, in order to better manage resources and optimise therapy for patients in the right care setting, it is essential to employ a rapid execution diagnostic method that is both free of detrimental effects and contraindications, and repeatable. Ultrasound meets all these requirements, but other methods such as CT, may be evaluated when establishing the diagnosis and the clinical management.

3.1 Point-of-care ultrasonography as first approach

Point-of-care ultrasonography (POCUS) has demonstrated to be a ubiquitous and quick way to detect pulmonary changes[97]. Since 2020, the use of lung ultrasonography (LUS) in COVID-19 has received much attention from specialists as it has the advantage of identifying and classifying
disease severity quickly and easily. Even if none of the LUS features is pathognomonic for COVID-19, there has been a great deal of evidence to support its clinical value. LUS may play a complementary role in the work-up of COVID-19 because in its setting it can be used to detect not only signs of pulmonary involvement, but also the disease progression or regression. However, due to the huge cardiovascular involvement in SARS-CoV-2 pneumonia, a comprehensive lung-cardiovascular assessment is needed, especially in the ICU setting.

A possible useful algorithm for emergency evaluation is the A.B.C. algorithm. It is based on the three step process of cardiac resuscitation protocol: Airway (A), Breathing (B), and Circulation (C)[97]. The airway evaluation is based on the POCUS examination of no obstruction to patient airflow. Endotracheal intubation is the fundamental procedure for providing invasive mechanical ventilation, hence ultrasound represents a good method to confirm the correct endotracheal tube placement. Scanning the anterior cervical area above the sternal notch and under the cricoid cartilage with the linear transducer placed in a transverse position gives confirmation of the correct placement of the endotracheal tube also in obese patients [98]. The correctly placed endotracheal tube provides a hyperechoic shadow (comet sign)[99]. An indirect way of assessing the correct placement of an endotracheal tube is scanning for lung sliding during ventilation. After the airways, dyspnoea assessment is mandatory. The BLUE protocol[100] is a standardized diagram for the rapid identification of the causes of dyspnoea, that can easily be used in imaging diagnosis of coronavirus disease (Fig. 2). It starts with checking for anterior lung sliding evaluating pleura. Presence of sliding excludes pneumothorax.
The pleura is a hyperechoic structure. Horizontal repetitions of the pleural line, the A-lines, represent a reverberation artifact and are usually present in the normal lung. B-lines are hyperechoic “comet tail” artefacts that start from the pleura and move with respiratory movements. The lung sliding sign demonstrates that the lung is ventilated. The association of the A profile with phlebothrombosis favours the diagnosis of pulmonary embolism [101].

The main findings in lung ultrasound in interstitial syndromes are B-lines [102]. The presence of B-lines can refer to pneumonitis, pulmonary contusion, pulmonary infarction, pleural disease or neoplasia. B-lines are present in patients with SARS-CoV-2 and become confluent with the disease progression [102]. According to the M-BLUE protocol, twelve areas (bilateral superior BLUE point, M point, PLAPS point, diaphragm point) are scanned for each patient [100]. A semi-quantitative scoring system is employed (Fig. 2). Therefore, a total score for the twelve regions of 0 is normal, and 36 would be the worst [100,103].

Other findings in the SARS-CoV-2 patients are: the pleural line thickening that implies a thick hyperechoic pleural line and the sub-pleural consolidations. The normal aerated lung tissue is replaced by tissue that mimics the aspect of other organs, for example liver, this being called “the tissue-like sign” [104]. Other findings can confirm
consolidation. The differentiation between lung consolidation and atelectasis can be done using the lung pulse sign, which is the transmission of heart beats at the pleural line through a non-inflated lung. This sign is present if the patient has atelectasis\cite{102,104,105}. The latter is an important reversible cause for breathing insufficiency and total lung atelectasis with mediastinal shift, and can be diagnosed using ultrasound or chest radiography. \textit{Pleural effusions} are rare in SARS-Cov-2 patients, though frequent in other critically ill patients\cite{102}.

SARS-CoV-2 can determine cardiac events related to the infection\cite{28,106}. Profound hypoxemia underlying pneumonia together with tachycardia might result in chest pain and electrocardiographic changes suggestive of myocardial involvement\cite{106}. All these events may induce an acute cardiovascular failure in COVID-19 patients.

Therefore, echocardiography should be performed on admission in patients with COVID-19 disease and should be repeated\cite{97,107} periodically.

3.2 Heart ultrasound in emergency patients

The evaluation of differential diagnosis for dyspnoea includes also assessment of heart ultrasound\cite{108}. Transthoracic echocardiography (TTE) is an easy diagnostic tool for early assessment of the cardiac function, but the choice of the echocardiography type (transthoracic-TTE vs. transesophageal-TEE) is closely related to the clinical conditions of each patient. Ventilation represents a key therapy also in emergency settings and in patients on spontaneous breathing and/or non-invasive ventilation, while TTE is more feasible and it can provide an answer for most clinical inquiries.

3.2.1 Left heart evaluation

Global cardiac function might decline in patients with viral infections. A global view of the heart mechanics is obtained through a subcostal approach or an apical four-chamber view (Fig. 3). Through the use of these windows, the diameters of the heart chambers and motion abnormalities are rapidly assessed\cite{107}. The left ventricle (LV) function, seen using the ejection fraction, is important when assessing a patient with shortness of breath, chest pain or sudden drop in arterial blood pressure, aiming at facilitating fast and accurate clinical decision making or therapies\cite{109}. 


Figure 3: Left heart evaluation needs a complete echocardiography evaluating parasternal long-axis (A) and apical 4 chamber (B) views. Using pulsed wave Doppler trans-mitral flow is evaluated (C). The apical 4 chamber view allows to perform tissue Doppler imaging analysis (D), able to make a doppler spectral analysis of the myocardial contraction velocity wave (E). A complete evaluation also includes the Speckle tracking evaluation to obtain the longitudinal strain (F). In particular the showed image was obtained in a 28-yr old girl with a COVID-19 myocarditis.

LV ejection fraction should be measured and clinically interpreted considering also the dosage of inotropic drugs if administered. Valvular (mitral and aorta) diseases should also be assessed, especially at first echocardiogram. The presence of valvular disease, even when it is moderate, is able to affect the course and severity of the lung disease and, obviously, therapies (especially fluid administration)[110].

In a prospective international survey, cardiac abnormalities were described in COVID-19 patients[111]. Out of 1216 patients, about 55% had abnormal echocardiogram, in most cases related to LV abnormalities (39%) due to new myocardial infarction (3%), myocarditis (3%), and TCM cardiomyopathy (2%). A severe cardiac disease was described in about 15% patients. Those findings were reported in both with and without a pre-existing cardiac disease, but only in the latter case echocardiographic abnormalities are closely related to the severity of COVID-19 symptoms[111].

In another single-centre study with TTE, 90 patients hospitalized for COVID-19 showed both severe and non-severe[112] echocardiographic features. Among the severe group patients, the right ventricle (RV) and the LV diameters were larger, while LV ejection fraction (LVEF) was decreased, and more frequent pericardial effusions were seen[112].

However, these alterations may not be permanent. In fact, in a short-term follow-up cross-sectional study, neither abnormalities were identified in the heart of COVID-19 survivors, nor cardiac differences were detected between patients with different severity of illness, suggesting that patients who recover from COVID-19 do not have considerable cardiac sequelae[113].
3.2.2 Right heart evaluation

Right heart failure or dysfunction can occur due to pre-existing pathologies such as chronic obstructive pulmonary disease, obstructive sleep apnoea, pulmonary hypertension or acute onset of new disease in the critically ill patients[107,109,114,115]. In addition, ventilation can be an important factor for right heart decompensation. Critically ill patients have higher risk of developing pulmonary embolism (PE), and current data suggest the high prevalence of embolic events in SARS-CoV-2 infections[15].

Cardiac ultrasound might demonstrate RV enlargement in such patients, the causes being PE, an increased pulmonary vascular resistance due to hypoxia or to aggressive non-invasive ventilation (NIV) [106,114,116]. Although transthoracic cardiac ultrasound is not the gold standard to diagnose PE, in the pandemic setting it might be a safe measure to complete the diagnosis, allowing fast treatment[106]. Signs that may be found in a patient with PE are RV hypokinesis with paradoxal septal movement and even akinesia of the RV mid free wall with normal motion of the apex[106,109,116]. In some cases of massive PE, the LV may be underfilled and hyperdynamic. RV to LV end-diastolic ratio higher than one should guide towards RV failure[106].

The echocardiographic assessment of the RV represents a pivotal element in the understanding of current COVID-19 disease status and in monitoring the disease progression, because the RV is directly and indirectly involved in the disease course.

The RV direct involvement occurs quite often. Due to interstitial pneumonia and pulmonary hypoxic vasoconstriction, the RV increases afterload. Ventilatory therapy (both non-invasive and invasive) affects RV dimension and function by influencing heart–lung interactions.

Though RV size can be assessed visually by the “eyeball” method in the short-axis and 4 chamber views (Fig. 4), it is advisable to quantitatively evaluate it by the RV/LV ratio end-diastolic area. The RV/LV area ratio is measured at end-diastole by tracing the areas of the two chambers in the apical four-chamber view on TTE or the mid-esophageal four-chamber view on TEE. In a RV focused apical four-chamber view, RV dilatation is defined by a diameter >41 mm at the base and >35 mm at the midlevel.[117] The RV dilatation/dysfunction is a common finding being detected in 39% of patients, and a small subset of patients who clinically deteriorated (20%) all showed the RV function deterioration[106].
Figure 4: Right heart evaluation need an apical 4 chamber view (A) useful to detect the tricuspid regurgitation velocity (B) and the tricuspid annular plane excursion (TAPSE) (C). The parasternal short-axis view (D) allows another possible evaluation of tricuspid regurgitation as well as the pulmonary artery analysis (E). A right ventricle longitudinal strain (F) is possible in advanced imaging from an apical 4 chamber view.

RV wall thickness is measured in diastole, from the subcostal view, using either M-mode or two-dimensional imaging. RV hypertrophy is identified by thickness >5 mm. Whenever RV wall thickness >5 mm is detected on ICU, it may indicate a chronic RV overload due to a previously unknown lung disease such as a chronic obstructive pulmonary disease. In a mechanically ventilated patient, RV hypertrophy may be caused by the mechanical ventilation itself, since the RV is able to thicken in response to increased intrathoracic pressure.[118]

The RV-right atrial (RA) pressure gradient can be estimated in presence of tricuspid regurgitation by the modified Bernoulli equation using the peak regurgitant jet velocity evaluated by continuous-wave Doppler[117]. In COVID-19, the development of increased systolic arterial pressures may be multi-factorial. Hypoxic pulmonary vasoconstriction is probably the main factor[119]. Secondly, lung disease contributes to alterations in pulmonary circulation, similarly to the role of PEs/thrombosis. Finally, ventilations are known to affect RV afterload[120,121]. In this setting, the RV has to face an augmented afterload, so it seems advisable to monitor pulmonary arterial pressure by means of echocardiography to early detect RV dilatation/dysfunction in these patients.

In a retrospective study on 112 COVID-19 patients with mild disease, Deng et al.[122] reported an incidence of pulmonary hypertension in 13%. On the contrary, in a series of 28 patients with severe disease[123] the systolic pulmonary arterial pressures were increased in all patients on admission but significantly decreased during hospitalization. In patients with mild disease, those with pulmonary hypertension had more severe lung involvement[106,119], and more severe patients had shorter pulmonary accelerating time, suggesting increased RV afterload[119].

In non-ventilated patients, Inferior vena cava diameter (IVC) and its collapse can be considered a good estimate of RA pressure. It is well known that IVC diameter <2.1 cm that collapses >50% with a sniff suggests normal RA pressure (3 mmHg), while an IVC diameter >2.1 cm that collapses <50% suggests high RA pressure of about 15 mmHg. In
patients with RV dysfunction, the IVC collapsibility should be interpreted with caution, considering also its trend and central venous pressure[117].

Tricuspid lateral annular motion (tricuspid annular plane systolic excursion, TAPSE) is an index of RV function. This parameter “captures” RV longitudinal motion and requires a proper alignment of M-mode cursor with the direction of RV longitudinal excursion from the apical view (Fig. 3). RV dysfunction is indicated by a TAPSE <15 mm being associated with poor prognosis in critically ill patients.

RV overload has also a prognostic role. In a prospective study on 94 consecutive patients, coupling RV function to the pulmonary circulation was evaluated as TAPSE to systolic pulmonary artery pressure (PASP) ratio[116]. The authors found that in non-survivors, PASP was increased while TAPSE decreased, and the TAPSE/PASP ratio was lower than in the survivors. The latter parameter results also as the only independent predictor of mortality (cut-off 0.635 mm/mmHg) next to P/F value at univariate/multivariable analysis[116].

3.3 Screening of deep vein thrombosis

Compressive ultrasound (CUS) for DVT[124] should be used for patients hospitalized for COVID-19 either with clinical symptoms of deep vein thrombosis (DVT), or with DVT clinical probability (Wells score >2) or with elevated D-dimers levels without clinical symptoms.

4-point CUS has been widely used both in USA and Europe, enabling the emergency physician to detect DVT with a non-invasive method of compression, analysing the absence of proximal venous incompressibility at the four points (femoral and popliteal, right and left)[110]. The required equipment consists of a standard ultrasound machine (with or without color doppler), which is typically a high frequency linear probe (7 to 10 MHz) optimally combined with a low-frequency convex probe (2 to 5 MHz). The ultrasound is carried out in mode B in a transverse plane. This compression test is repeated every 2 cm over a 12 cm segment at each level. The standard criterion for assessing vein permeability is its level of compressibility. Localization of the femoral vein is achieved in a transverse plane at the sapheno-femoral junction (“Mickey Mouse ears”), where the common femoral artery, common femoral vein, and great saphenous vein come together. The popliteal vein is localized in the popliteal fossa, in a posterior plane to the popliteal artery, and therefore it is more superficial and closer to the ultrasound probe when using a posterior approach. Total or partial incompressibility of the vein (indirect sign) is the only parameter required for a DVT diagnosis. The 4-point ultrasound is simple, safe, available, inexpensive, reliable (with a sensitivity and specificity of 90-100%) and rapid (between 3 and 5 min), and reduces the potential exposure to the virus limiting the risk of contamination.

In a prospective observational study, consecutive patients with a diagnosis of COVID-19 who developed PE were ultrasound screened for DVT in the lower extremities[124]. DVT was diagnosed in the emergency department in about 7% of patients who had central and bilateral PE. However, patients without DVT had higher median D-dimer levels, suggesting that PE should mainly result as local thrombo-inflammatory syndrome and not a real thromboembolic event.

3.4 Chest computerized tomography in COVID-19 emergency

Computed tomography (CT) is highly sensitive for diagnosis of patients with COVID-19, but it might not always be soon available. Several studies have underlined the importance of imaging in diagnosing COVID-19[125]. The typical CT feature in acute COVID-19 infection is ground-glass opacities (GGO) or mixed GGO, consolidation and vascular enlargement; moreover the lesions are more likely to display a peripheral distribution and bilateral involvement and are generally lower-lung predominant[125].
Next to GGO, the usually evaluated parameters in chest CT scans are: increased opacity of the lung, with preservation of bronchial and vascular margins, consolidation, crazy-paving pattern, cavity, and bronchial dilatation[126,127]. Vascular involvement is indicated by vessel dilatation, an increased diameter of vessel within or near opacifications clearly larger compared to vessels of the same generation in healthy lung tissue[126].

Thromboembolic complications with or without the presence of DVT are frequent and underestimated events. The diagnosis of PE mainly relies on CT scanning, but ultrasound is a diagnostic alternative for special clinical settings[108]. Performed as contrast-enhanced CT pulmonary angiography, it can detect or rule-out the PE: in fact, emerging evidence describes an increased hypercoagulability in COVID-19 patients.

The overall prevalence of acute PE diagnosed through CT ranged between 14-30%[62,128,129]. Noteworthy, despite prophylactic or therapeutic anticoagulation, the rate of PE in severe patients admitted to hospital ranged between 25–26%, supporting the hypothesis of a correlation between the severity of the disease and the prothrombotic phenotype of severely ill patients[130,131]. Four types of PE (subsegmental, segmental, lobar and central) were defined on the basis of the location of the thrombi, considering the most proximal pulmonary arterial branch involved[124,132]. Interestingly, pulmonary emboli had more frequent segmental distribution (51%) rather than lobar (31%) or central (13%) ones.[133] CT pulmonary angiography (CTPA) can assess not only the presence of pulmonary embolus but also the severity of the embolus as well as heart function and strain on the RV.

CTPA is becoming the standard of care for the evaluation of patients with suspected PE. In acute PE the diagnostic criteria include: arterial occlusion with failure to enhance the entire lumen due to a large filling defect; possibly enlarged artery compared with adjacent patent vessels[129,131]. A partial filling defect surrounded by contrast material produces the “polo mint” sign on images acquired perpendicular to the long axis of a vessel and the “railway track” sign on longitudinal images (Fig. 5). Moreover, even a peripheral intraluminal filling defect forms acute angles with the arterial wall. Peripheral wedge-shaped areas of hyper-attenuation that may represent infarcts, along with linear bands, have been demonstrated to be statistically significant ancillary findings associated with acute PE. Chronic PE can manifest as complete occlusive disease in vessels that are smaller than adjacent patent vessels. Other CTPA findings in chronic PE include: evidence of recanalization, webs or flaps, and partial filling defects that form obtuse angles with the vessel wall[127,134,135].
Figure 5: CT scan is able to identify both gross pulmonary embolism (A,B) and tinier obstructions in subsegmental artery (C,D). Embolism (Circles) is not related to site of pneumonia but to endotheliitis and not to pulmonary phlogosis (Triangles).

4. Cardiovascular imaging in critical care

COVID-19 gives severe lung involvement and hemodynamic alterations that therefore induce commonly cardiovascular complications showing a wide spectrum of severity[136]. Clinical studies and several evidences show that patients with severe COVID19, as critically ill patient, generally are affected by the “cytokine storm” which plays a crucial role in the disease progression and severity, and in influencing the COVID-19–associated acute respiratory distress syndrome (ARDS) and multiorgan dysfunction syndrome[137,138]. Cardiac involvement may occur in critically ill patients, either as a consequence of mechanical ventilation and a direct effect of SARS-CoV2 virus[138–140]. However, different approach should be used in cardiovascular evaluation of ICU patients.

4.1 Cardiovascular evaluation in different COVID-19 phenotypes

Direct cardiac involvement may present as a dilated cardiomyopathy, as a severe decrease in ventricular systolic function and pericardial effusion in case of viral myocarditis, as localized wall motion abnormalities, as a global ventricular depression in case of myocardial infarction with ST-elevation[141]. In patients with COVID-19 pneumonia, it may also occur an indirect involvement of the heart, that differs between two pulmonary phenotypes[142]: the L phenotype, which shows preserved compliance, and the H phenotype, with high pulmonary elastance. The cardiac abnormalities related to the previous phenotypes should be identified. In the L phenotype, during the setting of protective ventilation, less severe right heart impairment would be expected because the
pressure to deliver tidal volume should be lower. In this kind of dyspnoeic patients, either spontaneously breathing or on non-invasive respiratory support, the cardiac ultrasound may reveal ventricular interdependence elicited by the increased respiratory effort, causing considerable pleural negative pressure and showing diastolic ventricular septal shift, leading to left ventricular hypodiastole and reduced stroke volume. In contrast, repercussion on the right heart is more probable in the H phenotype because of positive pressure of mechanical ventilation. Hypoxic vasoconstriction of pulmonary circulation and superimposed pulmonary thromboembolic events may further precipitate the above said effects. The cardiac ultrasound exam reveals cardiac insults directly connected to ventilation. In this case, the previously reported alterations secondary to mechanical ventilation are found, with particular involvement of the RV, leading to ventricular dilation, tricuspid insufficiency, reduced systolic right heart function, and possible secondary left heart compression with a consequent reduction of the stroke volume[143]. A ventilator-induced heart dysfunction in patient with no previous cardiac dysfunction has been described[144]. Positive inspiratory pressure of mechanical ventilation has less influence on LV function, which needs to be assessed because it can be directly altered by right heart dysfunction. Considering that about 50% of COVID-19 pneumonia patients are reported to suffer from systemic arterial hypertension, diastolic function should always be closely evaluated. Likewise, specific attention should be addressed to the diastolic profile of COVID-19 patients, whose lung ultrasound reveals a pattern of increased extravascular lung water (“pattern B”), particularly when this is associated with reduced LV function. TTE helps in identifying patients at high risk for ventilator weaning failure and guides tailored therapeutic strategy. Finally, when mechanical respiratory and circulation support with extracorporeal membrane oxygenation (ECMO) is needed, both TTE and TEE are important to decide the device selection (venovenous vs. venoarterial) on the basis of concomitant cardiogenic cause, to assist device placement (cannulation) and monitor cardiac function and device-related complications [145].

4.2 ICU cardiovascular bed-side evaluation

Several studies during the first months of COVID-19 pandemic showed how cardiac injury is highly frequent in ICU patients[146]: cardiac troponin I levels were significantly higher in patients with severe infection than in those with non-severe infection[1]. Different possible mechanisms such as serious hypoxia, sepsis, systemic inflammation, PE, cytokine storm, stress cardiomyopathy rather than a typical viral lymphocytic myocarditis can explain troponin elevation in the setting of severe disease, related to non-ischaemic myocardial injury. On the other hand, troponin elevation could be caused by an ischaemic myocardial injury which must be investigated. Both ischaemic and non-ischaemic cardiomyopathy can be exacerbated by concomitant renal failure[147].

The overlap of infectious symptoms and classic symptoms of cardiac syndromes presents a diagnostic challenge; therefore, awareness and vigilant surveillance for possible cardiovascular sequelae is critical. In this context, cardiovascular imaging offers an important instrument to facilitate the diagnosis of clinically suspected conditions. Various imaging modalities contribute to diagnostic evaluation, management and prognosis such as chest x-ray, echocardiography, chest computed tomography (CT), magnetic cardio-resonance and coronary angiography.

Radiology is an important complement to clinical and epidemiological features, both in adult and paediatric population. Chest x-ray is frequently requested in patients with acute pulmonary symptoms admitted to the emergency department, as well as in the ICU, because it is inexpensive, suitable to be placed by the patient’s bed and has low radiation exposure. The most common findings refer to lung abnormalities while pleural effusion and altered cardimediastinal contour are infrequent. Cardiac findings on chest x-ray are restricted to enlargement of cardiac silhouette and the presence of pulmonary oedema.

On the contrary, reports on the use of heart ultrasound are increasing. The most common reliefs in patients with severe COVID-19 illness are: pericardial effusion,
pulmonary artery hypertension, reduced ejection fraction, and segmental wall motion
abnormality[122]. Other commonly reported echocardiographic findings are: diffuse
myocardial wall motion abnormality, LV enlargement and dysfunction, hyperdynamic
LV function, TCM, signs of increase in right atrial pressure including increased IVC
diameter and decreased IVC collapsibility[148]. Critical care chest ultrasonography has
been used to obtain real time information, enable decision-making in COVID-19 patients.
It is useful to provide hemodynamic evaluation as well as cardiac and respiratory function
monitoring at patient’s admission and during hospitalization.

A pragmatic strategy based on the use of focused cardiac ultrasound (FoCUS) seems
the most reasonable approach. Ultrasonography is an adjunct to the physical examination
at the point of care to recognize specific ultrasonography signs that represent a narrow
list of potential diagnoses in specific clinical settings. Numerous data support the fact that
non-cardiology trained users using small ultrasonography devices can assess LV
enlargement, LV systolic dysfunction, RV enlargement, left atrial (LA) enlargement, LV
hypertrophy, pericardial effusion, and right atrial (RA) pressure elevation more
accurately than the physical examination. In addition, FoCUS-trained providers may have
skills to perform ultrasonography imaging of body systems outside the heart to
supplement their cardiac evaluation[149].

FoCUS should be combined with lung ultrasound (LUS) for the evaluation of patients
with respiratory failure. LUS helps in the bedside detection of pulmonary pathologies,
monitors the progression of mechanical ventilation, and detects complications such as
pleural effusion, pneumothorax and atelectasis[150]. Moreover, Echocardiography is a
first-line imaging modality in cardiac assessment and it is an indispensable bedside tool,
allowing non-invasive quantification of heart performance in COVID-19 patients in
isolated wards. It also facilitates guided titration of hemodynamic support, institution and
adjustment of disease-specific therapies and optimization of treatment. Guarracino et
al.[143] discussed the importance of a comprehensive US approach to the patients’ care.
They suggest to perform always simultaneously cardiac, vascular and lung ultrasound in
ventilated patients, in order to gain a more comprehensive understanding of the
relationship between lung and potential cardiac and vascular abnormalities[143].

Garcia-Cruz et al. [151] confirmed the important use of ultrasounds, and introduced
the “ORACLE” protocol, designed to enable rapid image acquisition at the patient’s
bedside in approximately 20 minutes, while the image analysis was performed outside
the patient’s room to reduce the operators’ risk of infection. The protocol included
evaluation of left (O) and right (R) ventricular function, valves (A), pericardial effusion
(C), diastolic function and filling pressures, pulmonary hemodynamics, regional wall
motion, cardiac output, fluid responsiveness with IVC distensibility index (E), and
stratification of the severity of pulmonary affection (L) based on the LUS score. They
pointed out how the application of the ORACLE protocol in 82 patients with severe
disease had an impact on the patient’s management. In fact, the protocol has been useful
to obtain fluid infusion and optimization of preload in patients with fluid responsiveness,
to initiate inotropes in those with RV dysfunction and TCM, to avoid fluid overload in
patients with ARDS, helping in pericardial drainage when cardiac tamponade is
detected[151].

4.3 Imaging in ICU patients

CT is currently deemed as the most sensitive imaging tool when COVID-19 is
suspected, being capable to detect specific and highly suggestive signs: ground-glass
opacities with or without consolidation in the lung periphery. Cardiac involvement is
being frequently reported in chest CT. This procedure is useful to selected patients with
elevated levels of cardiac biomarkers, in case of inconclusive echocardiograms and signs
and symptoms of an acute coronary syndrome to rule out coronary artery disease. It is an
important tool for diagnosing stenosis, valve dysfunction, coronary dissection and
intracardiac device dysfunction. In various reports, pericardial effusion[139] and evidence
of myocarditis, including increased wall thickness, myocardial oedema and hypokinesia, have been described[152].

An additional type of imaging is the coronary angiography (CAG): it is the gold standard to evaluate the coronary artery lumen, and it is recommended only in patients with ST-segment elevation on EKG or new left bundle-branch block. In clinically suspected STEMI, coronary angiography should be considered whenever possible, since COVID-19 can trigger acute coronary syndromes. At the same time, if STEMI is excluded, alternative causes of troponin elevation with non-obstructive coronary arteries should be investigated.

It has been explained how pulmonary thrombosis and arterial and venous thromboembolism affecting a sizeable proportion of patients in ICU, could cause DVT, PE, ischaemic stroke, myocardial infarction and systemic arterial embolism[153]. Zotzmann et al.[154] retrospectively evaluated all SARS-CoV2-associated ARDS patients admitted to ICU who underwent lung ultrasound and a computed tomography pulmonary angiography (CTPA) that was considered the gold standard for the detection of PE. In addition, Wells score was calculated to estimate the probability of PE. In 90% of patients, lung ultrasound found subpleural consolidation: PE-typical large subpleural consolidations with a size ≥1 cm were detectable in 65% of patients and were significantly more frequent in patients with PE compared to those without. Large consolidations predicted PE with a sensitivity of 77% and a specificity of 71%. The Wells score was remarkably higher in patients with PE compared to those without and predicted PE. By combining the two modalities, and using LUS plus a Wells score ≥2 or <2, patients with almost sure/probable PE were compared to patients with possible/unlike PE: PE was predicted with a sensitivity of 100% and a specificity of 80%. Large consolidations detected in LUS were found frequently in COVID-19 ARDS patients with PE. In combination with a Wells score >2, this may indicate a high-risk for PE in COVID-19.[154]

Accumulating evidence suggests that despite the use of anticoagulant therapy, there is a high incidence of thromboembolism events leading to the hyperinflammatory state especially in ICU patients[131]. Worth noticing, the majority of patients admitted to the ICU who requires infusion of vasoactive agents or haemodialysis receives a central venous catheter (CVC) that often produces catheter-related thrombosis (CRT). This is considered a serious complication as it may cause PE, increase the risk of infections, cause catheter dysfunction or long-term central venous stenosis, and is associated with considerable healthcare costs[155]. Since COVID-19 coagulopathy causes an overall hypercoagulable state rather than a local prothrombotic state in only the pulmonary circulation, CRT is frequent in critically ill patients who have an indwelling CVC. In a multicenter case-control study[156], the association of COVID-19 with CRT was studied hypothesizing that COVID-19 predisposes to CRT in critically ill patients. The study population consisted of 82 critically ill adult patients admitted to the ICU in 2020. Patients were included if they had an indwelling or recently removed (≤48 h) CVC in the internal jugular, subclavian or femoral vein. At time of CVC insertion, standard dosage thromboprophylaxis was doubled and based on the body weight. Multiple certified operators performed one compression and duplex ultrasound examination of the CVC entry vein. This entry vein was scanned by compression every 2 cm, and duplex ultrasound used to assess residual flow. If the vein failed to collapse at any point, an echogenic thrombus or intraluminal filling defect was considered diagnostic for CRT. The control group consisted of patients with ruled out CRT. In cases vs. controls, the crude OR for CRT, given COVID-19 exposure, was 7.2 (95% CI: 1.32, 130). The OR for CRT, given the COVID-19 exposure adjusted for anticoagulant usage and catheter indwelling time, was 18.3 (95% CI: 2.31, 410). The main finding of this study is that COVID-19 highly predisposes critically ill patients to CRT, in agreement with previous researches investigating thrombotic complications in ICU patients[62]. Therefore, COVID-19 patients had a statistical higher rate of CRT as compared with COVID-19 free ones despite the presence of prophylactic heparin therapy[157].
Moreover, in patients requiring venovenous ECMO, the occurrence of VTE has been studied only using ultrasonography. Parzy et al.[158] through CT scan imaging demonstrate that coagulation and thrombosis are at the interplay between SARS-CoV-2 and ECMO: they report a 100% occurrence of VTE in 14 critically ill patients supported by venovenous ECMO for ARDS despite a high target and close monitoring of anticoagulation. In the light of the above, clinicians must be aware of the complications requiring high attention for thrombosis prevention and diagnosis in critically ill patients.

Patients with cardiovascular involvement are well known to have poor outcome[159], because of development of ARDS, acute kidney injury, coagulopathy, worsening radiological changes, requirement of ICU admission and non-invasive/invasive ventilation, and an ensuing high mortality[22]. Cardiac findings in different kinds of imaging offer important details of various cardiac parameters including structure (chamber diameter, wall thickness, valves, supporting structures), functions, pericardial involvement, pulmonary artery diameter, IVC and major vessels in patients with COVID19.

5. COVID-19 specificity advanced imaging

Advanced cardiac imaging may play a role in discriminating the broad spectrum of differential diagnoses. The easiest tools are represented by the advanced imaging techniques in echocardiography. Among them, the most important one is the myocardial strain evaluation using the speckle-tracking analysis. Similarly, other useful tools are the cardiac magnetic resonance (CMR) and the positron-emission tomography (PET) that, however, are both more difficult to use in acute patients. Finally, there is no specific advanced imaging useful to differentiate or help in arrhythmias’ management. However, being the latter issue an essential prospective, additional studies are needed[160] to further investigate this topic.

5.1 Echocardiography Longitudinal Strain

TTE may be empowered by advanced imaging techniques. The longitudinal strain (LS) measured by two-dimensional speckle-tracking echocardiography (2D-STE) is a recent method able to perform a more accurate and sensitive indicator of cardiac function in a variety of cardiovascular diseases[161,162] and a prognostic tool in different clinical settings[163,164]. RV LS (RVLS) is an evolution of the technique used in COVID-19 patients.

Xie et al.[165] investigated the prognostic implications of biventricular longitudinal strain in COVID-19 patients. They found that patients with cardiac injury had higher levels of coagulopathy and inflammatory biomarkers, higher incidence of complications, more mechanical ventilation therapies, and higher mortality. Patients with cardiac injury were characterized by decreased strain of both LV and RV. These results were correlated with higher biomarkers levels of inflammation and cardiac injury, and the presence of pericardial effusion[165,166]. Moreover, patients who died were afflicted by impaired LS, an independent predictor of mortality in a Cox analysis. Therefore, at 3-month follow-up visit after discharge in survivors, a significant improvement was observed in both right and left LS[165]. However, RVLS worsened in patients who experienced hospitalization due to their clinical conditions, especially if they had severe pneumonia[166].

Furthermore, RVLS is useful to evaluate patients who received ventilation. Abnormal LS was found in about 66% of patients ventilated in ICU, and it was associated with higher lung compliance, lower airway plateau pressures, lower tidal volume ventilation, and reduced LV function[167]. RV LS is not related to abnormal lung mechanics or ventilatory pressures[167]. A recent systematic review on LS both of LV and RV showed that lower LV-GLS and RV-LS measurements were associated with poor outcome in patients with COVID-19[168]. Authors evaluated clinical trials that analysed as outcome a composite of mortality and severe COVID-19. Their meta-analysis included seven studies and 612
patients. They found that each 1% decrease in LV-GLS was associated with 1.4x increased risk of poor outcome, while each 1% decrease in RV-LS was associated with 1.3x increased risk of poor outcome[168].

5.2 Heart computerized tomography

Computerized tomography (CT) emerged as one of the primary imaging modalities in the COVID era. CT can be used to evaluate chest pain, LV dysfunction, new onset of heart failure or cardiomyopathy, and evaluation of patients with possible angina and new arrhythmias[6]. Cardiac CT also allows the comprehensive assessment of pulmonary parenchyma and vessels as well as coronary arteries. Cardiac CT use shifted to become the preferred pathway in acute atrial arrhythmias for LA evaluation prior to cardioversion, and during atrial fibrillation ablation and evaluation of LA appendage closure[6]. Endocarditis evaluation changed to incorporate multiphase cardiac CT instead of the TEE for patients with low-risk echocardiography findings, persistent bacteremia and ongoing clinical suspicion. For patients with definitive endocarditis requiring surgical intervention, both pre-operative TEE and cardiac catheterization was routinely deferred when possible, in favour of cardiac CT to allow evaluation of peri-valvular complications and coronary anatomy in patients without known coronary disease. However, it is limited to expert centers and it is not routinely used.

5.3 Cardiovascular magnetic resonance

The role of cardiovascular magnetic resonance (CMR) in COVID-19 patients is not clear. Advances in multi-parametric CMR now include quantitative ischaemia assessments, and detailed tissue characterization including scar, diffuse fibrosis and oedema. During the COVID-19 pandemic, CMR has not been widely considered, as for the necessary limitations due to the strain put upon the healthcare system[169]. Accepted diagnostic indications for CMR should be considered appropriate in COVID 19 patients, but should not be performed unless it is clinically necessary and after a reconsideration of the best suited imaging techniques. Special attention should be given to the use of CMR contrast in patients with COVID-19. Renal function is often decreased and might contradict a clinically urgent CMR scan. In these patients, it should be recognised the importance of systemic inflammation, enhanced adrenergic stimulation, and renal failure in more advanced cases. Details of CMR are rather limited but it is useful to provide a diagnosis in patient with elevated troponin from unclear aetiology[170]. Whenever feasible, CMR can allow a non-invasive diagnosis of clinically suspected myocarditis, while a definite diagnosis and proof of SARS-CoV-2 infection and inflammation would require endomyocardial biopsy. One indication for a CMR might be suspicion of acute myocarditis, which has been reported in patients with COVID-19. Typical symptoms are elevated troponins, ventricular dysfunction and/or severe arrhythmias that cannot be explained by other diagnostics and imaging methods.

Esposito et al.[160] reported a series of eight patients with elevated troponin and electrocardiography alterations whose CMR findings fulfilled the 2018 Lake Louise Criteria for the diagnosis of myocarditis[171]. Despite all patients had no remarkable previous history of cardiovascular disease, CMR showed diffuse intense myocardial oedema, increased T1 and T2 mapping and a mild pericardial effusion in 75% of them[160]. However, other reports suggest that CMR patterns are heterogeneous but in general not different from any other typical form of active inflammation characterized by diffuse myocardial oedema. Late gadolinium enhancement (LGE) seems to be less-frequently observed in these patients[171], reflecting a limited myocyte necrosis at least in acute phase[160]. In fact, LGE has a non-ischemic pattern and it is predominantly located in the inferior and inferior-lateral segments[172].

CMR may be helpful to evaluate the presence of a myocardial injury. In this setting, patients may present a decreased LV ejection fraction, increased LV volumes, and raised
native T1 and T2. Wang *et al.*[173] confirmed these results in a small cohort of patients evaluated with CMR three months after recovery: LGE was found in 30% of them. These patients had significantly decreased LV peak global circumferential strain (GCS), RV peak both GCS and GLS as compared to non-LGE patients, while no difference was found between the non-LGE patients and healthy controls. Lesions were located in the mid myocardium and/or sub-epicardium with a scattered distribution[173]. In the so far largest prospective observational cohort study, Puntmann *et al.*[174] has described abnormal CMR findings, including raised myocardial native T1, raised myocardial native T2, myocardial LGE, or pericardial enhancement. A little but significant difference between patients who recovered at home vs. hospital for native T1 but not for native T2 mapping was described. Native T1 and T2 mapping is significantly correlated to high-sensitivity troponin T and it is independent of pre-existing conditions, severity and overall course of the acute illness[174].

5.4 Other advanced tools in COVID-19 imaging

Cardiac evaluation of metabolic pattern should be assessed using [18F]-2-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)[175]. It is a sensitive and quantitative technique to detect inflammatory process. Few cases are reported on the use of FDG-PET in COVID-19 patients[176–178]. Recently, Dietz *et al.*[179] using FDG-PET assessed the inflammatory status at the presumed peak of the inflammatory phase in non-critically ill patients. Next to lung inflammation, all patients demonstrated increased mediastinal lymph nodes glucose uptake. The worthy finding is that they described also a myocardial up-take related to SARS-CoV-2 infection.[179] Despite the fascinating perspectives, larger forthcoming studies are needed to evaluate FDG-PET utility for COVID-19 myocardial damage.

Artificial intelligence (AI) is a brand new tool rising in helping the daily medical practice and clinical imaging[180]. The use of AI has been also proposed for COVID-19[181,182] treatment. In CT, CMR and ultrasound modalities, AI has been applied for data retrieval, segmentation of medical organs, and diagnosis for COVID-19[183]. However, AI is far from being routinely used in daily practice or in acute settings.

6. Safety concerns

Regardless of the imaging modality used for patient care in the COVID-19 era, the safety of patients and healthcare providers remains a universal priority. The importance of proper PPE and limiting testing to the ones which have an impact on patient health as well as clinical management have been emphasized in COVID-19 recommendations[184–187]. In ventilated patients, especially those ventilated mechanically, TEE is able to overcome technical problems with acoustic views. However, to limit the virus spread exposure, TEE is recommended to selected patients. Both European Society of Cardiology[187] and American Society of Echocardiography[185] suggest limiting its use. In fact, TEE has inherent risks and limitations related to manpower and infection control. Airborne precautions are required during a TEE for suspected and confirmed cases, due to the increased risk for aerosolization[185,187]. The value of TEE in COVID-19 pandemic is seen in familiar domains, for instance patients whose adequate transthoracic echocardiographic windows cannot be generated. Similarly, frequent scenarios in ICU care of COVID-19 need to be addressed using TEE, such as hemodynamic instability during prone ventilation, serial evaluations of the lungs, during cardiac arrest resuscitation, and to guide venovenous ECMO cannulation[188]. However, comparison of possible advantages and disadvantages in different clinical settings (Table 1, Fig. 6) may help to choose the specific test and reduce the infection exposure.
Figure 6: Viral replication and host immune response synergistically determine disease progression. Through the three stages, different chest imaging modalities are useful to study the cardiovascular involvement. Transthoracic echocardiography can identify increasing pulmonary hypertension and right ventricular impairment. Cardiovascular complications related to viral infection or to systemic inflammation can occur at different stages of the disease, increasing the risk for adverse outcome, and require specific multimodality imaging assessment. CT: computed tomography; CTPA: computed tomography pulmonary arteriography; LUS: lung ultrasound; TTE: transthoracic echocardiography.
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<td>Difficult disinfection</td>
<td>Frequent patient intolerance and incompatibilities</td>
</tr>
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<td></td>
<td>Strain abnormalities</td>
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<td>Strain abnormalities</td>
</tr>
<tr>
<td>Nuclear imaging</td>
<td>Inflammation localization</td>
<td>Low resolution Not bedside Time-consuming Radiation exposure Difficult disinfection Limited indication in emergency</td>
<td>Inflammation localization</td>
</tr>
</tbody>
</table>
7. Conclusion

During COVID-19 pandemic, healthcare systems and health workers are making every effort to ensure the best treatments to each patient. In view of resources optimization, imaging can effectively support the assessment and prognostic evaluation of critically ill patients. The different techniques are able to provide different information. Ultrasound is the most reliable and easy to use in emergency setting and in ICU as first approach. It is also an amazing tool for frequent instrumental follow-ups. However, for many other diseases, there is the need for an increased diagnostic power, that only more complex machines are able to ensure. For this reason, a combination of different methods is the best possible way to perform an adequate patients’ care, reducing operators’ exposure to infection. Additional prospective studies are needed to develop an effective method which combines the different tools.

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